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Nodal aggressive non-Hodgkin's lymphoma in the adult: a review article

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A B S T R A C T

Background. The term *aggressive lymphoma* is a clinical definition encompassing different lymphoid tumurs which are potentially curable, but run a rapidly fatal course if not properly treated. Under this definition, no longer quoted in the REAL/WHO Classification, several histotypes are included that differ remarkably in cell size and morphology, phenotypic and molecular characteristics, kinetics and clinical presentation. Tailored approaches have been designed aiming to adapt therapy to each specific histotype.

Aim and design. Since aggressive lymphomas account for the majority of lymphoid neoplasms, and because some variation exists as to their categorization and treatment, the authors will discuss the more recent and consolidated findings in the etiology, pathogenesis, histopathology, diagnostics and therapy of such tumours based on both the evidence in the literature and their own expertise. In particular, each tumour type is individually discussed, as are the most critical areas in patient management.

Conclusions. An updated review of more recent biological and therapeutic aspects is intended to assist the hematologist, pathologist and practitioner in the optimal management of patients with aggressive lymphoma.

Key words: aggressive non-Hodgkin lymphoma, chemotherapy, chemoimmunotherapy, supportive therapy.

Aggressive non-Hodgkin lymphomas (NHL) can be of B or, less frequently, T-cell origin and are characterized by large lymph node masses and/or disseminated disease. In contrast to indolent neoplasms, a sizable fraction of aggressive lymphomas can be cured, but without treatment the disease is rapidly fatal.

In the present report, the reviewers' panel will discuss the more recent and consolidated findings in the etiology, pathogenesis, histopathology, diagnostics, and therapy of the following disease entities[1,2] diffuse large B-cell lymphoma (DLBCL), follicular lymphoma grade IIIB (FCLIIIB), Burkitt's lymphoma (BL), lymphoblastic lymphoma-leukemia (Lb-L), mantle cell lymphoma (MCL), transformed lymphoma originating from a low grade disease, peripheral T-cell lymphomas (PTCL), and the post-transplant lymphoproliferative disorders (PTLD).

Epidemiology

During the last five decades, the mortality from NHL has increased significantly from a rate of 3.2 deaths/100,000 person-years, to a rate of 7/100,000 person-years.[3-5] Because mortality rates are sensitive to improvements in survival, but are less sensitive to improvements in diagnostic strategies, the increase of the mortality rate for NHL provides solid evidence for the increase in incidence of these neoplasms. At present, in Europe and in the USA, the annual incidence of all NHL is estimated to be 15-20 cases/100,000.[3-5] Based on the data of the International Non-Hodgkin's Lymphoma Classification study, aggressive NHL in western countries account for approximately 50% of all NHL.[6] In particular, the entity known as DLBCL alone accounts for approximately 30% of all NHL. The median age of aggressive NHL considered as a whole falls between the sixth and seventh decade, although some specific types of aggressive NHL present at a lower median age, as exemplified by BL (median age 30 years). The distribution of aggressive NHL is overall similar between the two sexes (male:female ratio=1.5). One exception is MCL, which shows a marked predilection for the male sex (>70% of cases).

Etiology and pathogenesis

Causes and predisposing factors

Epidemiological studies have not documented environmental or occupational risk factors, with the possible exception of exposure to pesticides.[3] A relevant etiological factor that is significantly correlated to the development of aggressive B-cell NHL is host immunodeficiency, both congenital and acquired in its many forms.[5] The risk of aggressive NHL is most evident in patients affected by T-cell immunodeficiency. Notably, the relative risk of aggressive NHL is 100-200 in congenital immunodeficiency (ataxia-teleangectasia and Wiskott-Aldrich syndrome), 30-40 in common variable immunodeficiency, 250-400 in the course of HIV infection and 20-100 in post-transplant iatrogenic immunosuppression. In addition, some systemic autoimmune disorders, namely rheumatoid arthritis and systemic lupus erythematosus, are associated with an increased relative risk of DLBCL.[5] In these conditions, however, the relative risk is approximately 3-8 and therefore markedly lower that that observed in immunodeficiency conditions. The host's infection by several viruses may also predispose to or cause aggressive NHL, and the pathogenetic role of these viruses will be discussed in detail later in this review.

Molecular histogenesis

The histogenesis of lymphoma can be assessed by identifying the precise cellular subset from which a given lymphoma category derives. This is achieved by defining the lineage and the precise differentiation stage of the various types of lymphoma and by comparing them with characteristic features of the different maturation stages of normal lymphocytes.[7,8] To date, the histogenesis of lymphoma has been clarified reasonably well in the case of lymphomas derived from B cells, whereas is still poorly understood in the case of lymphomas originating from T cells.

Precursor B cells in the bone marrow attempt to perform immunoglobulin (Ig) gene rearrangement and, if successful, they are positively selected into the peripheral B-cell pool comprising naive B-cells.[7,8] For many B cells, the subsequent maturation steps are linked to the histological structure of the germinal center (GC).[7,8] Within the GC, antigen-activated B cells accumulate somatic point mutations within their rearranged Ig heavy and light chain genes (a phenomenon known as somatic hypermutation) which modify the affinity of their B-cell receptor to the antigen. Only B cells which have acquired mutations leading to high affinity binding are positively selected and differentiate into memory B-cells or plasmablasts, while the majority of B cells are eliminated by apoptosis within the GC.[7,8]

Lb-L stems from lymphoblasts, i.e. from B- and T-cell precursors undergoing the maturation process that leads to the development of effective, non-autoreactive lymphocytes apt to migrate from the bone marrow or thymus to the peripheral organs of the immune system.[1,2,7,8] Within aggressive B-cell NHL deriving from mature B cells, the use of somatic hypermutation as a specific marker of B-cell transition through the GC allows the definition of two broad histogenetic categories of these disorders:[1,2,7,8] *i*) lymphomas devoid of somatic Ig hypermutation, deriving from pre-GC B cells including MCL; *ii*) lymphomas associated with somatic Ig hypermutation and thus putatively derived from GC or post-GC B-cells. Among aggressive NHL, these include DLBCL, BL, and most PTLD (Figure 1).

General pathogenetic mechanisms of aggressive NHL

Molecular lesions of aggressive NHL include *i*) proto-oncogene activation by chromosomal translocation; *ii*) inactivation of tumor suppressor genes; and *iii)* virus-related alterations.[8] Chromosomal translocations are the dominant mechanism of proto-oncogene activation in aggressive NHL. A common feature of translocations of aggressive mature B-cell NHL is the placement of the proto-oncogene in the proximity of regulatory regions derived from Ig genes or other loci that are expressed at high levels in mature B cells,[8] thus leading to deregulated expression of the proto-oncogene. A different translocation mechanism is the formation of a fusion transcript, as exemplified by the t(2,5) translocation.[8] Proto-oncogenes deregulated in aggressive NHL include transcription factors, namely *c-MYC* and BCL-6; cell cycle regulators, namely cyclin D1; inhibitors of apoptosis, namely BCL-2; and signal transducers, namely ALK.

Tumor suppressor genes involved in aggressive NHL undergo biallelic inactivation and include cell cycle regulators, such as *p15* and *p16*; inducers of apoptosis, namely Death-associated protein kinase; and regulators of genomic integrity, such as p*53*, FHIT (*F*ragile *H*istidine *T*riad) and MGMT (O6-*M*ethyl*G*uanine DNA *M*ethyl*T*ransferase).[8]

Viruses associated with aggressive NHL may favor transformation by a direct mechanism through introduction of exogenous genes into target cells (EBV and HHV8), or by an indirect mechanism (HIV and HCV), through modifications of the microenvironment or host immunity or via chronic antigen stimulation.[5,8] EBV infection associates with BL (30% of sporadic and epidemic cases and 100% of endemic cases) and a fraction of PTLD.[9] The EBV-encoded proteins LMP-1 and EBNA-2 are capable of inducing B-cell transformation *in vitro* and *in vivo*.[9] HHV8 is a lymphotropic virus associated with primary effusion lymphoma, whose genome

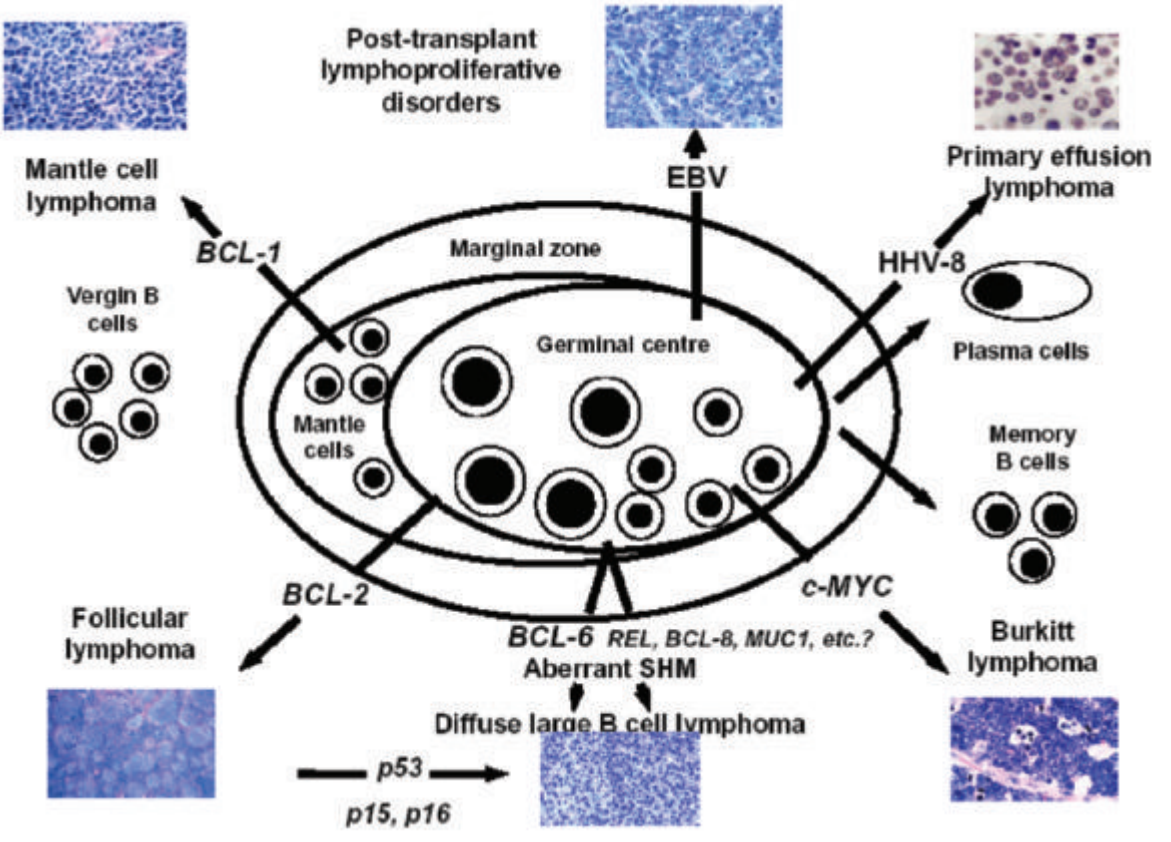

Figure 1. The figure depicts the histogenetic derivation and the molecular pathways associated with aggressive B-cell NHL. With the exception of mantle cell lymphoma, which derives from virgin B-cells in the follicular mantle, all other aggressive B-cell NHL derive from germinal center-experienced B cells. The predominant genetic lesion(s) associated with each single clinico-pathologic category of aggressive lymphoma is indicated in the figure. In the case of diffuse large B-cell lymphoma, multiple, partially overlapping, molecular pathways are involved in the pathogenesis of this neoplasm, as indicated in the figure. Other genetic lesions, not indicated in the figure, may also be involved in the pathogenesis of aggressive B-cell NHL. Abbreviations: NHL, non-Hodgkin lymphoma; PTLD, post-transplant lymphoproliferative disorders; SHM, somatic hypermutation.

codifies for several viral oncogenes, including a viral cyclin homologous to cyclin D.[10]

Several epidemiological studies indicate that HCV infection is significantly over-represented in B-cell NHL.[11-14] A recent meta-analysis of 48 studies has definitively established that the prevalence of HCV is higher in patients with B-cell NHL than in the general population (17% vs 1.5%; OR 10.8; 95% C.I. 7.4-16) or in other hematologic malignancies (13% vs 2.9%; OR 4.2; 95% CI: 2.5-7).[12] Such differences are particularly striking in Italian and Japanese populations, where the infection is endemic.[11,14] In general, the relationship between HCV and B-cell NHL is stronger for specific sub-types of indolent B-cell NHL.[14]

However, a significantly higher incidence of HCV infection has also recently been observed within aggressive cell B-NHL.[11,14,15] These forms are frequently characterized by extranodal involvement and usually have no previous history of indolent B-cell malignancy.

How HCV may provoke B-cell lymphoproliferative disorders is still unclear. In animal models, viral core and NS3 proteins induce a *mutator phenotype* causing double-stranded DNA breaks and enhancing the mutation frequency of proto-oncogenes (i.e. *BCL-6, p53, β-catenin*) and immunoglobulin genes with *hit-and-run*–like mechanisms.[16] However, the predominant hypothesis suggests that the virus is a putative exogenous stimulus triggering activation of target B-lymphocytes and possibly selecting clonal cell populations and leading to uncontrolled, HCV-antigen driven neoplastic clonal B-cell proliferation.

Molecular pathology

Diffuse large B-cell lymphoma

The molecular pathogenesis of DLBCL is complex and includes more than one disease variant.[1,2] Chromosomal translocations of band 3q27 are detected in 30-40% of cases and cause the rearrangement of *BCL-6*, a transcriptional repressor selectively expressed by GC B cells and controlling GC formation.[17,18] The translocation inhibits the down-regulation of *BCL-6* which is required for further differentiation of GC B cells, and creates a DNA error-prone GC microenvironment by functionally inactivating p53.[19,20] Translocations of *BCL-2* occur in approximately 20% of DLBCL arising *de novo* and in most cases transformed from a prior follicular phase.[21] Other molecular lesions occasionally involved in the pathogenesis of DLBCL include translocations of *BCL-8* and *MUC-1*, amplification of *REL*, and inactivation of the *p53* tumor suppressor gene.[22-24] Despite the molecular heterogeneity of DLBCL, most cases (70%) are affected by aberrant somatic hypermutation (SHM), which introduces multiple nucleotide substitutions in the coding and regulatory regions of several proto-oncogenes, namely *c-MYC, PAX-5, RhoH/TTF* and PIM-1.[25] Aberrant SHM is thought to be due to malfunctioning of the physiological process that is normally active in GC B cells. The precise pathogenetic role of aberrant SHM is still under investigation.

Gene profiling studies have revealed at least two variants of DLBCL, defined as *germinal center* and *activated B-cell like* DLBCL, with prognostic significance that is discussed later in this review.

Follicular lymphoma grade IIIB

The molecular pathogenesis of FCLIIIB is heterogeneous.[26,27] Rearrangements of BCL-6, resembling those in DLBCL, are detectable in approximately 50% of cases, whereas *BCL-2* translocations are restricted to a minority of cases. On these bases, FCLIIIB resembles DLBCL and apparently does not evolve from a follicular lymphoma of lower grade.

Burkitt's lymphoma

All cases of BL display chromosomal breaks at 8q24, on one side, and of one Ig gene, on the other.[1,2] The functional consequence is the deregulation of the *c-MYC* proto-oncogene through repositiong of the Ig regulatory regions.[28] *c-MYC* codes for a transcription factor that is ubiquitously expressed and involved in regulation of proliferation, differentiation and apoptosis.[28] In addition, *c-MYC* positively regulates the transcription of several genes, including TERT (*TElomerase Reverse Transcriptase*), whose product modulates telomerase activity.[29] The stimulation of telomerase induced by TERT increases the number of proliferative cycles that a cell can perform.[29] Other genetic lesions associated with a fraction of BL are inactivation of p53, FHIT and p16.[30,31] EBV infection is restricted to 30% of sporadic BL, whereas it is consistently present in endemic BL.[9]

Mantle cell lymphoma

MCL is typically associated with t(11;14)(q13;q32).[32] The translocation re-positions the BCL-1 locus at 11q13 with IgH and leads to homotopic deregulation of cyclin D_1, a gene located in proximity to the breakpoint and encoding a member of the D-type G1 cyclins which regulates the early phases of cell cycle.[32] As for other D-type cyclins, cyclin D1 is thought to act primarily as a growth factor sensor integrating extracellular signals with the cell cycle clock. The pathogenetic role of *BCL-1* activation in human neoplasia is suggested by the ability of cyclin D1 overexpression to transform cells *in vitro* and contribute to B cell lymphomagenesis in transgenic mice.[32]

Peripheral T-cell lymphoma

Few categories of peripheral T-cell lymphomas (PTCL) have been investigated at the molecular level. Anaplastic large cell lymphomas (ALCL) expressing the ALK (*Anaplastic Lymphoma Kinase*) protein associate with molecular derangements of the *ALK* gene.[33-36] Eighty-five per cent of ALK^+ ALCL bear the t(2;5)(p23;q35) translocation, involving the genes *ALK* on chromosome 2 and *NPM* (nucleophosmin or numatrin) on chromosome 5. The translocation gives rise to the fusion protein NPM/ALK. The *ALK* gene is not expressed in normal lymphoid cells, whereas *NPM* is ubiquitously expressed. Because of the t(2;5) translocation, expression of *ALK* is regulated by the *NPM* promoter and, therefore, is deregulated in neoplastic cells. In addition, because NPM/ALK can homodimerize, the translocation causes the constitutive activation of the catalytic domain of the ALK tyrosine kinase. In the remaining 15% of ALK^+ ALCL, *ALK* fuses to a partner gene other than *NPM* to produce variant ALK proteins, which gain the ability to homodimerize and, therefore, display constitutive kinase activity.

Post-transplant lymphoproliferative disorders

The clinical and morphological heterogeneity of Post-Transplant Lymphoproliferative Disorder (PTLD) correlates with the molecular heterogeneity of these disorders.[37] EBV infection associates with 100% of early PTLD (<1 year post-transplant), whereas it is restricted to 40-50% of late PTLD (>1 year post-transplant).[9,37]

Current concepts for a lymphoma classification

Lymphoid neoplasms are currently categorized

according to the REAL/WHO Classification,[1,2] which consists of a list of distinct diseases defined by an amalgamation of information on cell morphology, phenotype, genotype, clinical characteristics and identification of a normal counterpart if possible. Notably, the Classification does not provide grades of malignancy, in contrast to other approaches.[1,2] In fact, it was felt that the clinical behavior and therapeutic response of malignant lymphomas are not influenced by the cell size, number of mitotic figures and differentiation stage (as usually postulated for most, if not all, non-hematopoietic neoplasms), but rather depend on the category to which the tumur belongs, and, within each category, on a series of biological mechanisms which vary somewhat from patient to patient. Such a view is supported by the results of gene expression profiling techniques that allow the simultaneous evaluation of thousands of genes through m-RNA hybridization on micro-arrays containing DNA spots or oligonucleotides corresponding to the investigated genes.[38-44] The main limitations of these techniques are that they require optimally preserved m-RNA and complex statistical analysis; they are also very expensive.[45] In addition, the gene data need confirmation at the protein level, as the approximately 40,000 genes constituting our genome encode for more than 400,000 proteins.[46] Tissue micro-array represents an excellent tool for such validation: it consists in a recipient paraffin block containing tissue cores taken from hundreds of donor paraffin blocks.[47,48] Sections cut from the recipient block are used for the simultaneous determination of gene products by immunohistochemistry.

The data available from the combination of the genomic and tissue micro-array technologies are rapidly improving.[49-53]

B- and T-cell precursor (lymphoblastic) lymphoma/leukaemia

These tumours can occur either in a leukemic form or as a solid mass.[1,2] The former presentation is more common in B-Lb-L, while the latter is recorded in most T-cell precursor neoplasms.

Morphology

This is not predictive of either the (B or T) cell origin or the maturation stage within the specific cell lineage. Neoplastic cells display a high nuclear/cytoplasmic ratio, dense chromatin, hardly visible nucleoli, and a narrow rim of moderately basophilic cytoplasm. The nuclear contours are irregular, at times convoluted. In the past, the latter finding was regarded as pathognomonic of T-cell derivation, but it can also occur in B-Lb-L.[1,2] Mitotic figures are numerous. Histiocytes phagocytosing nuclear debris are encountered, which may produce a *starry-sky* pattern.

Phenotype

The phenotype can be adequately assessed in routine sections thanks to the currently available antigen retrieval techniques.[54] This permits the accurate subclassification of Lb-L as summarized in the foot note.[54] Notably, BSAP (i.e. the *PAX5* gene product) represents the first lineage marker during B-cell ontogeny, although it can be expressed in a proportion of acute myeloid leukemias carrying t(9;21).[55-58] Some molecules that are usually associated with the B-cell lineage (e.g. CD79a, CD10 and Bcl-6) can actually be detected in a proportion of T-Lb-L, since they are transiently expressed by immature T-cells.[59-61] Both B- and T-Lb-L lack myelo-monocytic, erythroid and megakaryocytic markers.[54] The negativity for cyclin D1 contributes to the distinction of B-Lb-L with a *mature* phenotype from MCL with blastoid morphology.[62,63] The search for cytokeratins represents a useful tool for the differential diagnosis between T-Lb-L and thymoma, which can contain huge amounts of T-lymphoblasts, but conversely to T-Lb-L shows a regular frame of cytokeratin$^+$ epithelial cells.[64] Immunohistochemistry also allows the distinction of Lb-L from other *small blue cell tumors*, including Ewing's sarcoma (vimentin$^+$/CD99$^+$), PNET (vimentin$^+$/ CD99$^+$/S100$^+$/$^-$/chromogranin$^+$/$^-$), neuroblastoma (NSE$^+$/ chromogranin$^+$/synaptophysin$^+$), chondrosarcoma (vimentin$^+$/ Sox9$^+$), and rhabdomyosarcoma (vimentin$^+$/desmin$^+$/striated-muscle actin$^+$).[65]

Mantle cell lymphoma

Morphology

This lymphoma is usually composed of small cells, characterized by *cleaved* nuclei with moderately dispersed chromatin and a minute central nucleolus.[1,2,66] The cytoplasm is narrow and grayish following Giemsa staining. The number of mitotic figures is usually low-moderate. Some epithelioid macrophages and flat hyaline venules are included in the lymphomatous growth. Three morphologic variants of the tumor (small cell, blastoid and polymorphic) are recognized that should be differentiated from B-cell chronic lymphocytic leukemia (B-CLL), Lb-L and DLBCL.[1,2,66] At the lymph node level, MCL gives rise to different growth

Foot note:

B-Lb-L, pro-B: CD34$^+$, TdT$^+$, BSAP$^+$, CD19$^+$, CD79a$^+$, CD20$^-$, CD10$^+$, Cμ$^-$, SlgM$^-$, T-cell markers$^-$;
B-Lb-L, pre-B: CD34$^{+/-}$, TdT$^{+/-}$, BSAP$^+$, CD19$^+$, CD79a$^+$, CD20$^{-/+}$, CD10$^+$, Cμ$^+$, SlgM$^-$, T-cell markers$^-$;
B-Lb-L, " mature": CD34$^-$, TdT$^-$, BSAP$^+$, CD19$^+$, CD79a$^+$, CD20+, CD10$^+$, Cμ-, SlgM$^+$, T-cell markers$^-$;
T-Lb-L, prothymocytic: CD34$^+$, TdT$^+$, CD3cyt$^+$, CD2$^+$, CD5$^{+/-}$, CD7$^+$, CD1a$^-$, CD4$^-$, CD8$^-$, B-cell markers$^-$;
T-Lb-L, thymocytic (cortical): CD34$^-$, TdT$^+$, CD3cyt$^+$, CD2/CD5/CD7$^+$, CD1a$^+$, CD4&CD8$^+$, B-cell markers$^-$;
T-Lb-L thymocytic (medullary): CD34$^-$, TdT$^-$, CD2/CD3/CD5/CD7$^+$, CD1a$^-$, CD4 or CD8$^+$, B-cell markers$^-$.

patterns: mantle zone-like, nodular and diffuse.[1,2,66] The tumor frequently involves the bone marrow (with variable location)[67,68] and the intestine, where it may produce the so-called lymphomatous polyposis.[69] It can present with a leukemic picture or prominent splenomegaly. The latter condition should be differentiated from splenic marginal-zone lymphoma (S-MZL).[70]

Phenotype

Besides positivity for CD19, CD20, CD79a, and BSAP, MCL shows almost regular expression of CD5 and cyclin D1.[1,2,66,71] The latter reflects the occurrence of t(11;14).[1,2,66] Notably, although characteristic, cyclin D1 positivity is not pathognomonic of the process, as it can be detected in other lymphoid neoplasms such as hairy cell leukemia, multiple myeloma and – more rarely and controversially – B-CLL.[72] In addition, it is absent in about 10% of MCL cases.[73] The recent production of a highly specific rabbit monoclonal antibody has markedly improved the detection of this marker, whose preservation – like that of CD5 – is critical and requires optimal fixation.[72] Staining for CD21 reveals irregular meshworks of follicular dendritic cells often connected with the hyaline vessels.[1,2,66] The search for CD23 (with a few exceptions),[74] CD10 and IRTA1 is negative, thus contributing to the distinction of MCL from B-CLL, follicular lymphoma (FL) and MZL.[75] Bcl-6 protein has recently been found in a proportion of MCL, throwing into doubt its relevance in differentiating FL and DLBCL.[76] Neoplastic cells are usually IgM^+/IgD^-, a finding that may be relevant for the differential diagnosis between MCL and S-MZL (IgM^+/IgD^+) especially in cases with medullary intrasinusoidal diffusion.[68] Cases with higher proliferation rates (Ki-67 rate >30%) have a more aggressive clinical course.[77] They are often characterized by expression of nuclear survivin, p53, and MDM2 and lack of $p27^{KIP1}$.[78]

Follicular lymphoma grade IIIB

Morphology

FLIIIB is almost exclusively composed of centroblasts and is included among the *aggressive lymphomas* because of its clinical behavior and peculiar molecular characteristics.[1,2,26,55,56] In particular, the diagnosis of FLIIIB is acceptable only when the tumour arises *de novo* and the follicular pattern predominates over a possibly associated diffuse large B-cell component (otherwise the tumor is a DLBCL secondary to FL).[1,2,55,56]

Phenotype

FLIIIB is characterized by positivity for CD20, BSAP and – sometimes to a lower extent – CD79a. CD10 and Bcl-6 are commonly expressed, although one of them (rarely both) can be lost.[1,2,55,56,79] Interestingly, *c-MYC* aberrations may produce a Burkitt-like morphology.[80] Finally, occasional expression of CD5 has been reported in the absence of cyclin D1 positivity, a fact that allows differentiation from MCL.[81,82] Bcl-2 protein negativity is found in the majority of FLIIIB cases, due to the absence of t(14;18) or unproductive *BCL-2* gene rearrangement.[1,2,55,56,58] Cases lacking t(14;18) usually carry a different chromosomal aberration.[26]

Diffuse large B-cell lymphoma

Morphology

DLBCL consists of large cells (mean diameter ≥20 μm), often characterized by pronounced nuclear polymorphism, prominent nucleoli and a rim of basophilic cytoplasm.[1,2,49,56] At the tissue level, the neoplasm grows diffusely, sometimes spreading through residual sinuses in the lymph node. Mitotic figures are always numerous. In a variable percentage of patients, DLBCL evokes a fibrotic reaction, which may become prominent in the retroperitoneum and mediastinum: in the latter site, the process reveals peculiar clinico-pathologic features that justify its identification as a distinct subtype of DLBCL.[83-85] In 20-25% of cases, one cytotype predominates over the others, thus allowing the identification of morphologic variants: centroblastic, with large multilobed nuclei, immunoblastic (with and without plasma cell differentiation), plasmablastic, and anaplastic.[1,2,49,56,86] A further cytological variant of DLBCL is the so-called T-cell-rich/histiocyte-rich B-cell lymphoma (T/HCRBCL).[49,87-89] This is characterized by the presence of scattered large tumor cells intermingled with a huge amount of reactive T-lymphocytes and/or histiocytes: its borders with lymphocyte predominant or lymphocyte-rich Hodgkin's lymphoma are not always sharp and transition from one tumor type to the other is possible.[87-90] In rare cases, DLBCL consists of epithelial-like or spindle-shaped elements[91] or is provided with prominent interlacing cytoplasmic projections, which produce a neuroblastoma-like appearance.[49,92] There is no consensus on the usefulness of a cytological classification of DLBCL.[49,93]

Phenotype

The neoplastic cells express a series of B-cell associated antigens, such as CD19, CD20, CD79a, and BSAP.[1,2,49,55,56] In approximately 30% of DLBCL of the immunoblastic and $CD30^+$ anaplastic types, the leukocyte common antigen/CD45 is absent.[94,95] The PU1 and LSP1 molecules have been found to be useful for the differential diagnosis between T/HRBCL and l lymphocyte predominant Hodgkin's lymphoma by showing opposite patterns ($PU1^-/LSP1^+$ vs. $PU1^+/LSP1^-$).[90] Recently, attention has been paid to CD5 positivity.[96] This occurs in the absence of cyclin D1 over-expression, a fact that allows the easy differentiation of $CD5^+$ DLBCL from polymorphic MCL.[96] The adverse prognostic rel-

evance of CD5 expression originally reported by Yamaguchi *et al.*[96] has not been confirmed by others.[97] Following the seminal paper of Alizadeh *et al.* in 2000,[38] further gene expression profiling studies based on larger series of cases have confirmed that DLBCL can be subdivided into subtypes depending on their gene signature: germinal-centre B-cell(GCB)-like, activated blood B-cell(ABC)-like, and type 3 or unclassified.[31,43,44] These subgroups have significantly different clinical behaviors and responses to therapy. After two initial unsuccessful studies.[97,98] Some groups have recently identified possible immunohistochemical gene expression profiling surrogates applicable at low cost to formalin-fixed, paraffin-embedded samples. By adopting the tissue micro-array strategy, Sàez *et al.* have detected eight biological markers (cyclin E, CDK1, SKP2, EBER, MUM1, CDK2, Bcl-6, and Rb-P) that can improve the capacity for predicting failure and survival in combination with the International Prognostic Index.[52] In another study, also based on tissue micro-arrays, Hans *et al.* have sub-classified 152 DLBCL, 142 of which had been successfully evaluated by gene expression profiling, into GC (n=64) and non-GC B-cell derived (n=86).[51] This sub-classification was based on the usage of three molecules: CD10, Bcl-6 and MUM1/IRF4. The 5-year overall survival for the GCB group ($CD10^+$/$Bcl\text{-}6^+$/IRF4) was 76% compared to 34% for the non-GCB one ($CD10^-$/$Bcl\text{-}6^+$/$IRF4^+$ or $CD10^-$/$Bcl\text{-}6^-$/$IRF4^+$).[51] Bcl-2 and cyclin D2 were adverse predictors in the non-GCB group.[51] Finally, Chang *et al.* analyzed 42 DLBCL by applying antibodies against CD10, Bcl-6, IRF4, and CD138 on conventional paraffin sections instead of tissue microarrays.[99] Based on marker combinations, the cases were subdivided into three groups showing expression of: a) CD10 and/or Bcl-6 alone, b) CD10 or Bcl-6 plus IRF4 or CD138, and c) IRF4 and/or CD138 in the absence of CD10 and Bcl-6.[99] The first group had a significantly better clinical outcome than the other two.[99] Further markers with possible prognostic relevance have recently been proposed: they include FOXP1, HLA-DRA, nuclear REL and amount of tumor -infiltrating $CD8^+$ T-lymphocytes.[100-102]

Transformed lymphomas

When dealing with DLBCL, one should remember that this tumor may represent the progression of a pre-existing indolent lymphoma, such as B-CLL, lymphoplasmacytic lymphoma (LPL), FL or MZL.[49,55,56,103-105] This event does not imply specific morphologic findings, the growth consisting of large, usually polymorphic cells. The phenotypic profile may maintain one or more of the expressions typical of the original process (such as CD5 and CD23 for B-CLL, CD10, Bcl-6 and Bcl-2 for FL, and IRTA1 for MZL).[49,55,56,103-105] Interestingly, frequent positivity for p53 and/or *c-myc* is detected due to the occurrence of an alteration of the corresponding gene(s), which represents a second hit in the natural history of the process.[49,55,56,103-105] This produces a kinetic advantage for one of the sub-clones, which assumes blastic morphology and rapidly predominates over the others, giving rise to a secondary DLBCL that is significantly more aggressive and chemo-resistant than *de novo* forms.[49,55,56,103-106]

Burkitt's lymphoma

Morphology

The endemic and sporadic forms of BL are characterized by the same morphology: they consist of homogenously medium-sized cells with a narrow rim of deeply basophilic vacuolated cytoplasm and a round nucleus with granular or reticulated chromatin and 2-6 nucleoli, usually at distance from the nuclear membrane.[1,2] The tumor tends to grow cohesively, has exceedingly high mitotic and apoptotic rates and contains numerous macrophages phagocytosing nuclear debris, which produce the typical *starry-sky pattern.*[1,2]

Phenotype

Neoplastic cells express B-cell markers, CD10 and Bcl-6, but lack Bcl-2.[107,108] The Ki-67 marking is 100%.[107,108] *In situ* hybridization (ISH) with EBER1 and 2 probes demonstrates regular EBV integration in the genome of neoplastic cells in the endemic form of the tumor .[1,2] This finding is less frequent found in sporadic BL, its incidence varying from 25% to 50% depending on HIV-negativity or positivity of the patient.[1,2] Fluorescence ISH (FISH) or chromogen-ISH (CISH) reveals abnormalities at the *C-MYC* locus on chromosome 8 [t(8;14), t(2;8) or t(8;22)].[109]

Burkitt-like or atypical Burkitt's lymphoma

This is a controversial entity that was included in the REAL/WHO Classification because of the belief that it should be treated more aggressively than DLBCL, although no definite proof exists as to its morphologic and biological homogeneity.[1,2,110] Unlike to true BL, neoplastic cells are variably sized, have a large cytoplasmic rim (at times with a paranuclear clear dot) and prominent nucleoli.[1,2] The morphologic similarities with BL might be due to the common *C-MYC* gene rearrangement.[1,2] In immunohistochemistry, they are $CD10^-$, $Bcl\text{-}6^-$ and $Bcl\text{-}2^+$. The Ki-67 rate is very high, but less than 100%.[107,108] EBV integration seldom occurs.[1,2]

Peripheral T-cell lymphoma

PTCL represents 10-15% of all lymphoid tumors in western countries, being endemic in some geographic areas such as the southern part of Japan, where is related to HTLV1 infection (so-called adult T-cell lymphoma/leukemia).[1,2] The family of PTCL includes neoplasms derived from peripheral T-lymphocytes and NK

cells.[1,2] With only three exceptions (mycosis fungoides, CD30+ lymphoproliferative disorders of the skin and large granular lymphocyte leukemia), all PTCL behave aggressively.[56,111-114] They can be roughly subdivided into *specified* and *unspecified* forms.[1,2] The former correspond to a series of rare, but distinct clinico-pathologic entities more often recorded at extra-nodal sites, while the latter refer to an array of morphologically heterogeneous neoplasms irrespective of their presentation.[1,2]

Morphology

PTCL consist of more or less polymorphic elements of variable size, provided with irregularly shaped nuclei and a rather wide rim of cytoplasm, more frequently clear in Giemsa staining. Neoplastic cells can be intermixed with reactive elements, such as follicular dendritic cell, histiocytes, eosinophils, plasma cells and epithelioid elements.[1,2,56,111-113] The latter can at times obscure the neoplastic population (so-called Lennert's lymphoma).[1,2,56,111-113] High-endothelium venules are comprised within the tumor, being prominent in the angioimmunoblastic/AILD-type.[1,2,56,111-113] In the lymph node, the lymphomatous growth selectively involves the paracortex, at times sparing reactive follicles (so-called T-zone pattern).[1,2,56,111-113] Hemophagocytosis by histiocytes may accompany the lymphomatous growth.[115]

Phenotype

PTCL show phenotypic aberrations consisting in CD4/CD8 restriction, loss or co-expression and/or loss of one or more of the T-cell associated antigens (CD2, CD3, CD5, CD6, and CD7).[1,2,56,111-113] They can express CD30 irrespective of anaplastic morphology as well as CD15 and cytotoxic markers, including TIA-1, granzyme B, perforin, CD56 and CD57.[1,2,56,111-113] Interestingly, TIA-1, granzyme B and perforin are absent in most nodal PTCL, while they are usually detected in extra-nodal PTCL and ALCL.[1,2,56,111-113] Finally, aberrant expression of CD20 and CD79a has at times been reported.[112,116] In the following, attention will be focused on two *specified* forms usually presenting in the node.[1,2]

AILD

This is characterized by diffuse effacement of the lymph node structure, low cellular density, abundant arborizing epitheliod venules and possible burnt-out (i.e. sclero-hyalinotic) residual follicles.[1,2,56,111-113] Lymphomatous cells are variably sized and have irregularly shaped nuclei and a wide rim of clear cytoplasm. They are admixed with EBV-infected B-immunoblasts, eosinophils, plasma cells and histiocytes.[1,2,56,111-113] In immuno-histochemistry, neoplastic cells show usual CD4 restriction, frequent CD10 expression and moderate Ki-67 marking.[117] Within this context, there is an abundant follicular dendritic cell component (CD21+/CD23+/CD35+) that contributes to producing the low cellular density.[1,2,56,111-113] B-immuno-blasts may undergo neoplastic transformation and give rise to an unrelated DLBCL.[118]

ALCL

This is the most frequent type of *specified* PTCL. The present review will focus on systemic ALCL, omitting the primary cutaneous lesions that are now included among *CD30+ lymphoproliferative disorders of the skin* (see above).[1,2,119]

Morphology

Systemic ALCL is mostly composed of very large cells (so-called hallmark cells) with an eccentric kidney-shaped nucleus, a rod-shaped nucleolus and a wide rim of basophilic cytoplasm with a clear paranuclear area.[120-124] The tumor tends to grow cohesively and to spread through sinuses, a fact that in the past led to a misdiagnosis of metastatic undifferentiated carcinoma or malignant histiocytosis.[120-124] Morphologic variants of the process have been described: giant-cell rich, lympho-histiocytic, small cell, mixed, Hodgkin's-like and, more rarely, sarcomatoid, signet-ring cell-like, and neutrophil, eosinophil or epithelioid cell-rich.[120-127] In reality, ALCL is always characterized by a morphologic spectrum: from small cells to hallmark cells.[120-124] However, one cytotype tends to predominate over the others, thus producing different patterns.[120-124] Notably, divergent cytotypes may be observed in biopsies taken from the same patient at different anatomic sites, either simultaneously or sequentially (e.g. at presentation and relapse).[120-124]

Phenotype

The tumor shows regular CD30 expression, common epithelial membrane antigen (EMA) positivity, frequent presentation of cytotoxic markers (TIA-1, granzyme B, and perforin), possible lack of the leukocyte common

Foot note:

t(2;5)(p23;q35)=fusion gene and chimeric protein NPM/ALK (with nuclear and cytoplasmic location);
t(1;2)(q25;p23)=fusion gene and chimeric protein TMP3/ALK (with cytoplasmic location);
inv(2)=hybrid gene and chimeric protein ATIC/ALK (with cytoplasmic location);
t(2;3)(p23;q21)=fusion gene and chimeric protein TGF/ALK (with cytoplasmic location);
t(2;11;2)(p23;p15;q31)=hybrid gene and chimeric protein CARS/ALK (with cytoplasmic location);
t(2;17)(p23;q23)=fusion gene and chimeric protein CLTL/ALK (with cytoplasmic location);
t(2;17)(p23;q25)=hybrid gene and chimeric protein ALO17/ALK (with cytoplasmic location);
t(2;19)(p23;p13)=fusion gene and chimeric protein TPM4/ALK (with cytoplasmic location);
t(2;22)(p23;q11.2)=hybrid gene and chimeric protein MYH9/ALK (with cytoplasmic location);
t(2;X)(p23;q11-12)=fusion gene and chimeric protein MSN/ALK (with cytoplasmic location).

antigen/CD45, occasional CD15 staining, and T- or null-phenotype.[95,120-124,128] This profile might make the distinction between ALCL and classic Hodgkin's lymphoma (CHL) difficult. In this respect, the search for BSAP is of paramount importance: in fact, this molecule is regularly lacking in ALCL, while it is usually expressed in the Hodgkin and Reed-Sternberg cells of cHL.[94] Recently, survivin positivity has been reported in a proportion of cases: it seems to correlate with a more aggressive clinical behavior.[129] Sixty to ninety per cent of systemic ALCL express ALH.[58,121-124,130,131] This molecule – which is not detected in normal lymphocytes, cHL and DLBCL with anaplastic morphology – is thought to be involved in the pathogenesis of the process[132-135] and can be located in the nucleus and/or cytoplasm.[58,121-124,130,131] It corresponds to translocations involving the *ALK* gene and different partners, leading to the formation of hybrid genes that encode for the chimeric proteins summarized in the foot note.[58,121-124,130,131,136,137] Notably, the cases carrying these translocations show an excellent response to therapy[58,121-124,130] with the exception of the leukemic cases,[138] and preferentially occur in the first two decades of life. By contrast, the ALK- anaplastic tumors have a much worse prognosis (5-year overall survival 30% vs. 85%) and occur in the elderly.[58,121-124,130] This has led to question of whether or not the term ALCL should be applied to large cell tumors with anaplastic morphology and T/null phenotype, but lacking the ALK protein.[139] Besides its prognostic impact, ALK positivity contributes – along with BSAP negativity (see above) – to identifing the rare forms of ALCL with Hodgkin's-like features and to differentiate them from cytologically aggressive cHL.[58,94,124]

Cytogenetic and molecular diagnosis

DLBCL, a histologically well-defined subset of NHL, is genetically heterogeneous. By G-banding, most cases show a complex hyperdiploid karyotype and diverse cytogenetic abnormalities that include recurring and non-recurring translocations, deletions, duplications and marker chromosomes. Conventional cytogenetic analysis performed on tumor biopsies allows the detection of clonal chromosomal abnormalities in more than 85% of cases.[140] Breakpoints are clustered at several sites including 14q32, 18q21, 1q21, 3q27, 1p36, 8q24, 3p21, 6q21, 1p22, and 22q11. Molecular cytogenetic techniques such as multicolor fluorescence in situ hybridization (M-FISH), spectral karyotyping (SKY), and comparative genomic hybridization (CGH) are providing a more comprehensive view of the genetic alterations in DLBCL.[141]

CGH has recently allowed researchers to demonstrate that 18q gains or amplification and 17p losses are associated with a particularly aggressive clinical behavior.[142] In up to 30% of cases DLBCL arise from the transformation of a low grade follicular NHL. During the clonal evolution, the neoplastic cells acquire additional cytogenetic and molecular abnormalities, but retain the t(14;18) rearrangement which can be used as a molecular marker for the detection and follow-up of these patients. Excluding known transformed FL, the translocation has been demonstrated in 18-20% of patients with *de novo* DLBCL. The *BCL-6* proto-oncogene was first identified at breakpoints on 3q27 involved in t(3;14) (q27;q32) and t(3;22) (q27;q11) and t(3;2) (q27;2p11) and subsequently, other translocations have been reported. In some DLBCL patients *BCL-6* deregulation is largely independent of chromosome 3q27 rearrangement and is due to somatic point mutations at the 5'-untranslated regulatory region.[143] Although several studies have been performed to investigate the relationship between *BCL-6* gene rearrangement or mutations and clinical outcome, such analyses are no longer clinically attractive.

Gene expression profile studies have recently revealed the existence of at least two molecularly distinct types of DLBCL. As mentioned earlier, the first is recognized as GC B-cell-like (GCB), strongly resembles normal GC B-cells, and is associated with a relatively good prognosis. The second subtype is the ABC-like which expresses a subset of genes characteristic of mitogenically activated B cells, more mature steps of B-cell differentiation and has a poor clinical outcome.[38,44,144]

In BL, the translocation t(8;14)(q24.1;q32) is present in 75-80% of all cases. The t(2;8)(p12;q24.1) and t(8;22)(q24.1;q11) variants make up the remainder of cases. The juxtaposition of the *c-MYC* oncogene mapped to 8q24.1 with the immunoglobulin chain is thought to lead to inappropriate expression of the oncogene thus inducing molecular transformation. The molecular detection of *c-MYC* rearrangement is easy by Southern blotting but not by DNA polymerase chain reaction (PCR) since the distribution of breakpoints spans over a very large genomic region. Therefore, although long distance PCR methods for the detection and monitoring of BL have been reported,[145] PCR analysis and other molecular diagnostic procedures are not routinely performed.

In the case of ALCL, the t(2;5) (p23;q35) is detected in about 50% of cases.[146] This translocation fuses the *ALK* gene (2p23) and the *NPM* gene (5q35), so that the ALK kinase becomes constitutively activated and triggers malignant transformation. The *NPM-ALK* fusion gene is found more frequently in children and young adults, and its presence is associated with a relatively good prognosis.[35] In about 10-20% of ALK$^+$ NHL, variant ALK fusions have been detected, among which the

ATIC-ALK rearrangement resulting from the inv(2)(p23q35) is probably the most recurrent. Other variants are TFG-ALK, CLTC-ALK (previously designated *CLTCL-ALK*), *TMP3-ALK* and *MSN-ALK*.[36] In the majority of these cases a molecular demonstration of these rearrangements can be made by reverse transcriptase-PCR and more rarely by DNA PCR.[147] Nonetheless, the relatively low number of these cases accounts for the negligible application of a routine molecular diagnostic investigation which does not add anything relevant to the immunohistochemical evaluation of ALK overexpression. Gene expression profile analysis revealed that ALK+ NHL and Hodgkin's disease share the differential expression of several genes.[148] Further studies are needed to clarify the biological and clinical significance of these gene expression patterns.

Mantle cell lymphoma is characterized by the presence of t(11;14)(q13;q32). As a consequence of this translocation the *PRAD1/BCL1* gene is repositioned near an immunoglobulin enhancer leading to overexpression of cyclin D1, a crucial cell cycle regulator. Conventional cytogenetics and FISH approaches have been established for a more accurate detection of t(11;14) and together allow a cytogenetic diagnosis in more than 90% of MCL patients.[149] In addition, CGH studies recently revealed gain or loss of genes located on chromosomes 10p13, 11q13, 11q22-11q23 and 13q14 which could be important for understanding the heterogeneous clinical behavior of this disease.[150]

More than 80% of breakpoints are clustered in a region of 80-100 bp of the *BCL1* gene, termed the major translocation cluster (MTC), but many other breakpoints are scattered over a region of more than 120 kb so that the investigation of genomic DNA by molecular techniques such as DNA PCR is often limited. As a consequence, genomic PCR fails to detect those patients carrying breakpoints falling outside the MTC region and allows the detection of only 50% of positive cases. Southern blot analysis reveals a higher number of positive cases but due to its complexity and time consuming nature is not routinely employed. Despite the relatively limited number of patients for whom DNA PCR provides informative results, this approach has been widely used for diagnostic purposes and to evaluate minimal residual disease. In this latter application, mixed results have been reported. Indeed, the achievement of a molecular remission was not predictive of a better clinical outcome when obtained after chemo-immuno therapy.[151] In contrast, improvement of event-free survival and overall survival were recorded when PCR-negative results were obtained after high dose chemotherapy, rituximab and hematopoietic stem cell transplantation. The use of quantitative reverse transcriptase-PCR for cyclin D1 has also been proposed,[152] but does not seem to offer better information than that afforded by to immunohistochemical protein evaluation which remains the gold standard for the evaluation of MCL.[153] Differential gene expression analysis allowed the precise measurement of tumor cell proliferation and the identification of subsets of patients whose median survival differed by more than 5 years.[154]

Pre- and post-treatment evaluation

A diagnosis of aggressive NHL cannot be established without the examination of tissue obtained at biopsy. On the basis of the lymphoma presentation, the biopsy can be taken from enlarged supeficial lymph nodes (in the neck, axillary or inguinal regions), lymphoid tissue in Waldeyer's ring, mediastinal nodes (by core needle biopsy or mediastinoscopy or mediastinotomy)[155,156] or retroperitoneal lymph nodes (by ultrasound-guided core needle biopsy or laparoscopy or laparotomy).[157,158] Once the diagnosis has been established the first critical step is the pre-treatment evaluation and staging to identify prognostic factors.

History and physical examination

A careful history and physical examination are the most important factors in evaluating a patient. The physical examination includes evaluation of all lymph node enlargement, recording the site and size of all abnormal lymph nodes, inspection of Waldeyer's ring, evaluation of the presence or absence of hepatosplenomegaly, inspection of the skin and detection of palpable masses. The presence or absence of constitutional symptoms should be noted as they are associated with an unfavorable outcome: fever >38°C, chills, night sweats, and/or unintentional weight loss of greater than 10% of body weight during the 6 months prior to diagnosis. Other symptoms may signal specific sites of involvement. An assessment of Karnovsky performance status is important in all patients, and especially for those entering clinical research trials.

Lymph node evaluation

Precise measurement and recording of the two-dimensional size and location of enlarged lymph nodes minimizes the likelihood of inter- and intra-observer variability in physical examination. At the time of diagnosis, a lymph node that is larger than 1 cm in its short transverse diameter should be considered compatible with involvement by NHL.

Liver and spleen assessment

Detection of an enlarged spleen or liver upon physical examination should be considered suspicious for involvement by lymphoma. Abdomen ultrasound and computed tomography scans are useful for measuring organ size and identifying the presence of tumor masses.

Laboratory studies

Blood counts

Laboratory studies that should be routinely performed in patients with NHL include a complete blood count to assess bone marrow reserves, and a white blood cell differential with careful examination of the peripheral blood to look for the presence of circulating lymphoma cells.

Serum chemistry and serology

Serum chemistry should include a mineral panel and an assessment of hepatic function and liver enzymes. Lactic dehydrogenase (LDH) is a strong indicator of tumor activity and is included in the International Prognostic Index.[159] The uric acid level may predict patients at increased risk of urate nephropathy. For patients with renal dysfunction, urine cytology has been recommended as a useful means of assessing involvement by lymphoma.[160] HIV, HBV, and HCV status should be determined in all patients.

Bone marrow assessment

A bone marrow aspirate and biopsy should be performed in all patients. Bilateral bone marrow biopsies have been recommended because they increase the sensitivity of detection of NHL involvement by 10-20%. However, an adequate (>2 cm) unilateral bone marrow specimen is generally sufficient.

Lumbar puncture

A lumbar puncture with examination of cerebrospinal fluid is recommended only in patients with signs or symptoms suggestive of central nervous system disease, or for those at high risk for involvement, for example, with massive head and neck disease, nasal and paranasal sinus involvement, spinal compression (with/without epidural space involvement), lymphoblastic or Burkitt's/Burkitt's-like lymphoma or mantle-cell lymphoma, disseminated disease with testicular involvement and possibly bone marrow involvement.

Endoscopy

This is recommended for certain histologic types (T-cell or Burkitt's lymphoma). In mantle-cell NHL, the bowel is often involved, characteristically as polyposis.

Imaging studies

Standard radiography assessment includes a chest X-ray and CT scans of the chest, abdomen and pelvis, as well as other apparently involved sites (e.g. neck, orbit, central nervous system). Magnetic resonance imaging (MRI) may assist in the assessment of bone disease that is equivocal on plain radiographs.[161]

Gallium scan

Single photon emission computed tomography (SPECT) with gallium scanning should be included as part of response assessment at centers with expertise in performing the study in clinically relevant situations (e.g. to distinguish masses with viable tumor from fibrosis). Evaluation of supradiaphragmatic disease is more accurate than that of subdiaphragmatic involvement.

Position emission tomography (PET)

PET scanning is a non-invasive metabolic imaging technique. It detects fluoro-2-deoxy-D-glucose (FDG) labeled with fluorine 18 taken up by tumor cells, as well as inflammatory tissue. PET scanning has a better resolution than gallium scanning, as well as a greater sensitivity. It also takes less time to perform. Because of its lack of specificity, PET scanning is not useful in the diagnosis of NHL. On the other hand, several recent studies have suggested a potential role for PET scanning in monitoring response to therapy by distinguishing active tumor from fibrotic tissue.[162-165]

Special lymphoma sites

Nodal lymphoma that also occurs in extranodal sites requires further staging studies that vary somewhat by site.

Central nervous system lymphoma

An MRI scan of the CNS and lumbar puncture should be performed. Assessment should also include an ocular slit lamp examination.

Testicular lymphoma

Involvement tends to be bilateral both at presentation and at the time of recurrence, so the controlateral testis should be carefully evaluated to plan optimal treatment. Patients with disseminated disease also involving the testicle have an increased risk of CNS involvement, about 20% in some series, and therefore a lumbar puncture and CT or MRI of the head are indicated.[166]

Gastric lymphoma

Although most of these tumors are confined to the stomach, extragastric involvement may occur either at diagnosis or as a manifestation of progression of disease. An endoscopic ultrasound may be helpful in assessing the degree of invasion of the gastric wall, establishing whether lymph nodes adjacent to the stomach are involved and identifying patients at high risk of bleeding or perforation without performing laparotomy.[167]

Breast lymphoma

Primary lymphoma of the breast accounts for fewer than 1% of cases of NHL. These tumors are often detected on routine mammography and mistakenly diagnosed as carcinoma of the breast. Once an ultrasound excludes the presence of a cystic lesion, a core needle biopsy or excisional biopsy is needed to make the diagnosis. There is also an increased risk of controlateral involvement.

Bone lymphoma

A patient with bone pain and swelling should undergo a bone scan. A bone scan should also be considered in patients with elevated levels of alkaline phosphatase. Radionuclide bone scans are highly sensitive - more sensitive than conventional radiographs - as an indicator of bone involvement.[168] However, bone scans are not as specific as conventional radiographs, and areas positive on the bone scan should be confirmed by plain radiographs or, if more complicated bone structures such as the facial bones are shown to be positive, by CT scans (and biopsied if need be). Bone involvement is found in less than 10% of patients without specific symptoms and a bone scan is not recommended as a routine staging procedure.

Staging and prognostic factors

Ann Arbor staging system

Once the evaluation procedures have been completed, patients are assigned an Ann Arbor stage for prognosis and treatment planning purposes.[169] This staging system reflects the number of sites involved and their relation to the diaphragm, the existence of B symptoms and the presence of extralymphatic involvement. Lymphatic structures are lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches. Involvevment of other structures is regarded as extralymphatic disease. Extralymphatic disease may be either localized or diffuse. Localized involvement of an extra-lymphatic site, a so-called E-lesion, is usually interpreted as a lesion which, although extralymphatic, can be sensibly contained in a curative radiation field, as initially described by Musshoff.[170]

The International Prognostic Index

In 1990, there was a consensus that an international classification system based on clinically relevant prognostic factors in large-cell lymphoma should be developed and utilized in this disease.[171] For this reason, 16 single institutions and cooperative groups in the United States, Europe and Canada participated in the The International Prognostic Index (IPI) project.[159] In 2031 patients of all ages, this model, based on age (<60 years vs. >60 years), tumor stage (I-II vs. III-IV), serum LDH concentration (normal vs. elevated), performance status (0-1 vs. ≥2) and number of extranodal disease sites (0-1 vs. ≥2), led to the identification of four risk groups with different predicted 5-year survival rates. (Table 1). In 1274 patients aged 60 or younger, an age-adjusted model based on tumor stage, serum LDH level and performance status identified four risk groups. These two indexes, the IPI and the age-adjusted international index, have been shown to be significantly more accurate than the Ann Arbor classification in predicting long-term survival.

Other prognostic factors

Most of the other prognostic factors are provided by further analysis of the lymphoma specimen. However, large studies in which the predictive value of these new parameters is analyzed should be performed; such studies could, for example, provide new insights into the influence of biological parameters on clinical outcome. The potential new biological prognostic indicators include parameters related to the proliferation rate of lymphoma cells, parameters related to lymphoma cells and their environment, cytokine production, the drug resistance of tumor cells, and, more recently, genetic profiling with specific prognostic evidence.[38,172]

Therapy of aggressive non-Hodgkin's lymphoma

Introduction

Aggressive lymphomas, once considered uniformly and rapidly fatal cancers, are today among the most successfully treated malignant diseases. In fact, following administration of doxorubicin-containing regimens, the five-year survival rate for the most common histotype (i.e. DLBCL) ranges between 26 and 75 percent, according to the prognostic variables[159] The treatment mainstay is aggressive, dose-intensive combination-chemotherapy. The negative impact of dose reductions has been well documented. In a study[173] a relative dose intensity for doxorubicin of over 75 percent was the single most important predictor of survival.

A second important general principle that applies to aggressive lymphoma management is their response to second-line chemotherapy. A sizable proportion of patients with good performance status who fail to respond to conventional regimens do achieve durable second remissions and possibly cures with salvage programs. Salvage options include newer non-cross resistant drugs, high-dose chemotherapy programs with autologous hematopoietic stem cell support, as well as hematopoietic stem cell allografting following either standard or reduced-intensity pre-transplant conditioning.

Table 1. Outcome according to risk group defined by the International Prognostic Index (IPI) (Shipp et al 1993).

International index all patients	*No. of risk factors*	*Complete remission rate (%)*	*5-yrs relapse-free survival (%)*	*5-yrs overall survival (%)*
Low	0 or 1	87	70	73
Low intermediate	2	67	50	51
High intermediate	3	55	49	43
High	4 or 5	44	40	26

Over the years, a variety of different chemotherapy regimens have been developed and tested. This multiplicity of choices applies mainly to advanced-stage disease. In fact, for the therapy of localized lymphomas there is a nearly complete consensus in favor of a combined modality approach, consisting of a limited number of cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy followed by localized irradiation.[174,175] Conversely, for advanced-stage aggressive lymphomas, CHOP or equivalent chemotherapy is a reasonably effective and appropriate treatment only for good prognosis patients. For patients in the worst prognostic subgroups, both *second generation* (adding non-cross resistant agents) and *third generation* regimens (adding more active agents in a shorter period of time) failed to show any significant improvement in remission rate, disease-free survival and overall survival over standard *first generation* CHOP.[176] For these latter patients there is a clear need for novel treatment approaches, including high dose chemotherapy and various forms of immunotherapy. Autografting of hematopoietic stem cells permits the use of drugs with predominant bone marrow toxicity at several-fold larger dosages and represents an effective means to overcome drug resistance. More recently, the addition of rituximab to CHOP was able to improve the results over standard CHOP with no increase in toxicity in at least two independent studies,[177,178] while radio-immunotherapy has shown remarkable activity in relapsed/refractory aggressive lymphomas.[179] Finally, several studies are underway to assess the role and the applicability of allogeneic stem cell transplantation as a means to exploit its associated graft-versus-lymphoma reaction.[180-182] The treatment of peripheral T-cell lymphoma, Burkitt's and Burkitt-like lymphoma, lymphoblastic lymphoma, mantlecell lymphoma and post-transplant lymphomas will be considered separately. All are uncommon but aggressive disorders that respond to specialized, usually complex regimens.

In conclusion, the appropriate treatment of aggressive lymphomas is far from being a settled issue. However, by taking into account the patient's age and clinical fitness, the histological classification, a definition of early versus advanced stage, and by paying attention to prognostic variables such as the IPI score and disease status (onset versus relapse/refractoriness), it is possible to individuate the most appropriate treatment among the many now available.

Diffuse large B cell lymphoma and follicular lymphoma grade III B

First line therapy of advanced stage

Since the introduction of anthracycline-containing combination chemotherapy regimens in the 1970s, aggressive NHL has been considered a curable disease.[183] CHOP chemotherapy was considered the gold standard treatment for aggressive NHL on the basis of a randomized trial showing no benefit on time to treatment failure and overall survival compared to those achieved with more intensified regimens.[176] However CHOP is curative in only approximately 40% of patients and numerous clinical studies have been carried out to find new treatment strategies that can increase the cure rate. Three main strategies have been evaluated: intensification of chemotherapy through addition of higher doses of chemotherapy or more frequent doses of existing agents; early high dose therapy (HDT) and autologous stem cell transplantation (ASCT) during first line therapy; combination of monoclonal antibodies with chemotherapy.

Intensified chemotherapy. Recent studies suggest the possible benefit of dose intensification strategies. The SWOG conducted a pilot study evaluating dose-intensified CHOP (CHOP-DI) with filgastrim support every 14 days for six planned courses. Treatment with CHOP-DI was safely administered and resulted in a 14% better survival than that of historical controls.[184] Moreover, two prospective randomized trials of a German cooperative group compared six cycles of CHOP-21, CHOP-14 (bi-weekly), CHOEP-21 (CHOP plus etoposide100 mg/m^2 days 1-3) and CHOEP-14 (bi-weekly) in a 2x2 factorial study design in patients older than 60 years (NHL-B2 protocol) and in patients younger than 60 years (NHL B1 protocol).[185,186] All patients also received radiotherapy (36 Gy) to sites of bulky or extranodal disease. In patients aged less than 60 years (all with low risk aggressive NHL), complete response time-to-treatment failure (TTF) were significantly improved

Table 2. Results of prospective and comparative trials of CHOP Rituximab in DLBCL.

Study	*Therapy*	*Complete remission (%)*	*2-year time-to-treatment failure (%)*	*2-year overall survival (%)*
Vose *et al.*,[196]	CHOP + R	61	80**	87**
Coiffier *et al.*,[177]	CHOP	63	38	57
	R-CHOP	76 $p<0.005$	57 $p<0.001$	70 $p=0.007$
Sehn et *al.*,[199]	CHOP	nr*	52	53
	R-CHOP	nr	71 $p=0.0009$	77 $p=0.0001$
Pfreundschuh *et al.*,[178]	chemo	68	61	86
	R-chemo	86 $p<0.0001$	80 $p<0.001$	95 $p<0.001$

**nr= not reported; **5-year time-to-treatment failure, 5-year overall survival.*

with CHOEP-14 and CHOEP-21, but not with CHOP-14. In contrast, in patients aged over 60 years of age (76% with low or low intermediate risk) CHOP-14 significantly improved time-to-treatment failure and overall survival. Recently the Groupe d' Etude des Lymphomes de l'Adulte (GELA) conducted a multicenter randomized trial of ACVBP (consisting of four cycles of an intensified CHOP-like regimen followed by sequential methotrexate, etoposide and cytarabine consolidation) demonstrating that this provided a survival advantage over eight cycles of standard CHOP.[187] Therefore it has become clear in recent years that, it is possible for some patients with aggressive NHL, to improve survival by intensification of chemotherapy. However this approach is still not recommended outside of the setting of clinical trials.

High dose therapy and autologous SCT during first line therapy. The use of HDT and autologousSCT in previously untreated patients is still controversial. A possible benefit for patients in partial response at the end of their first induction therapy has been postulated in some phase II studies.[188,189]The use of HDT and SCT was expected to ameliorate chemotherapy outcomes in high-risk DLBCL patients. Indeed, in some clinical trials the survival curve after early HDT/SCT (in first CR) or after employing a high dose sequential (HDS) therapy upfront proved superior to conventional chemotherapy, indicating the potential of this treatment to eradicate the disease.[190,191] These observations are in contrast with two meta-analyses[192,193] of up to 11 randomized trials, which showed a similar overall survivall in patients receiving first-line HDT/SCT or standard chemotherapy.[194] However in some studies HDT/SCT, when employed as a complete standard course of induction (rather than an abbreviated course) or where the HDT/SCT arm achieved less than 25% drop-outs, provided a significant increase of survival.[195] Furthermore, in all trials, no real benefit of HDT and ASCT was described for low risk IPI patients. At the present time the results of these comparative studies are conflicting, and thus the routine use of HDT and ASCT as consolidative therapy for newly diagnosed large cell lymphoma is not recommended outside of clinical trial. Recently chemoimmunotherapy has been shown to greatly improve the long-term outcomes of DLBCL and ongoing randomized studies should compare chemoimmunotherapy to HDT/SCT in first-line therapy for DLBCL.

Combination of chemotherapy and monoclonal antibodies. The most consistent improvement over CHOP chemotherapy in the treatment of aggressive NHL has come with the addition of the chimeric anti CD20 monoclonal antibody rituximab. A phase II study of CHOP plus rituximab as first line therapy has yielded an high response rate, 5 year-PFS and overall survivall both in high and low risk patients.[196] Subsequently a phase III study of GELA compared 8 cycles Rituximab plus CHOP (R-CHOP) with 8 cycles of CHOP alone in the treatment of 399 elderly previously untreated patients with DLCBL. Complete response rates, 2-year overall survivall and 2-year EFS were significantly better in the R-CHOP arm without increase of adverse events. The survival advantage obtained with R-CHOP suggests that this regimen should replace CHOP alone as the gold standard treatment.[177] Subsequent 5-year overall survivall and EFS follow up confirmed that superiority of R-CHOP was maintained over time and the benefit was not restricted to a subgroup of patients.[197] In a retrospective analysis of the same group of patients R-CHOP appeared significantly more effective in Bcl-2 positive than CHOP, suggesting that the benefit of rituximab might overcome the Bcl-2 associated chemo-resistance.[198] Also, a large retrospective study at British Columbia University confirmed a significant improvement of overall survivall and EFS in patients of age <60 and age >60 years when rituximab was combined with CHOP compared to an historical CHOP chemotherapy.[199] Moreoever an intergroup US study randomized a population of elderly patients to receive CHOP or CHOP plus rituximab with a different schedule to the GELA trial, and all responding patients were then randomized to receive either rituximab maintenance therapy or not. The study is ongoing and definitive results are not yet available.[200] Recently a phase III International study denominated MInT, was undertaken to address the val-

Table 3. Clinical stage, IPI risk factors and outcome for patients with limited disease.

Clinical stage	*IPI modified risk*	*Treatment*	*5-year median overall survival*	*Description*
I, IE	0	CHOP x 3+IFRT	>90%	Very limited
I-IE,II IIE (no bulky)	=1	CHOP x 3+IFRT	70%	Limited
II-IIE bulky	>1	CHOP x 8	50%	Advanced

Reprinted by permission of Miller. Hematology 2004.CHOPX3: three cycles of CHOP; CHOPx8: eight cycles of CHOP; IFRT: involved field radiotherapy.

ue of rituximab in 758 patients younger than 60 years with low or intermediate-low risk DLBCL. Rituximab was combined with CHOP or a CHOP-like regimen in the same schedule as that used in the GELA trial. Patients receiving rituximab with chemotherapy had significantly better complete remission rate, 2-year time-to-tratment failure and overall survival.[178] This is the first randomized trial supporting the use of rituximab in younger patients with low risk IPI, albeit in a selected subset of patients most of whom had with limited stage disease (Table 2).

First line therapy of limited stage lymphoma

Limited stage, also referred to as *early or localized stage* disease, accounts for approximately 15-20% of DLBCL. There is extreme heterogeneity of patients within the group described as having limited-stage lymphoma, making comparison of outcomes across this population difficult. Modern therapy for limited-stage NHL was developed when some studies focused on the concept of a brief course of chemotherapy (three cycles of CHOP) followed by involved field radiation therapy (IFRT) for patients in stage I-II.[174] Subsequently the SWOG compared, in 401 patients with localized disease, three cycles of CHOP followed by IFRT to eigth cycles of CHOP and found that the brief chemotherapy plus IFRT was superior to the eight cycles of CHOP.[201] In this study, bulky stage II disease was excluded because it is known to have a prognosis similar to that of advanced stage disease. The GELA group has recently reported the results of a randomized trial, in localized stage I-II including bulky disease, comparing three cycles of CHOP IFRT (329 patients) to ACVBP[319] an aggressive combination therapy used for advanced disease. With a median follow-up of 7.7 years, EFS and overall survivall rates were significantly higher in the group given ACVBP chemotherapy than in the group given CHOP plus radiotherapy (p<0.001 and p=0.001, respectively). This difference remains significant also in patients without bulky disease.[202]

A score incorporating four risk factors (stage II vs I, age >60 vs <60, increased vs normal serum LDH and PS>1 vs<1) defined as the *modified IPI score* for limited disease, was tested in two different series of patients with limited- stage disease. This four risk score can be assessed for each patient, and the prognosis determined based on the number of adverse risk factors. Patients without any risk factors (IPI score=0) defined *very limited disease* have an outstanding prognosis with 5 and 10-year overall survival exceeding 90%. Patients with stage I or II without bulky and at least one adverse risk factor (IPI score=1) should be placed in a group defined *limited disease* with a 5-10 years overall survivall of 70%. For these patients a brief chemotherapy plus IFRT should be considered the standard therapy. Although dose-dense chemotherapy in the GELA trial showed to be effective in this group of patients, the risk of toxicity due to dose-dense chemotherapy should be accurately balanced against the potential benefits. Patients with stage II with more than one risk factor (IPI score >1) or stage II bulky disease were defined as *advanced disease,* with a 5-10 years overall survivall approximately of 50% for whom standard chemotherapy or dose dense regimens should be considered[201,203] (Table 3).

Therapy of recurrent and refractory disease

Conventional treatment. At least 40% to 50% of patients with advanced-stage DLBCL do not attain a remission with initial therapy or relapse after achieving a remission. Selected patients may occasionally experience prolonged remissions with IFRT. A variety of drugs are active as single agents in patients with relapsed/refractory DLBCL. The most commonly used agents include etoposide,[204] cytarabine,[205] cisplatin,[206] mitoxantrone,[207] and ifosfamide.[208] Single-agent activity rates as high as 20% to 30% have been reported, although response durations are brief, and most patients are treated with combination chemotherapy regimens. Results of several commonly used salvage-chemotherapy regimens are presented in Table 4. Prognostic factors for patients treated with these salvage regimens are similar to the factors that are important for upfront treatment of newly diagnosed patients. These regimens are commonly used as short-duration treatments to reduce tumor burden before treatment with high-dose therapy and autologous hematopoietic SCT.[209-217] Although response rates exceeding 50% are commonly observed with these regimens, prior treatment frequently makes it difficult to administer repeat-

ed cycles of therapy, and few patients experience long-term disease-free survival with these regimens alone.

Approximately one third of patients with relapsed/refractory DLBCL respond to rituximab,[218] and rituximab is commonly added to the standard regimens. There is relatively little experience with the use of radiolabeled antibodies for DLBCL, although results appear to be poorer than those seen for indolent lymphomas.[219,220]

High-dose therapy. The poor results of treatment with conventional-dose salvage-chemotherapy regimens have led to the increasing use of high-dose therapy followed by autologous SCT for patients with relapsed or refractory lymphoma. A large number of phase II trials of autologous SCT for patients with relapsed/refractory DLBCL have been published[188,221-229] with a median 3-yr disease-free survival rate of 35% (range, 11%-71%), and virtually all demonstrate the prognostic importance of chemotherapy sensitivity before transplantation. These trials demonstrate that substantial numbers of patients with relapsed/refractory disease can experience long-term disease-free survival after autologous SCT. Other prognostic factors usually associated with favourable outcomes after transplantation include good performance status, younger age, absence of tumor bulk, and absence of extensive prior therapy. Despite the widespread use of autologous SCT for DLBCL, the value of this approach was not validated until the results of the International PARMA trial were published.[230,231] Consensus panel recommendations indicate that high-dose therapy followed by autologous SCT is now considered standard therapy for patients with chemotherapy-sensitive relapsed DLBCL.[232,233] There is less agreement on the use of autologous SCT for patients with resistant relapsed or refractory disease. There is a quite limited experience with the use of allogeneic transplantation as salvage treatment for relapsed or refractory disease.

Transformed lymphomas

Histopathological transformation of follicular lymphoma to large-cell aggressive NHL is an event occurring in 15-32% of patients.[234,235] The incidence appears to reach a plateau by 6 years after diagnosis and the median time to transformation is 66 months.[235,236] High β2-microglobulin serum levels at diagnosis and failure to achieve complete remission after first-line therapy predict a higher risk of transformation for follicular lymphoma.[234,235] The prognosis for transformed lymphoma is generally poor, the median survival from transformation being about 10 months. This accounts for a large part of mortality in patients with follicular lymphoma. Young patients with limited disease that is chemosensitive may experience prolonged survival and durable disease-free survival in transformed lymphoma can be obtained with standard chemotherapy as it can for *de novo* diffuse large-cell lymphoma. Therefore, data do not show a relevantly different behavior than that of *de novo* B-DLCL.[235-237] Age, response to salvage therapy, B symptoms, LDH values, bone marrow involvement, stage, no prior chemotherapy and early transformation are all factors predictive of poor survival after transformation[235-238] while response to CHOP-like regimens is a positive predictor of survival. [235,236] No evidence supports a net benefit from delaying autologous SCT at the moment of lymphoma transformation. A median overall survival of 40-60% at 4-5 years after autologous SCT has been reported, climbing to 69% in chemosensitive patients while the 5-year disease-free survival is about 30% in the over 200 patients included in published series. Survival after autologous SCT was not dissimilar to that reported for patients with non-transformed indolent NHL and primarily aggressive NHL undergoing autologous SCT.[103,237-239]

Recently high response rates, ranging from 50% to 80%, with an acceptable safety, were reported in transformed patients with less than 25% bone marrow involvement treated with ibritumomab and tositumomab and also with rituximab therapy.[240-243]

Mantle cell lymphoma

From a clinical viewpoint, MCL brings together the worst characteristics of indolent and aggressive lym-

Table 4. Chemotherapy salvage regimens for DLBCL.

Regimen	*Drugs*	*CR (%)*	*PR (%)*	*CR + PR (%)*
IMVP-16[208,209]	Ifosfamide, methotrexate, etoposide	37	25	62
DHAP[210]	Dexamethasone, cytarabine, cisplatin	28	26	54
ESHAP[211]	Etoposide, methylprednisolone, cytarabine, cisplatin	26	22	48
DICEP[212]	Cyclophosphamide, etoposide, cisplatin	52	26	78
DICE[213]	Dexametasone, ifosfamide, cisplatin, etoposide	23	44	67
ICE[214]	Ifosfamide, carboplatin, etoposide	28	44	72
IEV[215]	Ifosfamide, epirubicin, etoposide	32	45	77
I-CHOPE[216]	Doxorubicin,vincristine, etoposide, cyclophosphamide, prednisone	17	31	48
EPOCH[217]	Etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone	36	34	70

CR: complete remission; PR: partial remission.

phomas. Like indolent lymphomas, it is rarely if ever curable with standard chemotherapy, but unlike the former the median survival is approximately 3 to 4 years only.[244-247]

Given the common involvement of extranodal sites, including the gastrointestinal tract, Waldeyer's ring and CNS, staging should always include upper and lower gastrointestinal tract endoscopy and lumbar puncture.

Various adverse prognostic factors have been identified for MCL, including a high International Prognostic Index score,[248] an increased mitotic index, p53 gene mutations, and a blastic morphology. However, their practical use in stratifying patients for different therapies is of little value in a disease in which even the favorable risk patients have a median overall survival of only 5 years,[248] and no evidence of plateau in the survival curve. Only occasional patients present with isolated peripheral blood and marrow lymphocytosis, and may have an indolent course, similar to that of patients with chronic lymphocytic leukemia. These rare forms cannot be easily distinguished from atypical chronic lymphocytic leukemia carrying the bcl1 translocation.[249]

Twenty to 60 percent of CHOP-treated patients achieve a complete response[151,250,251] with a median duration of remission of only one to three years.[151,252-256] The addition of newer agents, such as fludarabine, taxanes, flavopirifol or bortezomib, used alone or in combination, either failed to show a substantial benefit, or the reports are too preliminary, as for the promising agent bortezomib,[257,258] to allow firm conclusions. The only possible exception is rituximab, in particular when used in combination with chemotherapy. In a phase II study, approximately 30 percent of 25 informative chemo-therapy-naïve patients treated with rituximab and CHOP, achieved molecular remission in peripheral blood or bone marrow. However, the molecular complete responses were not predictive of improved progression-free survival.[151] More R-CHOP was compared with CHOP in a randomized trial as first-line therapy for MCL.[259]

A significantly higher rate of complete responses and longer of time-to-treatment-failure was observed, while the time-to-progression was not improved. An adequate follow-up is clearly needed for a final assessment of the long-term results with this approach. Rituximab has also been used in association with thalidomide with interesting results.[260]

In contrast to the limited success with conventional-dose chemotherapy, very encouraging results were recently reported by two groups using more aggressive induction treatments as first-line therapy.[261,262] Both studies made use of rituximab, in combination with either sequential administration of multiple high-dose chemotherapy cycles and stem cell autografting,[261] or with an aggressive multiagent acute lymphoblastic leukemia-like induction therapy (Hyper-CVAD/M-A) without stem cell transplant.[262] Of note, in the former study the use of rituximab had a critical role as an *in vivo* purging agent, and allowed reinfusion of tumor - free stem cells in the vast majority of treated patients.[261] Both regimens achieved complete and durable responses in a very high proportion of patients, with a 54-month event-free-survival rate of 87 percent following rituximab, high-dose sequential therapy and autografting and a 24-month freedom-free-survival rate of 80 percent, respectively. Toxicities were comparable and manageable, suggesting that high-dose or dose-intense chemo-immunotherapy has a role in the initial management of MCL, at least in clinically fit patients less than 65 years of age. A similarly promising approach is high-dose chemo-immunotherapy with 131I-tositumomab and autologous stem cell support.[263] For patients in chemosensitive relapse, allogeneic transplantation with reduced-intensity conditioning appears to be a potentially effective strategy, safer than full-dose allografting.[263]

In summary, elderly patients with a MCL should be treated with a regimen containing rituximab, such as R-CHOP or equivalent. In treating young, otherwise healthy patients, it is important to consider that long-term remissions, and possibly cures, could be obtained with aggressive or high-dose rituximab-supplemented regimens. For relapsed chemosensitive patients, reduced-intensity allogeneic bone marrow transplantation should always be considered. In general, given the invariably dismal outlook for conventionally-treated patients with MCL, it is recommended to refer these patients to a center offering a clinical trial, or fully capable of safely delivering high-dose therapy with or without autologous or allogeneic transplantation in first remission.

Lymphoblastic lymphoma

Lymphoblastic lymphoma is a rare disease (2% of NHL) arising from immature T cells in 85-90% of cases and more rarely from immature B cells. It is more common in children and adolescents. Mediastinal involvement is present in 80% of patients while the bone marrow and CNS are infiltrated in about 20% of cases. With chemotherapeutic regimens designed for lymphoma patients, such as CHOP the clinical outcome is poor while the application of ALL-type protocols produces excellent responses. In children with lymphoblastic lymphoma, regimens similar to treatments for ALL produced 5-year disease-free survival rates ranging from 70-90%. In adults, leukemia-type regimens produce response rates usually higher than 70% but the 5-year disease-free survival rate in adults remains about 50%. In a recent paper summarizing the outcome of adult patients with T-lymphoblastic lym-

Table 5. Main regimens for Burkitt'lymphoma.

Regimen	*Complete remission*	*Disease-free/event-free survival*	*Overall survival*
LMB 81-84-86-89[271]	83-89%	61-71% at 2-3 years	66-74% at 2-3 years
B-NHL 83-86272	63-74%	50-71% at 4-8 years	49-51% at 4-8 years
CODOX-M/IVAC[274-276]	75-92%	65-85% at 21 months-2 years	73% at 3 years
Hyper-CVAD[278]	81%	61% at 3 years	49% at 3 years
CALGB[279,280]	80%	50% at 4 years	45-52% at 3-4 years
INT-MILAN[281]	77%	68% median follow-up 28.7 months	78% median follow-up 28.7 months

phoma treated according to ALL protocols of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) Holtzer and co-workers reported that 93% of patients achieved a complete remission. In this study, 36% of patients relapsed within 12 months. The majority of relapses (47%) occurred in the mediastinum despite irradiation. The estimates for overall survival, continuous complete remission, and disease-free survival at 7 years were 51%, 65%, and 62%, respectively.[264] More recently, Thomas *et al.* reported the results obtained at the MD Anderson Cancer Center in 33 patients treated with the hyper–CVAD regimens (fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone) followed by radiotherapy to the mediastinal disease. Using this approach, a high proportion of patients (91%) achieved complete remission, and 9% achieved partial response. Within a median of 13 months, 30% of patients had relapsed or progressed. Estimates for 3-year progression-free and overall survival for the 33 patients were 66% and 70%, respectively. No parameters (eg, age, stage, LDH, β2 microglobulin) appeared to influence outcome except for CNS disease at presentation.[265]

Both autologous and allogeneic hematopoietic SCT have been used in an attempt to improve survival. Prolonged remissions and long-term survival of patients with lymphoblastic lymphoma have been obtained using either autologous or allogeneic transplantation for recurrent or refractory disease.[266]

Local radiation therapy can significantly decreases the risk of mediastinal recurrence in adult patients with mediastinal T-cell lymphoblastic lymphoma and the benefit of adjuvant radiation therapy (26-39 Gy) seems particularly evident in patients treated with more intensive chemotherapy regimens.[267]

Burkitt's lymphoma

Adult sporadic, non-immundeficiency associated Burkitt's lymphoma (BL) and its variant, Burkitt's-like lymphoma (BLL), represent aggressive forms of B-NHL clinically characterized by rapid growth and frequent extra-nodal involvement.[268-271] Despite their intrinsic aggressiveness, however, it is now well known that adult BL/BLL may have a favorable outcome if adequately treated with specific treatments. Indeed, during the last ten years, different generations of intensive chemotheraputic regimens, generally derived from pediatric protocols initially found to be highly effective in the treatment of children with BL, and subsequently tailored to older patients, have been developed for adult BL (Table 5).[272-281] These regimens differs from other *conventional* approaches to NHL as they are mainly based on the principles that: i) BL cells, due to their high proliferative activity, are very sensitive to S-phase specific drugs administered at high doses and at short intervals; ii) CNS prophylaxis is of paramount importance for successful treatment. Thus, current strategies for the treatment of BL generally represent a sort of *dose-dense*, multi-agent intensified approach, with tendentially shortened duration of therapy and minimal treatment delays. Such regimens usually include fractionated (or hyper-fractionated) cyclophosphamide or analogs (postulating that a fractionated schedule would ensure exposure of dividing tumor cells to the alkylating activity of these drugs) and high dose ara-C and methotrexate (to cross the blood-brain barrier), alternated with additional non-cross-resistant cytostatics. Adjunctive aggressive CNS prophylaxis with intrathecal triple administrations of cytostatics also represents an essential part of these regimens. The further administration of cranial irradiation is not recommended in patients without marrow involvement for CNS prophylaxis, in order to avoid severe neurological sequelae.[280] Some of these regimens also include a cytoreductive phase to minimize the risk of tumor lysis syndrome.[272,273,279,280] Some are based on a sequence of multiple induction, consolidation and maintenance cycles,[272,281] while others have introduced the concept of alternated *blocks* of combined chemotherapy.[273,280]

Overall, using these approaches, it has been estimated that 63-92% of patients achieve complete remission and 50-85% of them maintain these remissions for at least two years following therapy (Table 4). More than half of these patients may be considered cured. Older patients, however, show a worse outcome, due to lower percentages of subjects completing the treatment,

higher mortality and toxicity, and higher disease progression and relapse rates, which are probably not simply related to treatment toxicity. Advanced stage, bulky-disease, poor performance status, and high LDH levels are also usually considered poor prognostic factors for this disease, whereas leukemic phase and CNS involvement do not seem to have additional prognostic relevance if patients are treated with modern schemes. Of interest, early stage BL (Ann Arbor I-III or St. Jude I-II) may be successfully treated with the same regimens applied to advanced stages, with shorter duration of the therapy and a reduced total number of cycles.

Up-front autologous SCT for BL has rarely been incorporated into clinical trials.[277] In a retrospective study, the 3-year actuarial overall survival rate was 72% for patients transplanted in first co,plete remission.[282] For these patients, disease bulk at the time of autologousSCT was the only factor predictive of progression-free survival and overall survival. However, since long-term overall survival following autologous SCT appears to be quite similar to that achieved by brief duration, intensive chemotherapy alone and transplant-related mortality may exceed that of chemotherapy alone, autologous SCT is not currently recommended as consolidation after first line CT in patients in complete remission.[282,283]

Complete remission is usually achieved after 4-6 weeks of treatment. An early and careful assessement of response (after 6-8 weeks of therapy), including, if necessary, repeated biopsies or PET-imaging in doubtful cases, is mandatory, since failure to achieve complete remission is a very poor prognostic factor. In adults with BL who relapse, this usually occurs within the first year, although late relapses (up to 5 years after the completation of chemotherapy) have been described. These patients, as well as those who do not achieve complete remission, have a very poor prognosis even when treated with combined chemotherapy, including non-cross-reactive agents not employed in front-line therapy, such as ifosfamide and cisplatin. High-dose therapy followed by autologous SCT for patients with relapsed disease is superior to conventional-dose salvage regimens, with a 3-year overall survival of 37% for patients in chemo-sensitive relapse and 7% for chemo-resistant patients.[282] In a recent study,[281] patients who failed to achieve complete remission after a very brief induction phase, did obtain complete remission after a high-dose, stem-cell-supported, sequential chemotherapy program.

Neoplastic cells of BL strongly express CD20 antigen on their surface in the great majority of cases. Therefore, an anti-CD20 monoclonal antibody (rituximab) has been integrated into the most recent versions of some of the previously described regimens. Preliminary data appear promising, suggesting the possibility of a further improvement of the percentages of complete remission and of long-survivors.[281,284,285]

Peripheral T-cell lymphomas

PTCL have been difficult to classify and treat for several reasons. The first reason is their rarity, because in western countries PTCL account for 10-15% of aggressive lymphomas. The second reason is their morphologic heterogeneity, since it has been difficult to stratify them according to different histological subtypes. Indeed, the Working Formulation classification, devised in the 1980s, did not recognize T-cell lymphomas and clustered together many aggressive diseases of different biology under the general term of *intermediate-grade lymphomas*.

Therefore CHOP (or CHOP-like regimens), the standard chemotherapy for working formulation intermediate grade lymphoma, was considered for many years the optimal therapy for T-cell neoplasms. In 1994, the REAL classification gathered together the different T-cell subtypes under a single broad category termed *PTCL*. Gisselbrecht *et al.*[286] reported the results of the largest prospective study published so far: 288 PTCL patients were treated with different anthracycline-containing regimens. The 5-year overall survival and event-free survivals were 41% and 33%, respectively; the outcome of PTCL was significantly worse than that of DLBCL. Other authors confirmed in smaller studies that second or third-generation chemotherapy regimens were not able to modify the natural history of PTCL, and the 5-year overall survival remained between 25-40%. When the main subgroups defined by the REAL classification were analyzed, only anaplastic large cell lymphoma (ALCL) associated with t(2;5) had a prognosis equivalent to or better than that of to DLBCL. For the other subtypes, most authors agreed on the adverse prognostic effect of the T-cell phenotype. Considering that standard chemotherapy regimens proved to be unsatisfactory for PTCL, many investigators began to explore the use of high dose chemotherapy (HDT) and autologous SCT. Rodriguez *et al.*[287] reported 3-year overall survival and progression-free survivals of 39% and 32%, respectively, in a small cohort of patients who had relapsed after or who were refractory to conventional chemotherapy. Song *et al.*[288] reviewed the experience of the Toronto University in a larger cohort of patients with relapsed or primary refractory PTCL, and compared their outcome with that of DLCBL patients transplanted for the same indications over the same time period. The 3-year overall survival and event free survivals were not statistically different for PTCL and DLBCL. These two studies agreed on the similar outcome of aggressive relapsed B and T lymphomas, but other authors[289,290] have questioned the advantage of HDT in this subset of patients. Moreover, as was

observed with standard chemotherapy, even with HDT the prognosis of T-cell lymphomas differs among the various subtypes: in fact, while ALCL with t(2;5) has a good prognosis, patients with unspecified PTCL have a poor outcome, with a 5-years event-free survival ranging between 16% and 23%.

To define the clinical outcome of unspecified PTCL better and to assess a prognostic model specifically devised for PTCL, the Intergruppo Italiano Linfomi (IIL)[291] retrospectively analyzed 385 cases and identified four risk groups on the basis of four clinical parameters (age, performance status, LDH, bone marrow involvement): patients classified in groups 3 and 4 had a very dismal prognosis, with a 5-year survival probability of only 26%. The conclusion of the investigators was that for patients with unspecified PTCL and an adverse score novel therapeutic strategies (such as monoclonal antibodies and allogeneic transplantation) were required. A recent pilot study[292] evaluating the efficacy of alemtuzumab (anti-CD52 humanized antibody) in heavily pre-treated PTCL patients showed a considerable antitumor activity, with a 36% overall response rate. However, infectious complications and hematologic toxicity were unacceptably high, leading to early discontinuation of the study. In conclusion, PTCL are a rare and heterogeneous group of malignancies with a dismal prognosis. Considering the disappointing results of standard and high-dose chemotherapy (except for ALCL) large prospective studies should be encouraged in order to investigate the efficacy of novel approaches, such as monoclonal antibodies or frontline allogeneicSCT.

Post-transplant lymphoproliferative diseases

PTLDs constitute a group of potentially life-threatening complications of solid organ transplantation. The incidence of PTLD differs in relation to the type of transplanted organ. At 10 years, the actuarial risk for developing this devastating complication is around 3% and 8% in the case of heart or kidney transplant, respectively.[293] The type and the intensity of immune suppression significantly affect the risk of developing PTLD and this is particularly evident in the case of allogeneic hematopoietic stem cell transplantation if *in vitro* or *in vivo* T-cell depletion is used to decrease the severity of graft versus host disease. The PTLD classification has been recently updated by the World Health Organization and encompasses three main categories: a) early lesions (reactive plasmacytic hyperplasia and infectious mononucleosis–like lesions), b) polymorphic PTLD and c) monomorphic PTLD (to be classified according to the lymphoma classification). While the role of Epstein-Barr virus (EBV) is firmly established in the development of B-cell PTLD, this virus is not a common finding in the few cases of T cell-derived PTLD.[294,295] Moreover, as time goes by from transplantation, the proportion of EBV-negative, B-cell derived PTLD increases remarkably and these cases generally have a worse prognosis than their EBV-positive counterparts.[293] Most PTLD of B-cell phenotype originate from cells that have experienced the germinal center reaction, since the neoplastic clone carries clues of the somatic hypermutation process targeting immunoglobulin variable genes (IgV) in the germinal center microenvironment.[296]

Therapeutic strategies for these lymphoproliferative disorders must be adapted first to the performance status of the patients and second to the type and stage of the PTLD. It is now well established that reduction or discontinuation of immunosuppressive drugs are the first options of PTLD treatment. This strategy alone, however, is fully effective only for polyclonal, EBV-driven, early lesions which may exhibit complete and durable responses. In this setting, evaluating the EBV viral load has been used as a tool for preventing PTLD and monitoring the clinical benefit of reducing or discontinuing of immunosuppressive drugs. Surveillance studies in patients with high EBV loads in peripheral blood have been found to be sensitive but not specific predictors of PTLD development. When reduction in immunosuppression fails, the use of the anti-CD20 chimeric monoclonal antibody, rituximab, represents an attractive second-line therapeutic option because of its low toxicity and its ability to reduce the number of B cells in which massive proliferation of EBV particles is occurring. Rituximab therapy can rapidly induce reduction of lymph node enlargement[297] and this may be particularly evident in cases showing massive disease infiltration of the lungs.[298]

For patients with monoclonal NHL, particularly if EBV-negative and late developing, reduction of immunosuppressive drugs is not sufficient. Surgical resection and local radiotherapy followed by rituximab administration, may represent a valid therapeutic option for patients with localized stage I or II NHL of B-cell origin and low performance status.[299]

Cellular therapies have been tested based on the *in vitro* generation of EBV-specific T-cell lines.[300,301] These innovative treatments were shown to be effective in reducing the viral load and were remarkably well tolerated. However, the recent availability of rituximab and the highly demanding requirements of Good Manufacturing Practices (GMP) in laboratories reduced the initial enthusiasm for these therapies, at least for the treatment of the relatively benign EBV-driven early lesions.

All patients with advanced stage disease and acceptable performance status should rapidly initiate aggressive chemotherapy soon after discontinuation of any immunosuppressive treatment. Conventional chemo-

therapy programs were initially described as less effective and more toxic in PTLD with often unacceptable mortality rates. More recently, the toxicity-related mortality rate has been decreasing (down to 25%)[302] even when high dose chemotherapy programs and autologous SCT are used (*personal data*).

During the chemotherapeutic programs immune suppression with azathioprine, cyclosporine A or tacrolimus must remain withdrawn since the risk of organ rejection is negligible while the patient is under treatment with cytotoxic drugs. At the end of treatment, immunosuppressive treatments can be restarted, general by within one month, paying attention to T-cell counts in the peripheral blood.

Allogeneic stem cell transplantation as salvage treatment for aggressive lymphomas

The role of allogeneicSCT in the treatment of relapsed aggressive lymphomas is still a matter of debate. The existence of a graft-versus-tumor effect is largely accepted for myeloid leukemias. In lymphoid diseases, and in particular in aggressive lymphomas, the evidence for a graft-versus lymphoma effect is less documented, being mainly supported by reports describing lymphoma regression after cyclosporine withdrawal or cell therapy with donor lymphocyte infusions. In addition, a case-controlled study of the European Blood and Marrow Transplantation (EBMT) group showed a significantly lower rate of relapse in patients with aggressive lymphoma developing chronic graft-versus-host disease after allogeneicSCT.[303] However, a recent retrospective analysis, by Bierman *et al.* failed to show a lower relapse risk when allogeneic and syngeneic transplants were compared. That said, the study had several limitations because it was retrospective and some of the patients characteristics were different or missing among the allogeneic, syngeneic and autologous transplant groups.[304]

The role of allogeneicSCT in aggressive NHL is difficult to assess due to the few prospective studies and a common bias in patient selection: in fact, the majority of single center studies have a very limited number of patients, often presenting with poor-risk factors, who are heavily pretreated (including a failed autologous SCT) and who are frequently affected by a refractory disease. Dhedin *et al.* evaluate the largest series of myeloablative allogeneicSCT for aggressive lymphomas, and reported 5-year overall and progression-free survival and PFS rates of 41% and 40%, respectively. It is noteworthy that the 5-year overall survival rate was 76% for patients allografted in complete remission. The treatment-related mortality, however, was relevant (44%).[305] A retrospective analysis of the EBMT group on 242 patients with intermediate-grade disease reported an overall of 50% and a progression-free survival of 43%; in comparison with 9488 autologous SCT patients, relapse was reduced, but overall survival was significantly worse because of the higher transplant-related mortality in the allogeneic cohort.[283] Taken together all these studies have suggested a potential role for allogeneic SCT in the salvage treatment of aggressive lymphomas, but have also highlighted that the major concern is transplant-related mortality, which is exceedingly high, and which limits the widespread application of the procedure.

It has recently been shown that reduced intensity conditioning regimens can be used to obtain the engraftment of allogeneic stem cells with limited organ toxicity, and a rather low transplant-related mortality. This strategy has been effective in producing clinical and molecular remissions in advanced hematologic malignancies, but the experience with reduced intensity conditioning regimens in lymphomas is still quite limited. Initially encouraging results were reported by Khouri *et al.:* transplant-related mortality at day 100 was 0% and the 2-year progression-free and overall survivals were 61% and 71%, respectively.[306] An EBMT retrospective analysis on 188 lymphoma patients reported, in the subgroup of aggressive lymphomas, 1-year progression-free and overall survivals of 32% and 52%, respectively.[307] Recently, Morris *et al.* reported the outcome of relapsed and refractory lymphoma patients receiving an alemtuzumab-containing reduced intensity conditioning regimen followed by allogeneicSCT: the 3-year transplant-related mortality and profression-free survival was better in low-grade histologies.[308]

Finally, very few studies have addressed the role of allogeneicSCT in rare aggressive lymphoma subtypes such as LbL, BL and PTCL. Prolonged remissions and long-term survival of patients with LbL have been obtained after allogeneicSCT for relapsed or refractory disease.

A retrospective study was recently conducted on behalf of the Lymphoma Study Writing Committee of the International Bone Marrow Transplant Registry: the efficacy of allogeneic transplantation was offset by the high transplant-related mortality. Not surprisingly, a lower relapse rate was observed in allotransplant recipients at 1 and 5 years, but no difference was noted in overall survivall between recipients of autologous or allogeneic SCT.[309] AllogeneicSCT was also an effective salvage treatment for BL patients in chemosensitive relapse.[283] However, although the outcome after allogeneic transplants appeared better than that after autologous ones in terms of relapse rate, the transplant-related mortality was relevant and there was no improvement in the overall survival. A multicenter pilot study employing reduced intensity conditioning followed by allogeneicSCT has been recently conducted in relapsed PTCL: although the number of patients was

limited, the outcome was encouraging, with estimated 3-year progression-free and overall survivall of 64% and 81%, respectively. The estimated probability of transplant-related mortality at 2 years was only 6%.[182]

Supportive therapy

Management of neutropenia

Granulopoiesis-stimulating growth factors, namely G-CSF and GM-CSF, are usually employed to manage chemotherapy-induced neutropenia, in order to reduce its duration and severity.[310] Meta-analyses of several clinical studies[311,312] have documented that growth factors, when used as prophylaxis in patients with NHL undergoing *conventional* chemotherapy, reduce the risk of chemotherapy-induced neutropenia, febrile neutropenia, hospital admissions and hospital stay due to infection, treatment delays and documented infections. However, infection-related mortality, use of intravenous antibiotics, tumor response, and overall clinical outcome are not significantly modified by growth factors.[311,312]

Predictive parameters for calculating the risk of developing febrile neutropenia in NHL are age, performance status, chemotherapy-intensity, bone marrow involvement, renal or cardiac co-morbidity, albumin, hemoglobin and LDH levels.[313-315] The ASCO guidelines concerning the use of growth factors for managing neutropenia,[310] currently under revision, suggest that they should not be used as primary prophylaxis for chemotherapy-induced neutropenia, febrile neutropenia unless the risk of febrile neutropenia is 40% or greater. More recent data, however, based on updated pharmaco-economic evaluations, support the possible clinical benefit and the cost neutrality of primary prophylaxis in settings in which the risk of febrile neutropenia is 30% or even 20%.[313-315] In general, when indicated, primary prophylaxis with growth factors seems to be more effective than secondary prophylaxis in preventing febrile neutropenia.[316] However, the cost-effectiveness of G-CSF has recently been disputed in the context of elderly patients receiving standard CHOP chemotherapy.[317]

Peg-filgrastim is a compound created by addition of a poly-ethylene-glycol molecule to filgrastim with a novel, self-regulating phamacokinetic profile characterized by neutrophil-mediated clearance.[318,319] As a result, serum levels of peg-filgrastim after a single administration remain elevated during chemotherapy-induced neutropenia, febrile neutropenia and decline rapidly as neutrophil count recovers. Data from randomized trials have evidenced that a single, fixed, once-per-cycle dose of peg-filgrastim (6 mg) administered 24 hours after chemotherapy is safe, well tolerated and has an efficacy similar to that provided by daily injections of filgrastim in patients receiving chemotherapy for NHL.[320-322] Peg-filgrastim might be particularly indicated when the risk of severe neutropenia and associated infections is higher and when the nadir and duration of neutropenia are unpredictable, such as in patients who receive more intensive regimens.[318,319,323,324] Data are being accumulated on the impact of chemotherapy-induced neutropenia, febrile neutropenia on clinical outcomes in terms of quality of life, delay in therapy and ultimately, on response and survival. In fact, treatment delays or decreasing dose-intensity due to myelotoxicity or infective episodes during standard chemotherapy can compromise outcomes in a potentially curable malignancy, such as aggressive NHL.[325] In addition, G-CSF has recently been employed to make feasible dose-dense regimens which have been demonstrated to be superior to standard treatments in terms of responses and survival.[184-186]

Management of anemia

Anemia profounfly affects the quality of life of NHL patients and may also have prognostic significance. It is present in more than one-third of patients at diagnosis. Although less frequently than in low grade NHL, severe anemia (grade 3-4) may be observed during treatment in about 20% of elderly patients with aggressive NHL receiving chemotherapy. As in other types of cancers, the pathogenesis of anemia in NHL is multifactorial; however, cytokine-mediated anemia of chronic disease, with associated inadequate production of endogenous erythropoietin (EPO), may play a relevant role.

Packed-red cell transfusions represent the standard treatment for severe and acute anemia. In all other cases, recombinant (r-) epoetins (α or β r-EPO, darbepoetin α) represent valuable options, with the major goals of improving quality of life and preventing or reducing transfusions.[326-328] Although studies specifically focused on the use of epoetins for treating anemia in NHL are scarce, useful information may be extrapolated from recently published guidelines[326,327] meta-analyses,[328] and some clinical trials including these malignancies alone or among other tumors.[329-333]

According to ASCO/ASH evidence-based guidelines, r-EPO is recommended for patients with chemo-therapy-associated anemia and a hemoglobin concentration below 10 g/dL (8-10 g/dL). Clinical circumstances should determine the use of r-EPO for patients with less severe anemia (Hb between 10 and 12 g/dL). The ASCO/ASH guidelines[326] also suggest that r-EPO should be started only after tumor-reduction due to initial chemo-radiotherapy has not allowed improvement of baseline hemoglobin levels. Recent data, however, indi-

cate that early (frontline) r-EPO treatment in mildly anemic patients (hemoglobin 10-12 g/dL) undergoing chemotherapy could provide better improvement in terms of Hb and transfusion requirement, quality of life and care resource utilization and work with respect to delayed (when the hemoglobin declines to <9 g/dL) administration of r-EPO.[334]

The more recently published EORTC guidelines[327] suggest that r-EPO may be initiated, in patients receiving chemo-radiotherapy, at hemoglobin values of 9-11 g/dL. Anemia-related symptoms should drive the choice of administering r-EPO to patients with the same levels of hemoglobin who are not receiving chemo-radiotherapy. In selected cases (i.e. for patients who are scheduled to receive intensive chemotherapy) r-EPO may be considered to prevent a further decline of hemoglobin. r-EPO is also recommended in cases of severe anemia in combination with transfusions. Although an optimal dose of 150 U/kg thrice weekly for at least 8-12 weeks was initially suggested for r-EPO,[326] fixed, rather than body-weight adjusted doses, are currently recommended.[327] Alternatively, weekly, equivalent single-dose schedules (30,000-40,000-60,000 qw) may represent further options.[327,331,333] Dose-escalation can be useful in the absence of response in selected patients. The use of epoetins after autologous stem cell transplantation is not currently recommended, but positive experiences in this context have recently been published.[335]

Darbepoetin is a novel erythropoiesis stimulating protein (NESP) which, compared to human α or β r-EPO, has a greater sialylated carbohydrate content permitting a prolonged serum half-life.[336] Darbepoetin once-weekly can be recommended at the initial dose of 2.25 μg/kg as an alternative to r-EPO α or β.[327,332] There is currently less evidence on the value of administering darbepoetin α at higher dosages and at longer intervals (300-500 μg every 1-3 weeks) and these require strategies further studies.

Treatment with epoetins should be continued until target hemoglobin-levels or significant clinical improvement are achieved. Individualized titration of the lowest effective maintenance dose should be performed repeatedly. In patients with adequate iron stores, there is no indication to prolong r-EPO administration beyond 6-8 weeks in the absence of response. However, a supply of iron, particularly if administered intravenously, may optimize responses in patients developing functional or absolute iron deficiency while receiving r-EPO for chemotherapy-related anemia.[337]

According to published guidelines,[326-327] the target hemoglobin concentration should be 12-13 g/dL.

Recently, the FDA recommended 12 g/dL as the upper limit to maintain, as higher levels have been found to be associated with a possible increased risk of thromboembolic events.[338]

A new, pegylated form of r-EPO with a prolonged half-life, also known as CERA (continuous erythropoietic receptor activator), allowing single administrations every one to three weeks, has demonstrated significant erythropoietic activity in chemotherapy-treated aggressive NHL in phase I-II studies.[339] Confirmatory phase III studies are in progress.

The question of whether tumor response and clinical outcome of patients may be positively or negatively influenced by administrations of epoetins, is currently being debated.[340,341] Some data suggest that hematology patients with documented anemia who received r-EPO along with chemotherapy might have better survival than those who did not.[329] By contrast, in patients with solid cancer, some reports suggest the possibility that prophylaxis of anemia with r-EPO could negatively affect the patient's outcome.[342,343] Pending additional information in this setting, the prophylactic use of r-EPO in non-anemic patients with cancer should currently be discouraged.

Management of thrombocytopenia

As in other hematologic malignancies, prevention and treatment of hemorrhage secondary to thrombocytopenia in aggressive NHL is generally managed by the transfusion of platelets. The need for such transfusion is related to the degree and duration of *critical* thrombocytopenia. A platelet count greater than 10×10^9/L is usually considered safe in the absence of factors associated with increased tendency to bleed.[344]

Interleukin-11 was successfully shown to reduce the incidence of severe thrombocytopenia in patients receiving intensive chemotherapy, and its use has now received approval from the FDA for this purpose.[345,346] Initial clinical trials of recombinant thrombopoietin, the central regulator of megakaryocytopoiesis and thrombopoiesis, and its analogs, mainly Peg-MGDF (megakaryocytic growth and development factor) have been shown to enhance platelet recovery after chemotherapy.[347] However, the clinical use of these agents has been largely limited by the observation that their administration, may induce the formation of antibodies that neutralize native thrombopoietin and cause thrombocytopenia.[347]

Among a number of second generation platelet growth factors recently developed, AMG 531 is a 60,000 Da Mpl receptor agonist made in *E. Coli,* currently under clinical investigation, containing four peptide sequences that have been molecularly engineered in a Fc carrrier domain.[348] These peptides have no homology to TPO but have been selected because they avidly bind to the Mpl receptor and stimulate megakaryocyte maturation and proliferation. Preliminary *in vivo* studies indicate that AMG 531 induces a

dose-dependent rise in the platelet count that peaks 7-9 days after intravenous or subcutaneous injection in healthy subjects, without additional effects on other blood cell counts and no antibody formation to thrombopoietin.[349]

Other issues in supportive therapy

Large tumor masses and high proliferation rate (as observed, for example, in Burkitt's lymphoma) enhance the risk of tumor lysis syndrome, which results in marked hyperuricemia and renal failure and occurs as large numbers of malignant cells are rapidly destroyed during cytotoxic chemotherapy.[350] Standard treatment for tumor lysis syndrome includes adjustments in the chemotherapy regimen, vigorous hydration, administration of a uric acid synthesis inhibitor such as allopurinol, and alkalinization. The use of rasburicase, a recombinant form of the enzyme urate-oxidase, has been shown to provide effective prophylaxis and/or treatment against tumor lysis syndrome in aggressive NHL.[351]

Severe mucositis is common after intensive treatments and is generally managed by parental nutrition, topical therapies and narcotics. Recently, a recombinant keratinocyte growth factor (palifermin) has been succesfully employed to reduce the duration and severity of oral mucositis after intensive chemotherapy and radiotherapy for hematologic cancers, including NHL.[352]

NHL remains the second most common tumor in HIV-infected patients. Improvements in supportive care, in particular, highly active antiretroviral therapy (HAART), have allowed therapeutic approaches in these patients similar to those used in non-HIV-infected individuals, including tranplant regimens.[353] Likewise, lamivudine may prevent viral reactivation in NHL patients undergoing chemotherapy who are carriers of the hepatitis B virus.[354,355]

Patients with aggressive NHL with concomitant HCV infection but without signs of liver dysfunction can receive standard therapies and even autologous transplantation.[11]Recent reports suggest that antiviral therapy with (peg)-interferon and ribavirin may induce tumor remissions in some patients with HCV-positive low-grade NHL (mainly splenic lymphoma with villous lymphocytes and marginal zone).[356-358] However, in patients with more aggressive NHL, this anti-viral treatment may provoke elevated myelotoxicity if combined with chemotherapy (personal observations). Clinical trials are in progress to test the role of antiviral therapy after completion of standard chemotherapy programs in these patients (Musto *et al.,* submitted for publication).

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References

1. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW. Tumours of haematopoietic and lymphoid tissue. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology et Genetics. Lyon: IRAC Press 2001:191-4.
3. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER Cancer Statistics Review, 1975-2001, National Cancer Institute. Bethesda, MD. Available from URL http://seer.cancer.gov/csr/1975 _2001/, 2004.
4. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002; 38:99-166.
5. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene 2004; 23:6524-34.
6. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89:3909-18.
7. Stevenson FK, Sahota SS, Ottensmeier CH, Zhu D, Forconi F, Hamblin TJ. The occurrence and significance of V gene mutations in B cell-derived human malignancy. Adv Cancer Res 2001; 83: 81-116.
8. Gaidano G, Dalla-Favera R. Pathobiology of non-Hodgkin's lymphomas. In: Hoffman R, Benz Jr, EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, McGlave P, eds. Hematology. Basic Principles and Practice, 4th ed. Elsevier, Philadelphia, 2005, pp. 1307-24.
9. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer 2004; 4:757-68.
10. Gaidano G, Carbone A. Primary effusion lymphoma: a liquid phase lymphoma of fluid-filled body cavities. Adv Cancer Res 2001; 80:115-46.
11. Musto P. Hepatitis C virus infection and B-cell non-Hodgkin's lymphomas: more than a simple association. Clin Lymphoma 2002; 3:150-60.
12. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology 2003; 125: 1723-32.
13. Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S. B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review. Int J Cancer 2004; 10:1-8.
14. Mele A, Pulsoni A, Bianco E, Musto P, Szklo A, Sanpaolo MG, et al. Hepatitis C virus and B-cell non-Hodgkin's lymphoma: an Italian multicenter case control study. Blood 2003; 102:996-9.
15. Tomita N, Kodama F, Takabayashi M, Kawano T, Yamaji S, Fujimaki K, et al. Clinical features and outcome in HCV-positive aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 2003; 44:1159-64.
16. Machida K, Cheng KT, Sung VM, Shimodaira S, Lindsay KL, Levine AM, et al. Hepatitis C virus induces a mutator phenotype: enhanced mutations of immuno-globulin and protooncogenes. Proc Natl Acad Sci USA 2004; 101: 4262-7.
17. Ye BH, Lista F, Lo Coco F, Knowles DM, Offit K, Chaganti RS, et al. Alterations of a zinc finger-encoding gene, BCL-6, in diffuse large-cell lymphoma. Science 1993; 262:747-50.
18. Ye BH, Cattoretti G, Sen Q, Zhang J, Hawe N, de Waard R, et al. The BCL-6 proto-oncogene controls germinal-centre formation and Th2-type inflammation. Nat Genet 1997; 16:161-70.
19. Ye BH, Chagant S, Chang CC, Niu H, Corradini P, Chaganti RS, et al. Chromosomal translocations cause deregulated BCL6 expression by promoter substitution in B cell lymphoma. EMBO J 1995; 14:6209-17.
20. Phan RT, Dalla-Favera R. The BCL6 proto-oncogene suppresses p53 expression in germinal-centre B cells. Nature 2004; 432:635-9.
21. Volpe G, Vitolo U, Carbone A, Pastore C, Bertini M, Botto B, et al. Molecular heterogeneity of B-lineage diffuse large cell lymphoma. Genes Chromosomes Cancer 1996; 16:21-30.

22. Dyomin VG, Rao PH, Dalla-Favera R Chaganti RS. BCL8, a novel gene involved in translocations affecting band 15q11-13 in diffuse large-cell lymphoma. Proc Natl Acad Sci U S A 1997; 94:5728-32.
23. Rao PH, Houldsworth J, Dyomina K, Parsa NZ, Cigudosa JC, Louie DC, et al. Chromosomal and gene amplification in diffuse large B-cell lymphoma. Blood 1998; 92;234-40.
24. Dyomin VG, Palanisamy N, Lloyd KO, Dyomina K, Jhanwar SC, Houldsworth J, et al. MUC1 is activated in a B-cell lymphoma by the t(1;14)(q21;q32) translocation and is rearranged and amplified in B-cell lymphoma subsets. Blood 2000; 95:2666-71.
25. Pasqualucci L, Neumeister P, Goossens T, Nanjangud G, Chaganti RS, Kuppers R, et al. Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. Nature 2001; 412: 341-6.
26. Bosga-Bouwer AG, van Imhoff GW, Boonstra R, van der Veen A, Haralambieva E, van den Berg A, et al. Follicular lymphoma grade 3B includes 3 cytogenetically defined subgroups with primary t(14;18), 3q27, or other translocations: t(14;18) and 3q27 are mutually exclusive. Blood 2003; 101:1149-54.
27. Katzenberger T, Ott G, Klein T, Kalla J, Muller-Hermelink HK, Ott MM. Cytogenetic alterations affecting BCL6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B-cell component Am J Pathol 2004; 165:481-90.
28 Boxer LM, Dang CV. Translocations involving c-myc and c-myc function. Oncogene 2001; 20:5595-610.
29. Wu KJ, Grandori C, Amacker M, Simon-Vermot N, Polack A, Lingner J, et al. Direct activation of TERT transcription by c-MYC. Nat Genet 1999; 21:220-4.
30. Lindstrom MS, Wiman KG. Role of genetic and epigenetic changes in Burkitt lymphoma. Semin Cancer Biol 2002; 12:381-7.
31. Hussain A, Gutierrez MI, Timson G, Siraj AK, Deambrogi C, Al-Rasheed M, et al. Frequent silencing of fragile histidine triad gene (FHIT) in Burkitt's lymphoma is associated with aberrant hypermethylation. Genes Chromosomes Cancer 2004; 41:321-9.
32. Bertoni F, Zucca E, Cotter FE. Molecular basis of mantle cell lymphoma. Br J Haematol 2004; 124:130-40.
33. Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994; 263:1281-4.
34. Pulford K, Lamant L, Espinos E, Jiang Q, Xue L, Turturro F, Delsol G, Morris SW. The emerging normal and disease-related roles of anaplastic lymphoma kinase. Cell Mol Life Sci 2004; 61:2939-53.
35. Falini B, Pulford K, Pucciarini A, Carbone A, De Wolf-Peeters C, Cordell J, et al. Lymphomas expressing ALK fusion protein(s) other than NPM-ALK. Blood 1999; 94:3509-15.
36. Kutok JL, Aster JC. Molecular biology of anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma. J Clin Oncol 2002; 20:3691-702.
37. Capello D, Cerri M, Muti G, Berra E, Oreste P, Deambrogi C, et al. Molecular histogenesis of posttransplantation lymphoproliferative disorders. Blood 2003;102:3775-85.
38. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403:503-11.
39. Shipp MA, Ross KN, Tamayo P, Weng AP, Kutok JL, Aguiar RC, et al. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 2002; 8:68-74.
40. Thieblemont C, Nasser V, Felman P, Leroy K, Gazzo S, Callet-Bauchu E, et al. Small lymphocytic lymphoma, marginal zone B-cell lymphoma, and mantle cell lymphoma exhibit distinct gene-expression profiles allowing molecular diagnosis. Blood 2004; 103:2727-37.
41. Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003; 198:851-62.
42. Savage KJ, Monti S, Kutok JL, Cattoretti G, Neuberg D, De Leval L, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 2003; 102:3871-9.
43. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci USA 2003; 100:9991-6.
44. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:1937-47.
45. Asyali MH, Shoukri MM, Demirkaya O, Khabar KS. Assessment of reliability of microarray data and estimation of signal thresholds using mixture modeling. Nucleic Acids Res 2004; 32:2323-35.
46. Wulfkuhle J, Espina V, Liotta L, Petricoin E. Genomic and proteomic technologies for individualisation and improvement of cancer treatment. Eur J Cancer 2004; 40:2623-32.
47. Simon R, Mirlacher M, Sauter G. Tissue microarrays. Biotechniques 2004; 36:98-105.
48. Milanes-Yearsley M, Hammond ME, Pajak TF, Cooper JS, Chang C, Griffin T, et al. Tissue micro-array: a cost and time-effective method for correlative studies by regional and national cancer study groups. Mod Pathol 2002; 15:1366-73.
49. Pileri SA, Dirnhofer S, Went P, Ascani S, Sabattini E, Marafioti T, et al. Diffuse large B-cell lymphoma: one or more entities? Present controversies and possible tools for its subclassification. Histopathology 2002; 41:482-509.
50. Tzankov A, Pehrs AC, Zimpfer A, Ascani S, Lugli A, Pileri S, et al. Prognostic significance of CD44 expression in diffuse large B cell lymphoma of activated and germinal centre B cell-like types: a tissue microarray analysis of 90 cases. J Clin Pathol 2003; 56:747-52.
51. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004; 103:275-82.
52. Saez AI, Saez AJ, Artiga MJ, Perez-Rosado A, Camacho FI, Diez A, et al. Building an outcome predictor model for diffuse large B-cell lymphoma. Am J Pathol 2004; 164:613-22.
53. Marafioti T, Pozzobon M, Hansmann ML, Delsol G, Pileri SA, Mason DY. Expression of intracellular signaling molecules in classical and lymphocyte predominance Hodgkin disease. Blood 2004; 103:188-93.
54. Pileri SA, Ascani S, Milani M, Visani G, Piccioli M, Orcioni GF, et al. Acute leukaemia immunophenotyping in bone-marrow routine sections. Br J Haematol 1999; 105:394-401.
55. Pileri SA, Ascani S, Sabattini E, Fraternali-Orcioni G, Poggi S, Piccioli M, et al. The pathologist's view point. Part I-indolent lymphomas. Haematologica 2000; 85:1291-307.
56. Pileri SA, Ascani S, Sabattini E, Fraternali-Orcioni G, Poggi S, Piccioli M, et al. The pathologist's view point. Part II - aggressive lymphomas. Haematologica 2000; 85:1308-21.
57. Tiacci E, Pileri S, Orleth A, Pacini R, Tabarrini A, Frenguelli F, et al. PAX5 expression in acute leukemias: higher B-lineage specificity than CD79a and selective association with t(8;21)-acute myelogenous leukemia. Cancer Res 2004; 64:7399-404.
58. Falini B, Mason DY. Proteins encoded by genes involved in chromosomal alterations in lymphoma and leukemia: clinical value of their detection by immunocytochemistry. Blood 2002; 99:409-26.
59. Pilozzi E, Pulford K, Jones M, Muller-Hermelink HK, Falini B, Ralfkiaer E, et al. Co-expression of CD79a (JCB117) and CD3 by lymphoblastic lymphoma. J Pathol 1998; 186:140-3.
60. Conde-Sterling DA, Aguilera NS, Nandedkar MA, Abbondanzo SL. Immunoperoxidase detection of CD10 in precursor T-lymphoblastic lymphoma/leukemia: a clinicopathologic study of 24 cases. Arch Pathol Lab Med 2000; 124:704-8.
61. Hyjek E, Chadburn A, Liu YF, Cesarman E, Knowles DM. BCL-6 protein is expressed in precursor T-cell lymphoblastic lymphoma and in prenatal and postnatal thymus. Blood 2001; 97:270-6.
62. Soslow RA, Zukerberg LR, Harris NL, Warnke RA. BCL-1 (PRAD-1/cyclin D-1) overexpression distinguishes the blastoid variant of mantle cell lymphoma from B-lineage lymphoblastic lymphoma. Mod Pathol 1997; 10:810-7.
63. Chan NP, Ma ES, Wan TS, Chan LC. The spectrum of acute lymphoblastic leukemia with mature B-cell phenotype. Leuk Res 2003; 27:231-4.
64. Ascani S, Went P, Liberati AM, Piccaluga PP, Zinzani PL, Pileri SA. Difficult diagnostic and therapeutic cases: CASE 1. true thymic hyperplasia in a patient treated for T-cell lymphoma. J Clin Oncol 2004; 22:953-4.

65. Devoe K, Weidner N. Immunohistochemistry of small round-cell tumors. Semin Diagn Pathol 2000; 17:216-24.
66. Swerdlow SH, Williams ME. From centrocytic to mantle cell lymphoma: a clinicopathologic and molecular review of 3 decades. Hum Pathol 2002; 33:7-20.
67. Wasman J, Rosenthal NS, Farhi DC. Mantle cell lymphoma. Morphologic findings in bone marrow involvement. Am J Clin Pathol 1996; 106:196-200.
68. Schenka AA, Gascoyne RD, Duchayne E, Delsol G, Brousset P. Prominent intrasinusoidal infiltration of the bone marrow by mantle cell lymphoma. Hum Pathol 2003; 34:789-91.
69. Smir BN, Ramaika CA, Cho CG, Gulley ML. Molecular evidence links lymphomatous polyposis of the gastrointestinal tract with mantle cell lymphoma. Hum Pathol 1995; 26:1282-5.
70. Dogan A, Isaacson PG. Splenic marginal zone lymphoma. Semin Diagn Pathol 2003; 20:121-7.
71. Liu Z, Dong HY, Gorczyca W, Tsang P, Cohen P, Stephenson CF, et al. CD5- mantle cell lymphoma. Am J Clin Pathol 2002;118:216-24.
72. Cheuk W, Wong KO, Wong CS, Chan JK. Consistent immunostaining for cyclin D1 can be achieved on a routine basis using a newly available rabbit monoclonal antibody. Am J Surg Pathol 2004; 28: 801-7.
73. Yatabe Y, Suzuki R, Tobinai K, Matsuno Y, Ichinohasama R, Okamoto M, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: a clinicopathologic comparison of cyclin D1-positive MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood 2000; 95:2253-61.
74. Schlette E, Fu K, Medeiros LJ. CD23 expression in mantle cell lymphoma: clinicopathologic features of 18 cases. Am J Clin Pathol 2003; 120:760-6.
75. Went P, Ascani S, Strom E, Brorson SH, Musso M, Zinzani PL, et al. Nodal marginal-zone lymphoma associated with monoclonal light-chain and heavy-chain deposition disease. Lancet Oncol 2004; 5:381-3.
76. Camacho FI, Garcia JF, Cigudosa JC, Mollejo M, Algara P, Ruiz-Ballesteros E, et al. Aberrant Bcl6 protein expression in mantle cell lymphoma. Am J Surg Pathol 2004; 28:1051-6.
77. Raty R, Franssila K, Joensuu H, Teerenhovi L, Elonen E. Ki-67 expression level, histological subtype, and the International Prognostic Index as outcome predictors in mantle cell lymphoma. Eur J Haematol 2002; 69:11-20.
78. Quintanilla-Martinez L, Davies-Hill T, Fend F, Calzada-Wack J, Sorbara L, Campo E, et al. Sequestration of p27Kip1 protein by cyclin D1 in typical and blastic variants of mantle cell lymphoma (MCL): implications for pathogenesis. Blood 2003; 101:3181-7.
79. Eshoa C, Perkins S, Kampalath B, Shidham V, Juckett M, Chang CC. Decreased CD10 expression in grade III and in interfollicular infiltrates of follicular lymphomas. Am J Clin Pathol 2001; 115: 862-7.
80. Au WY, Horsman DE, Gascoyne RD, Viswanatha DS, Klasa RJ, Connors JM. The spectrum of lymphoma with 8q24 aberrations: a clinical, pathological and cytogenetic study of 87 consecutive cases. Leuk Lymphoma 2004; 45:519-28.
81. Barry TS, Jaffe ES, Kingma DW, Martin AW, Sorbara L, Raffeld M, et al. CD5+ follicular lymphoma: a clinicopathologic study of three cases. Am J Clin Pathol 2002; 118:589-98.
82. Tiesinga JJ, Wu CD, Inghirami G. CD5+ follicle center lymphoma. Immunophenotyping detects a unique subset of "floral" follicular lymphoma. Am J Clin Pathol 2000; 114:912-21.
83. Pileri SA, Zinzani PL, Ascani S, Orcioni GF, Gamberi B, Piccioli M, et al. Diffuse large B-cell lymphoma with primary retroperitoneal presentation: clinicopathologic study of nine cases. Ann Oncol 2001; 12:1445-53.
84. Pileri SA, Zinzani PL, Gaidano G, Falini B, Gaulard P, Zucca E, et al. Pathobiology of primary mediastinal B-cell lymphoma. Leuk Lymphoma 2003; 44(Suppl 3):S21-6.
85. Pileri SA, Gaidano G, Zinzani PL, Falini B, Gaulard P, Zucca E, et al. Primary mediastinal B-cell lymphoma: high frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of immunoglobulins. Am J Pathol 2003; 162:243-53.
86. Haralambieva E, Pulford KA, Lamant L, Pileri S, Roncador G, Gatter KC, et al. Anaplastic large-cell lymphomas of B-cell phenotype are anaplastic lymphoma kinase (ALK) negative and belong to the spectrum of diffuse large B-cell lymphomas. Br J Haematol 2000; 109:584-91.
87. Lim MS, Beaty M, Sorbara L, Cheng RZ, Pittaluga S, Raffeld M, et al. T-cell/histiocyte-rich large B-cell lymphoma: a heterogeneous entity with derivation from germinal center B cells. Am J Surg Pathol 2002; 26:1458-66.
88. Boudova L, Torlakovic E, Delabie J, Reimer P, Pfistner B, Wiedenmann S, et al. Nodular lymphocyte-predominant Hodgkin lymphoma with nodules resembling T-cell/histiocyte-rich B-cell lymphoma: differential diagnosis between nodular lymphocyte-predominant Hodgkin lymphoma and T-cell/histiocyte-rich B-cell lymphoma. Blood 2003; 102:3753-8.
89. De Wolf-Peeters C, Achten R. 'T-cell-rich large B-cell lymphoma'-'histiocyte-rich, T-cell-rich large B-cell lymphoma'-'T-cell/histiocyte-rich large B-cell lymphoma': will we ever see the wood for the trees? Histopathology 2002; 41: 269-71.
90. Marafioti T, Mancini C, Ascani S, Sabattini E, Zinzani PL, Pozzobon M, et al. Leukocyte-specific phosphoprotein-1 and PU.1: two useful markers for distinguishing T-cell-rich B-cell lymphoma from lymphocyte-predominant Hodgkin's disease. Haematologica 2004; 89:957-64.
91. Cerroni L, El-Shabrawi-Caelen L, Fink-Puches R, LeBoit PE, Kerl H. Cutaneous spindle-cell B-cell lymphoma: a morphologic variant of cutaneous large B-cell lymphoma. Am J Dermatopathol 2000; 22:299-304.
92. Koo CH, Shin SS, Bracho F, Johnston WH, Rappaport H. Rosette-forming non-Hodgkin's lymphomas. Histopathology 1996; 29:557-63.
93. Diebold J, Anderson JR, Armitage JO, Connors JM, Maclennan KA, Muller-Hermelink HK, et al. Diffuse large B-cell lymphoma: a clinicopathologic analysis of 444 cases classified according to the updated Kiel classification. Leuk Lymphoma 2002; 43:97-104.
94. Pileri SA, Ascani S, Zinzani PL, Gaidano G, Piccioli M, Rossi M, et al. Diffuse large B-cell lymphoma (DLBCL), anaplastic variant. Report on a problematic case primarily arising in the stomach. Haematologica 2002; 87:ECR40.
95. Falini B, Pileri S, Stein H, Dieneman D, Dallenbach F, Delsol G, et al. Variable expression of leukocyte-common (CD45) antigen in CD30 (Ki1)-positive anaplastic large-cell lymphoma: implications for the differential diagnosis between lymphoid and nonlymphoid malignancies. Hum Pathol 1990; 21: 624-9.
96. Yamaguchi M, Seto M, Okamoto M, Ichinohasama R, Nakamura N, Yoshino T, et al. De novo CD5^{+} diffuse large B-cell lymphoma: a clinicopathologic study of 109 patients. Blood 2002; 99:815-21.
97. Colomo L, Lopez-Guillermo A, Perales M, Rives S, Martinez A, Bosch F, et al. Clinical impact of the differentiation profile assessed by immunophenotyping in patients with diffuse large B-cell lymphoma. Blood 2003; 101:78-84.
98. Linderoth J, Jerkeman M, Cavallin-Stahl E, Kvaloy S, Torlakovic E, Nordic Lymphoma Group Study. Immunohistochemical expression of CD23 and CD40 may identify prognostically favorable subgroups of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Study. Clin Cancer Res 2003; 9:722-8.
99. Chang CC, McClintock S, Cleveland RP, Trzpuc T, Vesole DH, Logan B, et al. Immunohistochemical expression patterns of germinal center and activation B-cell markers correlate with prognosis in diffuse large B-cell lymphoma. Am J Surg Pathol 2004; 28:464-70.
100. Barrans SL, Fenton JA, Banham A, Owen RG, Jack AS. Strong expression of FOXP1 identifies a distinct subset of diffuse large B-cell lymphoma (DLBCL) patients with poor outcome. Blood 2004; 104:2 933-5.
101. Houldsworth J, Olshen AB, Cattoretti G, Donnelly GB, Teruya-Feldstein J, Qin J, et al. Relationship between REL amplification, REL function, and clinical and biologic features in diffuse large B-cell lymphomas. Blood 2004; 103:1862-8.
102. Rimsza LM, Roberts RA, Miller TP, Unger JM, LeBlanc M, Braziel RM, et al. Loss of MHC class II gene and protein expression in diffuse large B-cell lymphoma is related to decreased tumor immunosurveillance and poor patient survival regardless of other prognostic factors: a follow-up study from the Leukemia and Lymphoma Molecular Profiling Project. Blood 2004; 103:4251-8.
103. Lerner RE, Burns LJ. Transformed lymphoma: an Achilles' heel of non-Hodgkin's lymphoma. Bone Marrow Transplant 2003; 31:531-7.
104. Lossos IS, Levy R. Higher grade transformation of follicular lymphoma: phenotypic tumor progression associated with

diverse genetic lesions. Semin Cancer Biol 2003; 13:191-202.
105. Nakamura N, Abe M. Richter syndrome in B-cell chronic lymphocytic leukemia. Pathol Int 2003; 53:195-203.
106. Moller MB, Nielsen O, Pedersen NT. Frequent alteration of MDM2 and p53 in the molecular progression of recurring non-Hodgkin's lymphoma. Histopathology 2002; 41:322-30.
107. Hutchison RE, Finch C, Kepner J, Fuller C, Bowman P, Link M, et al. Burkitt lymphoma is immunophenotypically different from Burkitt-like lymphoma in young persons. Ann Oncol 2000; 11 (Suppl 1):35-8.
108. Spina D, Leoncini L, Megha T, Gallorini M, Disanto A, Tosi P, et al. Cellular kinetic and phenotypic heterogeneity in and among Burkitt's and Burkitt-like lymphomas. J Pathol 1997; 182:145-50.
109. Haralambieva E, Banham AH, Bastard C, Delsol G, Gaulard P, Ott G, et al. Detection by the fluorescence in situ hybridization technique of MYC translocations in paraffin-embedded lymphoma biopsy samples. Br J Haematol 2003; 121: 49-56.
110. Evens AM, Gordon LI. Burkitt's and Burkitt-like lymphoma. Curr Treat Options Oncol 2002; 3:291-305.
111. Ascani S, Zinzani PL, Gherlinzoni F, Sabattini E, Briskomatis A, de Vivo A, et al. Peripheral T-cell lymphomas. Clinicopathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. Ann Oncol 1997; 8:583-92.
112. Kluin PM, Feller A, Gaulard P, Jaffe ES, Meijer CJ, Muller-Hermelink HK, et al. Peripheral T/NK-cell lymphoma: a report of the IXth Workshop of the European Association for Haematopathology. Histopathology 2001; 38:250-70.
113. Pileri SA, Ascani S, Sabattini E, Falini B. Peripheral T-cell lymphoma: a developing concept. Ann Oncol 1998; 9:797-801.
114. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103:2474-9.
115. Falini B, Pileri S, De Solas I, Martelli MF, Mason DY, Delsol G, et al. Peripheral T-cell lymphoma associated with hemophagocytic syndrome. Blood 1990; 75: 434-44.
116. Yao X, Teruya-Feldstein J, Raffeld M, Sorbara L, Jaffe ES. Peripheral T-cell lymphoma with aberrant expression of CD79a and CD20: a diagnostic pitfall. Mod Pathol 2001; 14:105-10.
117. Attygalle A, Al-Jehani R, Diss TC, Munson P, Liu H, Du MQ, et al. Neoplastic T cells in angioimmunoblastic T-cell lymphoma express CD10. Blood 2002; 99: 627-33.
118. Xu Y, McKenna RW, Hoang MP, Collins RH, Kroft SH. Composite angioimmunoblastic T-cell lymphoma and diffuse large B-cell lymphoma: a case report and review of the literature. Am J Clin Pathol 2002; 118:848-54.
119. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 2003; 49:1049-58.
120. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985; 66: 848-58.
121. Benharroch D, Meguerian-Bedoyan Z, Lamant L, Amin C, Brugieres L, Terrier-Lacombe MJ, et al. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. Blood 1998; 91:2076-84.
122. Falini B. Anaplastic large cell lymphoma: pathological, molecular and clinical features. Br J Haematol 2001; 114:741-60.
123. Falini B, Bigerna B, Fizzotti M, Pulford K, Pileri SA, Delsol G, et al. ALK expression defines a distinct group of T/null lymphomas ("ALK lymphomas") with a wide morphological spectrum. Am J Pathol 1998; 53:875-86.
124. Stein H, Foss HD, Durkop H, Marafioti T, Delsol G, Pulford K, et al. CD30$^+$ anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000; 96:3681-95.
125. Pileri S, Falini B, Delsol G, Stein H, Baglioni P, Poggi S, et al. Lymphohistiocytic T-cell lymphoma (anaplastic large cell lymphoma CD30$^+$/Ki-1+ with a high content of reactive histiocytes). Histopathology 1990; 16:383-91.
126. Suzuki R, Seto M, Nakamura S, Nakagawa A, Hara K, Takeuchi K. Sarcomatoid variant of anaplastic large cell lymphoma with cytoplasmic ALK and α-smooth muscle actin expression: a mimic of inflammatory myofibroblastic tumor. Am J Pathol 2001; 159:383-4.
127. Falini B, Liso A, Pasqualucci L, Flenghi L, Ascani S, Pileri S, et al. CD30$^+$ anaplastic large-cell lymphoma, null type, with signet-ring appearance. Histopathology 1997; 30:90-2.
128. Rosso R, Paulli M, Magrini U, Kindl S, Boveri E, Volpato G, et al. Anaplastic large cell lymphoma, CD30/Ki-1 positive, expressing the CD15/Leu-M1 antigen. Immunohistochemical and morphological relationships to Hodgkin's disease. Virchows Arch A Pathol Anat Histopathol 1990; 416:229-35.
129. Schlette EJ, Medeiros LJ, Goy A, Lai R, Rassidakis GZ. Survivin expression predicts poorer prognosis in anaplastic large-cell lymphoma. J Clin Oncol 2004; 22:1682-8.
130. Shioda M, Mori S. [Identification of a t(2;5)-associated novel chimeric protein p80 and its clinicopathological significance in anaplastic large cell lymphoma]. Rinsho Ketsueki 1996; 37:422-5.
131. Pileri SA, Pulford K, Mori S, Mason DY, Sabattini E, Roncador G, et al. Frequent expression of the NPM-ALK chimeric fusion protein in anaplastic large-cell lymphoma, lympho-histiocytic type. Am J Pathol 1997; 150:1207-11.
132. Yee HT, Ponzoni M, Merson A, Goldstein M, Scarpa A, Chilosi M, et al. Molecular characterization of the t(2;5) (p23; q35) translocation in anaplastic large cell lymphoma (Ki-1) and Hodgkin's disease. Blood 1996; 87:1081-8.
133. Piccaluga PP, Ascani S, Fraternali Orcioni G, Piccioli M, Pileri A Jr, Falini B, et al. Anaplastic lymphoma kinase expression as a marker of malignancy. Application to a case of anaplastic large cell lymphoma with huge granulomatous reaction. Haematologica 2000; 85:978-81.
134. Gu TL, Tothova Z, Scheijen B, Griffin JD, Gilliland DG, Sternberg DW. NPM-ALK fusion kinase of anaplastic large-cell lymphoma regulates survival and proliferative signaling through modulation of FOXO3a. Blood 2004; 103:4622-9.
135. Horie R, Watanabe M, Ishida T, Koiwa T, Aizawa S, Itoh K, et al. The NPM-ALK oncoprotein abrogates CD30 signaling and constitutive NF-kappaB activation in anaplastic large cell lymphoma. Cancer Cell 2004; 5:353-64.
136. Cools J, Wlodarska I, Somers R, Mentens N, Pedeutour F, Maes B, et al. Identification of novel fusion partners of ALK, the anaplastic lymphoma kinase, in anaplastic large-cell lymphoma and inflammatory myofibroblastic tumor. Genes Chromosomes Cancer 2002; 34: 354-62.
137. Tort F, Pinyol M, Pulford K, Roncador G, Hernandez L, Nayach I, et al. Molecular characterization of a new ALK translocation involving moesin (MSN-ALK) in anaplastic large cell lymphoma. Lab Invest 2001; 81:419-26.
138. Onciu M, Behm FG, Raimondi SC, Moore S, Harwood EL, Pui CH, et al. ALK-positive anaplastic large cell lymphoma with leukemic peripheral blood involvement is a clinicopathologic entity with an unfavorable prognosis. Report of three cases and review of the literature. Am J Clin Pathol 2003; 120:617-25.
139. ten Berge RL, de Bruin PC, Oudejans JJ, Ossenkoppele GJ, van der Valk P, Meijer CJ. ALK-negative anaplastic large-cell lymphoma demonstrates similar poor prognosis to peripheral T-cell lymphoma, unspecified. Histopathology 2003; 43:462-9.
140. Cigudosa JC, Parsa NZ, Louie DC, Filippa DA, Jhanwar SC, Johansson B, et al. Cytogenetic analysis of 363 consecutively ascertained diffuse large B-cell lymphomas. Genes Chromosomes Cancer 1999; 25:123-33.
141. Nanjangud G, Rao PH, Hegde A, Teruya-Feldstein J, Donnelly G, Qin J, et al. Spectral karyotyping identifies new rearrangements, translocations, and clinical associations in diffuse large B-cell lymphoma. Blood 2002; 99:2554-61.
142. Bea S, Colomo L, Lopez-Guillermo A, Salaverria I, Puig X, Pinyol M, et al. Clinicopathologic significance and prognostic value of chromosomal imbalances in diffuse large B-cell lymphomas. J Clin Oncol 2004; 22:3498-506.
143. Pasqualucci L, Bereschenko O, Niu H, Klein U, Basso K, Guglielmino R, et al. Molecular pathogenesis of non-Hodgkin's lymphoma: the role of Bcl-6. Leuk Lymphoma. 2003; 44(Suppl 3):S5-12.
144. Staudt LM. Gene expression profiling of lymphoid malignancies. Annu Rev Med 2002; 53:303-18.
145. Basso K, Frascella E, Zanesco L, Rosolen A. Improved long-distance polymerase

chain reaction for the detection of t(8;14)(q24;q32) in Burkitt's lymphomas. Am J Pathol 1999; 155:1479-85.
146. Duyster J, Bai RY, Morris SW. Translocations involving anaplastic lymphoma kinase (ALK). Oncogene 2001; 20:5623-37.
147. Downing JR, Shurtleff SA, Zielenska M, Curcio-Brint AM, Behm FG, Head DR, et al. Molecular detection of the (2;5) translocation of non-Hodgkin's lymphoma by reverse transcriptase-polymerase chain reaction. Blood 1995; 85: 3416-22.
148. Trempat P, Villalva C, Xerri L, Armstrong F, Duplantier MM, Delsol G, et al. Gene Expression profiling in anaplastic large cell lymphoma and hodgkin's disease. Leuk Lymphoma 2004; 45:2001-6.
149. Remstein ED, Kurtin PJ, Buno I, Bailey RJ, Proffitt J, Wyatt WA, et al. Diagnostic utility of fluorescence in situ hybridization in mantle-cell lymphoma. Br J Haematol 2000; 110:856-62.
150. Kohlhammer H, Schwaenen C, Wessendorf S, Holzmann K, Kestler HA, Kienle D, et al. Genomic DNA-chip hybridization in t(11;14)-positive mantle cell lymphomas shows a high frequency of aberrations and allows a refined characterization of consensus regions. Blood 2004; 104:795-801.
151. Howard OM, Gribben JG, Neuberg DS, Grossbard M, Poor C, Janicek MJ, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol 2002; 20:1288-94.
152. Hui P, Howe JG, Crouch J, Nimmakayalu M, Qumsiyeh MB, Tallini G, et al. Real-time quantitative RT-PCR of cyclin D1 mRNA in mantle cell lymphoma: comparison with FISH and immunohistochemistry. Leuk Lymphoma 2003; 44: 1385-94.
153. Yatabe Y, Suzuki R, Tobinai K, Matsuno Y, Ichinohasama R, Okamoto M, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: a clinicopathologic comparison of cyclin D1-positive MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood 2000; 95:2253-61.
154. Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003; 3:185-97.
155. Andersson T, Lindgren PG, Elvin A. Ultrasound guided tumour biopsy in the anterior mediastinum. An alternative to thoracotomy and mediastinoscopy. Acta Radiol 1992, 33:423-6.
156. Zinzani PL, Corneli G, Cancellieri A, Magagnoli M, Lacava N, Gherlinzoni F, et al. Core needle biopsy is effective in the initial diagnosis of mediastinal lymphoma. Haematologica 1999; 84:600-3.
157. Pappa VI, Hussain HK, Reznek RH, Whelan J, Norton AJ, Wilson AM, et al. Role of image-guided core-needle biopsy in the management of patients with lymphoma. J Clin Oncol 1996; 14:2427-30.
158. Zinzani PL, Colecchia A, Festi D, Magagnoli M, Larocca A, Ascani S, et al. Ultrasound-guided core-needle biopsy is effective in the initial diagnosis of lymphoma patients. Haematologica 1998; 83:989-92.
159. The international non-Hodgkin's lymphoma prognostic factors project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329:987-94.
160. Cheson BD, Schumann JL, Schumann GB. Urinary cytodiagnostic abnormalities in 50 patients with non-Hodgkin's lymphomas. Cancer 1984; 54:1914-9.
161. Altehoefer C, Blum U, Bathmann J, Wustenberg C, Uhrmeister P, Laubenberger J, et al. Comparative diagnostic accuracy of magnetic resonance imaging and immunoscintigraphy for detection of bone marrow involvement in patients with malignant lymphoma. J Clin Oncol 1997; 15:1754-60.
162. Zinzani PL, Magagnoli M, Chierichetti F, Zompatori M, Garraffa G, Bendandi M, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. Ann Oncol 1999; 10:1181-4.
163. Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, et al. Whole-body positron emission tomography using 18 F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999; 94:429-33.
164. Spaepen K, Stroobants S, Dupont P, Vandenberghe P, Thomas J, de Groot T, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002; 13:1356-63.
165. Zinzani PL, Fanti S, Battista G, Tani M, Castellucci P, Stefoni V, et al. Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients. Br J Cancer 2004; 91:850-4.
166. Crellin AM, Hudson BV, Bennett MH, Harland S, Hudson GV. Non-Hodgkin's lymphoma of the testis. Radiother Oncol 1993, 27:99-106.
167. Tio TL, den Hartog Jager FC, Tytgat GN. Endoscopic ultrasonography in detection and staging of gastric non-Hodgkin's lymphoma. Scand J Gastroenterol Suppl 1986; 123:52-8.
168. Anderson KC, Kaplan WD, Leonard RC, Skarin AT, Canellos GP. Role of 99mTc methylene diphosphonate bone imaging in the management of lymphoma. Cancer Treat Rep 1985; 69:1347-51.
169. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's disease staging classification. Cancer Res 1971; 31: 1860-1.
170. Musshoff K. Therapy and prognosis of two different forms of organ involvement in cases of malignant lymphoma (Hodgkin's disease, reticulum cell sarcoma, lymphosarcoma) as well as a report about stage division in these diseases. Klin Wochenschr 1970; 48:673-8.
171. Coiffier B, Shipp MA, Cabanillas F, Crowther D, Armitage JO, Canellos GP. Report of the first workshop on prognostic factors in large-cell lymphomas. Ann Oncol 1991; 2:213-7.
172. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:1937-47.
173. Kwak LW, Halpern J, Olshen RA, Horning SJ. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol 1990; 8:963-77.
174. Connors JM, Klimo P, Fairey RN, Voss N. Brief chemotherapy and involved field radiation therapy for limited-stage, histologically aggressive lymphoma. Ann Intern Med 1987; 107:25-30.
175. Tondini C, Zanini M, Lombardi F, Bengala C, Rocca A, Giardini R, et al. Combined modality treatment with primary CHOP chemotherapy followed by locoregional irradiation in stage I or II histologically aggressive non-Hodgkin's lymphomas. J Clin Oncol 1993; 11:720-5.
176. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002-6.
177. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:235-42.
178. Pfreundschuh M, Trümper L, Devinder G, Österborg A, Pettengell R, Trneny M, et al. First analysis of the completed Mabthera International (MinT) trial in young patients with low risk diffuse large B-cell lymphoma (DLBCL): addition of rituximab to a CHOP-like regimen significantly improves outcome of all patients with the identification of a very favorable subgroup with IPI=0 and no bulky disease(abstract). Blood 2004; 104:8a.
179. Gordon LI, Molina A, Witzig T, Emmanouilides C, Raubtischek A, Darif M, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. Blood 2004; 103: 4429-31.
180. Jones, R.J. Ambinder RF, Piantadosi S, Santos GW. Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. Blood 1991; 77:649-53.
181. Ratanatharathorn V, Uberti J, Karanes C, Abella E, Lum LG, Momin F, et al. Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. Blood 1994; 84: 1050-5.
182. Corradini P. Dodero A, Zallio F, Caracciolo D, Casini M, Bregni M, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004; 22:2172-6.
183. DeVita VT Jr, Canellos GP,Chabner B, Schein P, Hubbard SP, Young RC. et al.

Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet 1975; 1:248-50.
184. Blayney DW, Le Blanc MI, Grogan T, Gaynor ER, Chapman RA, Spiridonidis CH, et al. Dose intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine and prednisone may improve survival in intermediate-and high grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003; 21:2466-73.
185. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rudolph C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.
186. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rube C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004; 104:634-41.
187. Tilly E, Lepage E, Coiffier B, Blanc M, Herbrecht R, Bosly A, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 2003; 102: 4284-9.
188. Philip T, Armitage JO, Spitzer G, Chauvin F, Jagannath S, Cahn JY, et al. High dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate grade or high grade non-Hodgkin's lymphoma. N Engl J Med 1987; 316:1493-8.
189. Martelli M, Vignetti M, Zinzani PL, Gherlinzoni F, Meloni G, Fiacchini M, et al. High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin and cytarabine in aggressive non Hodgkin's lymphoma with partial response to front line chemotherapy: a prospective randomized Italian multicenter study. J Clin Oncol 1996; 14:534-42.
190. Haioun C, Lepage E, Gisselbrecht C, Salles G, Coiffier B, Brice P, et al. Survival benefit of high dose therapy in poor risk aggressive non Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol-a Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000; 18:3025-30.
191. Gianni AM, Bregni M, Siena S, Brambilla C, Di Nicola M, Lombardi F, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997; 336: 1290-7.
192. Greb A, Schiefer DH, Bohilius J, Schwarzer G, Engert A. High dose chemotherapy with autologous stem cell support is not superior to conventional dose chemotherapy in the first line of aggressive non-hodgkin lymphoma – results of a comprehensive meta-analysis(abstract). Blood 2004; 104:263a.
193. Strehl J, Mey U, Glasmacher A, Djulbegovic B, Mayr C, Gorschluter M, et al. High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis. Haematologica 2003; 88:1304-15.
194. Martelli M, Gherlinzoni F, De Renzo A, Zinzani PL, De Vivo A, Cantonetti M et al. Early autologous stem cell transplantation versus conventional chemotherapy as front-line therapy in high risk, aggressive non Hodgkin's lymphoma: an Italian multicenter randomized trial. J Clin Oncol 2003; 21:1255-62.
195. Milpied N, Deconinck E, Gaillard F, Delwail V, Foussard C, Berthou C, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med 2004; 350:1287-95.
196. Vose JM, Link BK, Grossbard ML, Czuczman M, Grillo-Lopez A, Benyunes M, et al. Long term follow-up of a phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated aggressive non-Hodgkin's lymphoma (NHL) (abstract). Blood 2002; 100:361a.
197. Coiffier B, Feugier P, Sebban C, Bouabdallah R, Delwail V, Tilly H, et al. Long term results of the GELA study, R-CHOP vs CHOP in elderly patients with diffuse large-B-cell lymphoma (abstract). Bood 2004; 104:388a.
198. Mounier N, Briere J, Gisselbrecht C, Emile JF, Lederlin P, Sebban C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003;101:4279-84.
199. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, MacPherson N, O Reilly SE, et al. Introduction of combined CHOP-rituximab therapy dramatically Improved outcome of diffuse large B-cell lymphoma (DLBC) in British Columbia (BC). J Clin Oncol 2005; 23:5027-33.
200. Habermann TM, Weller EA, Morrison VA, Cassileth PA, Cohn JB, Dakhil SR, et al. Phase III trial of rituximab-CHOP (R-CHOP) vs. CHOP with a second randomization to maintenance rituximab (MR) or observation in patients 60 years of age and older with diffuse large B-cell lymphoma (DLBCL) (abstract). Blood 2003;102:6a.
201. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998; 339:21-6.
202. Reyes F, Lepage E, Ganem G, Molina TJ, Brice P, Coiffier B,et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 2005;352:1197-205
203. Shenkier TN, Voss N, Fairey R, Gascoyne RD, Hoskins P, Klasa R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. J Clin Oncol 2002; 20:197-204.
204. Schmoll H. Review of etoposide single-agent activity. Cancer Treat Rev 1982; 9 (Suppl):21-30.
205. Shipp MA, Takvorian RC, Canellos GP. High-dose cytosine arabinoside. Active agent in treatment of non-Hodgkin's lymphoma. Am J Med 1984; 77:845-50.
206. Cavalli F, Jungi WF, Nissen NI, Pajak TF, Coleman M, Holland JF, et al. Phase II trial of cis-dichlorodiammineplatinum (II) in advanced malignant lymphoma: a study of the Cancer and Acute Leukemia Group B. Cancer 1981; 48:1927-30.
207. Bajetta E, Buzzoni R, Valagussa P, Bonadonna G. Mitoxantrone: an active agent in refractory non-Hodgkin's lymphomas. Am J Clin Oncol 1988; 11:100-3.
208. Case DC Jr, Anderson J, Ervin TJ, Gottlieb A. Phase II trial of ifosfamide and mesna in previously treated patients with non-Hodgkin's lymphoma: Cancer and Leukemia Group B study 8552. Hematol Oncol 1991; 9:189-96.
209. Cabanillas F. Ifosfamide combinations in lymphoma. Semin Oncol 1990; 17(2 Suppl 4):58-62.
210. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose ara-C and dexamethasone (DHAP). Blood 1988; 71:117-22.
211. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, et al. ESHAP-an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994; 12:1169-76.
212. Neidhart JA, Kubica R, Stidley C, Pfile J, Clark D, Rinehart J. Multiple cycles of dose-intensive cyclophosphamide, etoposide, and cisplatinum (DICEP) produce durable responses in refractory non-Hodgkin's lymphoma. Cancer Invest 1994; 12:1-11.
213. Goss P, Shepherd F, Scott JG, Baker M, Sutton D, Sutcliffe S. DICE (dexamethasone, ifosfamide, cisplatin, etoposide) as salvage therapy in non-Hodgkin's lymphomas. Leuk Lymphoma 1995; 18:123-9.
214. Hamlin PA, Zelenetz AD, Kewalramani T, Qin J, Satagopan JM, Verbel D, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2003; 102:1989-96.
215. Zinzani PL, Tani M, Molinari AL, Stefoni V, Zuffa E, Alinari L, et al. Ifosfamide, epirubicin and etoposide regimen as salvage and mobilizing therapy for relapsed/refractory lymphoma patients. Haematologica 2002; 87:816-21.
216. Lichtman SM, Niedzwiecki D, Barcos M, Carlisle TL, Cooper MR, Jhonson JL, et al. Phase II study of infusional chemotherapy with doxorubicin, vincristine and etoposide plus cyclophosphamide and prednisone (I-CHOPE) in resistant diffuse aggressive non-Hodgkin's lymphoma: CALGB 9255. Cancer and Leukemia Group B. Ann Oncol 2000; 11:1141-6.
217. Gutierrez M, Chabner BA, Pearson D, Steinberg SM, Jaffe ES, Cheson BD, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. J Clin Oncol 2000; 18:3633-42.

218. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92:1927-32.
219. Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000; 96:1259-66.
220. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999; 17:3793-803.
221. Petersen FB, Appelbaum FR, Hill R, Fisher LD, Bigelow CL, Sanders JE, et al. Autologous marrow transplantation for malignant lymphoma: a report of 101 cases from Seattle. J Clin Oncol 1990; 8: 638-47.
222. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, et al. High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. J Clin Oncol 1993; 11:1846-51.
223. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 1995; 13:588-95.
224. Stockerl-Goldstein KE, Horning SJ, Negrin RS, Chao NJ, Hu WW, Long GD, et al. Influence of preparatory regimen and source of hematopoietic cells on outcome of autotransplantation for non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 1996; 2:76-85.
225. Caballero MD, Rubio V, Rifon J, Heras I, Garcia-Sanz R, Vazquez L, et al. BEAM chemotherapy followed by autologous stem cell support in lymphoma patients: analysis of efficacy, toxicity and prognostic factors. Bone Marrow Transplant 1997; 20:451-8.
226. Rapoport AP, Lifton R, Constine LS, Duerst RE, Abboud CN, Liesveld JL, et al. Autotransplantation for relapsed or refractory non-Hodgkin's lymphoma (NHL): long-term follow-up and analysis of prognostic factors. Bone Marrow Transplant 1997; 19:883-90.
227. Stiff PJ, Dahlberg S, Forman SJ, McCall AR, Horning SJ, Nademanee AP, et al. Autologous bone marrow transplantation for patients with relapsed or refractory diffuse aggressive non-Hodgkin's lymphoma: value of augmented preparative regimens-a Southwest Oncology Group trial. J Clin Oncol 1998; 16:48-55.
228. Popat U, Przepiork D, Champlin R, Pugh W, Amin K, Mehra R, et al. High-dose chemotherapy for relapsed and refractory diffuse large B-cell lymphoma: mediastinal localization predicts for a favorable outcome. J Clin Oncol 1998; 16:63-9.
229. Zinzani PL, Tani M, Gabriele A, Gherlinzoni F, De Vivo A, Ricci P, et al. High-dose therapy with autologous transplantation for aggressive non-Hodgkin's lymphoma: the Bologna experience. Leuk Lymphoma 2004; 45:321-6.
230. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333:1540-5.
231. Blay J, Gomez F, Sebban C, Bachelot T, Biron P, Guglielmi C, et al. The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. Parma Group. Blood 1998; 92: 3562-8.
232. Shipp MA, Abeloff MD, Antman KH, Carroll G, Hagenbeek A, Loeffler M, et al. International consensus conference on high-dose therapy with hematopoietic stem cell transplantation in aggressive non-hodgkin's lymphomas: report of the jury. J Clin Oncol 1999; 17:423-9.
233. Hahn T, Wolff SN, Czuczman M, Fisher RI, Lazarus HM, Vose J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant 2001; 7:308-31.
234. Gallagher CJ, Gregory WM, Jones AE, Stansfeld AG, Richards MA, Dhaliwal HS, et al. Follicular lymphoma: prognostic factors for response and survival. J Clin Oncol 1986; 4:1470-80.
235. Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol 1997; 15: 1587-94.
236. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995; 13:1726-33.
237. Williams CD, Harrison CN, Lister TA, Norton AJ, Blystad AK, Coiffier B, et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. J Clin Oncol 2001; 19:727-35.
238. Friedberg J, Neuberg D, Gribben J, Mauch P, Anderson K, Soiffer R, et al. Autologous bone marrow transplantation following histologic transformation of indolent B cell non-Hodgkin's lymphoma. Blood 1998;92: 727a(abstract 2982).
239. Foran JM, Apostolidis J, Papamichael D, Norton AJ, Matthews J, Amess JA, et al. High-dose therapy with autologous haematopoietic support in patients with transformed follicular lymphoma: a study of 27 patients from a single centre. Ann Oncol 1998; 9:865-9.
240. Vose JM, Wahl, Saleh M, Rohatiner AZ, Knox SJ, Radford JA, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000; 18: 1316-23.
241. Leonard J, Zelenetz A, Vose J, Coleman M, Kaminski M. Bexxar induces durable complete response in patients with relapsed (REL) and refractory (REF) low-grade (LG) or transformed (LG) non-Hodgkin's lymphoma (NHL) confirmed by masked independent review. Ann Oncol 2002; 13 (abstract 297).
242. Witzig TE, White CA, Gordon LI, Wiseman GA, Emmanouilides C, Murray JL, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. J Clin Oncol 2003; 21:1263-70.
243. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20:2453-63.
244. Meusers P, Engelhard M, Bartels H, Binder T, Fulle HH, Gorg K, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis. Hematol Oncol 1989; 7:365-80.
245. Zucca E, Fontana S, Roggero E, Pedrinis E, Pampallona S, Cavalli F. Treatment and prognosis of centrocytic (mantle cell) lymphoma: a retrospective analysis of twenty-six patients treated in one institution. Leuk Lymphoma 1994; 13: 105-10.
246. Norton AJ, Matthews J, Pappa V, Shamash J, Love S, Rohatiner AZ, et al. Mantle cell lymphoma: natural history defined in a serially biopsied population over a 20-year period. Ann Oncol 1995; 6:249-56.
247. Vandenberghe E, De Wolf-Peeters C, Vaughan Hudson G, Vaughan Hudson B, Pittaluga S, Anderson L, et al. The clinical outcome of 65 cases of mantle cell lymphoma initially treated with non-intensive therapy by the British National Lymphoma Investigation Group. Br J Haematol 1997; 99:842-7.
248. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16:2780-95.
249. Cuneo A, Bigoni R, Negrini M, Bullrich F, Veronese ML, Roberti MG, et al. Cytogenetic and interphase cytogenetic characterization of atypical chronic lymphocytic leukemia carrying BCL1 translocation. Cancer Res 1997; 57:1144-50.
250. Bosch F. Lopez-Guillermo A, Campo E, Ribera JM, Conde E, Piris MA, et al. Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. Cancer 1998; 82:567-75.
251. Zucca E, Roggero E, Pinotti G, Pedrinis E, Cappella C, Venco A, Cavalli F, et al. Patterns of survival in mantle cell lymphoma. Ann Oncol 1995; 6:257-62.
252. Velders GA, Kluin-Nelemans JC, De Boer CJ, Hermans J, Noordijk EM, Schuuring E, et al. Mantle-cell lymphoma: a population-based clinical study. J Clin Oncol 1996; 14:1269-74.

253. Fisher RI, Dahlberg S, Nathwani BN, Banks PM, Miller TP, Grogan TM et al. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. Blood 1995; 85:1075-82.
254. Shivdasani RA, Hess JL, Skarin AT, Pinkus GS. Intermediate lymphocytic lymphoma: clinical and pathologic features of a recently characterized subtype of non-Hodgkin's lymphoma. J Clin Oncol 1993; 11:802-11.
255. Campo E, Raffeld M, Jaffe ES. Mantle-cell lymphoma. Semin Hematol 1999; 36:115-27.
256. Ruskone-Fourmestraux A, Delmer A, Lavergne A, Molina T, Brousse N, Audouin J, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: prospective clinicopathologic study of 31 cases. Groupe D'etude des Lymphomes Digestifs. Gastroenterology 1997; 112:7-16.
257. O'Connor O.A., The emerging role of bortezomib in the treatment of indolent non-Hodgkin's and mantle cell lymphomas. Curr Treat Options Oncol 2004; 5:269-81.
258 Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005; 23:667-75.
259. Lenz G, Dreyling M, Hoster E, Wormann B, Duhrsen U, Metzner B, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005; 23: 1984-92.
260. Kaufmann H, Raderer M, Wohrer S, Puspok A, Bankier A, Zielinski C, et al. Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma. Blood 2004; 104:2269-71.
261. Gianni AM, Magni M, Martelli M, Di Nicola M, Carlo-Stella C, Pilotti S, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and *in vivo* rituximab-purged stem cell autografting (R-HDS regimen). Blood 2003; 102:749-55.
262. Romaguera JE, et al. Mantle cell lymphoma (MCL) - Update on results after R-HCVAD without stem cell transplant. Ann Oncol 2002.
263. Gopal AK, Rajendran JG, Petersdorf SH, et al. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. Blood 2002;99:3158-316.
264. Hoelzer D, Gokbuget N. Treatment of lymphoblastic lymphoma in adults. Best Pract Res Clin Haematol 2002; 15:713-28.
265. Thomas DA, O'Brien S, Cortes J, Giles FJ, Faderl S, Verstovsek S, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. Blood 2004; 104: 1624-30.
266. Levine JE, Harris RE, Loberiza FR Jr, Armitage JO, Vose JM, Van Besien K, et al. A comparison of allogeneic and autologous bone marrow transplantation for lymphoblastic lymphoma. Blood 2003; 101:2476-82.
267. Dabaja BS, Ha CS, Thomas DA, Wilder RB, Gopal R, Cortes J, et al. The role of local radiation therapy for mediastinal disease in adults with T-cell lymphoblastic lymphoma. Cancer 2002; 94: 2738-44.
268. Levine AM. Challenges in the management of Burkitt's lymphoma. Clin Lymphoma 2002; 3(Suppl 1):S19-25.
269. Evens AM, Gordon LI. Burkitt's and Burkitt-like lymphoma. Curr Treat Options Oncol 2002; 3: 291-305.
270. Kasamon YL, Swinnen LJ. Treatment advances in adult Burkitt's lymphoma and leukemia. Curr Opin Oncol 2004; 16:429-35
271. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood 2004; 104:3009-20.
272. Soussain C, Patte C, Ostronoff M, Delmer A, Rigal-Huguet F, Cambier N, et al. Small non-cleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. Blood 1995; 85:664-74.
273. Hoelzer D, Ludwig WD, Thiel E, Gassmann F, Loffler H, Fonatsch C, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. Blood 1996; 87:495-508.
274. Magrath I, Adde M, Shad A, Venzon D, Seibel N, Gootember J, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996; 14: 925-34.
275. Mead GM, Sydes MR, Walewski J, Grigg A, Hatton CS, Pescosta N, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002; 13:1264-74.
276. Lacasce A, Howard O, Lib S, Fisher D, Weng A, Neuberg D, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004; 45:761-7.
277. Smeland S, Blystad AK, Kvaloy SO, Ikonomou IM, Delabie J, Kvalheim G, et al. Treatment of Burkitt's/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. Ann Oncol 2004; 15:1072-8.
278. Thomas DA, Cortes J, O'Brien S, Pierce S, Faderl S, Albitar M, et al. Hyper- CVAD program in Burkitts's type adult acute lymphoblastic leukemia. J Clin Oncol 1999; 17:2461-70.
279. Lee EJ, Petroni G, Schiffer CA, Freter CE, Johnson JL, Barcos M, et al. Brief duration, high intensity chemotherapy for patients with small noncleaved-cell lymphoma or FAB L3 acute lymphocytic leukemia: results of Cancer and Leukemia Group B study 9251. J Clin Oncol 2001; 19:4014-22.
280. Rizzieri DA, Johnson JL, Niedzwiecki D, Lee EJ, Vardiman JW, Powell BL, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251. Cancer 2004; 100:1438-48.
281. Di Nicola M, Carlo-Stella C, Mariotti J, Devizzi L, Massimino M, Cabras A, et al. High response rate and manageable toxicity with an intensive, short-term chemotherapy programme for Burkitt's lymphoma in adults. Br J Haematol 2004; 126:815-20.
282. Sweetenham JW, Pearce R, Taghipour G, Blaise D, Gisselbrecht C, Goldstone AH. Adult Burkitt's and Burkitt's-like non-Hodhkin's lymphoma - outcome for patients treated with high-dose therapy and autologous stem-cell transplantation in first remission or at relapse: results of the European Group for Blood and Marrow Transplantation.J Clin Oncol 1996; 14:2465-72.
283. Peniket AJ, Ruiz de Elvira MC, Taghipour G, Cordonnier C, Gluckman E, de WitteT, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003; 31:667-78.
284. Hoelzer D, Baur KH, Giagounidis A, Ludwig WD, Glasmacher A, Duehrsen U, et al. Short intensive chemotherapy with rituximab seems successful in Burkitt NHL, mature B-ALL and other high grade B-NHL(abstract). Blood 2003;102:70a.
285. Thomas DA, Cortes J, Faderl S, O'Brien S, Beran M, Koller C, et al. Outcome with the hyper-CVAD and rituximab regimen in Burkitt (BL) and Burkitt-like (BLL) leukemia/lymphoma (abstract). Blood 2004; 104:901a.
286. Gisselbrecht C, Gaulard P, Lepage E, Coiffier B, Briere J, Haioun C, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998; 92:76-82.
287. Rodriguez J, Munsell M, Yazji S, Hagemeister FB, Younes A, Andersson B, et al. Impact of high-dose chemotherapy on peripheral T-cell lymphomas. J Clin Oncol 2001; 19:3766-70.
288. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003; 120:978-85.
289. Tarella C, Cuttica A, Caracciolo D, Zallio F, Ricca I, Bergui L, et al. High-dose sequential (HDS) chemotherapy for high-risk non-Hodgkin's lymphoma: long-term analysis and future developments. Ann Hematol 2001; 80(Suppl 3): B123-6.
290. Cortelazzo S, Tarella C, Dodero A, Gianni AM, Zallio F, Zanni M, et al. Long-term follow-up of high-dose chemotherapy followed by autologous stem cell transplantation in peripheral T-cell lymphomas at diagnosis (abstract). Blood 2004; 104:909a.
291. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-

cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103:2474-9.
292. Enblad G, Hagberg H, Erlanson M, Lundin J, MacDonald AP, Repp R, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004; 103:2920-4.
293. Dotti G, Fiocchi R, Motta T, Gamba A, Gotti E, Gridelli B, et al. Epstein-Barr virus-negative lymphoproliferate disorders in long-term survivors after heart, kidney, and liver transplant. Transplantation 2000; 69:827-33.
294. Draoua HY, Tsao L, Mancini DM, Addonizio LJ, Bhagat G, Alobeid B. T-cell post-transplantation lymphoproliferative disorders after cardiac transplantation: a single institutional experience. Br J Haematol 2004; 127:429-32.
295. Rajakariar R, Bhattacharyya M, Norton A, Sheaff M, Cavenagh J, Raftery MJ, et al. Post transplant T-cell lymphoma: a case series of four patients from a single unit and review of the literature. Am J Transplant 2004; 4:1534-8.
296. Cerri M, Capello D, Muti G, Rambaldi A, Paulli M, Gloghini A, et al. Aberrant somatic hypermutation in post-transplant lymphoproliferative disorders. Br J Haematol 2004; 127:362-4.
297. Dotti G, Rambaldi A, Fiocchi R, Motta T, Torre G, Viero P, et al. Anti-CD20 antibody (rituximab) administration in patients with late occurring lymphomas after solid organ transplant. Haematologica 2001; 86:618-23.
298. Cook RC, Connors JM, Gascoyne RD, Fradet G, Levy RD. Treatment of post-transplant lymphoproliferative disease with rituximab monoclonal antibody after lung transplantation. Lancet 1999; 354:1698-9.
299. Dotti G, Fiocchi R, Motta T, Mammana C, Gotti E, Riva S, et al. Lymphomas occurring late after solid-organ transplantation: influence of treatment on the clinical outcome. Transplantation 2002; 74: 1095-102.
300. Comoli P, Labirio M, Basso S, Baldanti F, Grossi P, Furione M, et al. Infusion of autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. Blood 2002; 99:2592-8.
301. Heslop HE, Savoldo B, Rooney CM. Cellular therapy of Epstein-Barr-virus-associated post-transplant lymphoproliferative disease. Best Pract Res Clin Haematol 2004; 17:401-13.
302. Mamzer-Bruneel MF, Lome C, Morelon E, Levy V, Bourquelot P, Jacobs F, et al. Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: a report of 16 cases observed in a single center. J Clin Oncol 2000; 18:3622-32.
303. Chopra R, Goldstone AH, Pearce R, Philip T, Petersen F, Appelbaum F, et al. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. J Clin Oncol 1992; 10:1690-5.
304. Bierman PJ, Sweetenham JW, Loberiza FR Jr, Taghipour G, Lazarus HM, Rizzo JD, et al. Syngeneic hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma: a comparison with allogeneic and autologous transplantation - the Lymphoma Working Committee of the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. J Clin Oncol 2003; 21: 3744-53.
305. Dhedin N, Giraudier S, Gaulard P, Esperou H, Ifrah N, Michallet M, et al. Allogeneic bone marrow transplantation in aggressive non-Hodgkin's lymphoma (excluding Burkitt and lymphoblastic lymphoma): a series of 73 patients from the SFGM database. Societé Francaise de Greffe de Moelle. Br J Haematol 1999; 107:154-61.
306. Khouri IF, Saliba RM, Lee M-S, Giralt S,Younes A, Couriel D et al. Nonablative allogeneic stem cell transplantation (AST) for non-Hodgkin's lymphoma (NHL): improved outcome with low incidence of acute GVHD and treatment related mortality. Blood 2001; 98(Suppl. 1):416a.
307. Robinson SP, Goldstone AH, Mackinnon S, Carella A, Russell N, de Elvira CR, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002; 100:4310-6.
308. Morris E, Thomson K, Craddock C, Mahendra P, Milligan D, Cook G, et al. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. Blood 2004; 104:3865-71.
309. Levine JE, Harris RE, Loberiza FR, Jr., Armitage JO, Vose JM, Van Besien K, et al. A comparison of allogeneic and autologous bone marrow transplantation for lymphoblastic lymphoma. Blood 2003; 101:2476-82.
310. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994; 12:2471-508.
311. Hackshaw A, Sweetenham J, Knight A. Are prophylactic haematopoietic growth factors of value in the management of patients with aggressive non-Hodgkin's lymphomas? Br J Cancer 2004; 90:1302-5.
312. Bohlius J, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev 2004; 3:CD003189.
313. Scott S. Identification of cancer patients at high risk of febrile neutropenia. Am J Health Syst Pharm 2002; 59(15 Suppl 4):S16-9.
314. Lyman GH, Morrison VA, Dale DC, Crawford J, Delgado DJ, Fridman M. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003; 44:2069-76.
315. Zelenetz AD. Risk models for chemotherapy-induced neutropenia in non-Hodgkin's lymphoma. Oncology (Huntingt) 2003; 17(11 Suppl 11):21-6.
316. Scott SD, Chrischilles EA, Link BK, Delgado DJ, Fridman M, Stolshek BS. Days of prophylactic filgrastim use to reduce febrile neutropenia in patients with non-Hodgkin's lymphoma treated with chemotherapy. J Manag Care Pharm 2003; 9(2 Suppl):15-21.
317. Doorduijn JK, Buijt I, van der Holt B, van Agthoven M, Sonneveld P, Uyl-de Groot CA. Economic evaluation of prophylactic granulocyte colony stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma. Haematologica 2004; 89: 1109-17.
318. Wolf T, Densmore JJ. Pegfilgrastim use during chemotherapy: current and future applications. Curr Hematol Rep 2004; 3:419-23.
319. Crawford J. Once-per-cycle pegfilgrastim (Neulasta) for the management of chemotherapy-induced neutropenia. Semin Oncol 2003; 30(4 Suppl 13):24-30.
320. Vose JM, Crump M, Lazarus H, Emmanouilides C, Schenkein D, Moore J, et al. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. J Clin Oncol 2003; 21: 514-9.
321. Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003; 14:29-35.
322. Grigg A, Solal-Celigny P, Hoskin P, Taylor K, McMillan A, Forstpointner R, et al. Open-label, randomized study of pegfilgrastim vs. daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma. 2003; 44:1503-8.
323. Musto P, Scalzulli PR, Melillo L, Nobile M, Dell'Olio M, La Sala A, et al. Peg-filgrastim after autologous peripheral blood stem cell transplantation in hematological malignancies (abstract). Blood 2004; 104:384b.
324. Staber PB, Holub R, Linkesch M, Schimdt H, Neumeister P. Fixed-dose single administration of peg-filgrastim vs daily filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2005; 35:889-93.
325. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 2004; 22:4302-11.
326. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennet CL, Cella BD, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. Blood 2002; 100:2303-20.
327. Bokemeyer C, Aapro MS, Courdi A, Fou-

bert J, Link H, Osterborg A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer 2004; 40:2201-16.
328. Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennet C, et al. Erythropoietin for patients with malignant disease. Cochrane Database Syst Rev 2004; (3):CD003407.
329. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001; 19:2865-74.
330. Osterborg A, Brandberg Y, Molostova V, Iosava G, Abdulkadyrov K, Hedenus M, et al. Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin β, in hematologic malignancies. J Clin Oncol 2002; 20:2486-94.
331. Cazzola M, Beguin Y, Kloczko J, Spicka I, Coiffier B. Once-weekly epoetin β is highly effective in treating anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoietin production. Br J Haematol 2003; 122:386-93.
332. Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, et al. Darbepoetin α 20000161 Study Group. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol 2003;122: 394-403.
333. Dammacco F, Marschner N, Gambacorta M. Epoetin α improves hemoglobin levels and quality of life parameters in anemic patients with hematological malignancies receiving chemotherapy: interim results from the EPOLYM trial. Hematol J 2004; 5(Suppl 2):S177.
334. Strauss DJ. Epoetin α therapy for patients with hematological malignancies and mild anemia. Clin Lymphoma 2003; 4(Suppl. 1):S13-7.
335. Baron F, Frere P, Fillet G, Beguin Y. Recombinant human erythropoietin therapy is very effective after an autologous peripheral blood stem cell transplant when started soon after engraftment. Clin Cancer Res 2003; 9:5566-72.
336. Smith R. Applications of darboepoietin-α, a novel erythropoiesis-stimulating protein, in oncology. Curr Opin Hematol 2002; 9:228-33.
337. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004; 22:1301-7.
338. Luksenburg H, Weir A, Wager R. Safety concerns with Aranesp (darbepoetin α) Amgen, Inc. and Procrit (epoetin α) Ortho Biotech, L.P., for the treatment of anemia associated with cancer chemotherapy. FDA briefing document, May 4, 2004.
339. Osterborg A, Hellmann A, Steegmann JL, Couban S. CERA (continuous erythropoietin receptor activator): dose-response trial of subcutaneous (SC) administration once every 3 weeks (Q3W) to patients with aggressive non-Hodgkin's lymphoma and anemia receiving chemotherapy (abstract). Blood 2004; 104:142b.
340. Hudis CA, Van Belle S, Chang J, Muenstedt K. rHuEPO and treatment outcomes: the clinical experience. Oncologist 2004; 9(Suppl. 5):55-69.
341. Anonymous. Epoetin: for better or for worse? Lancet Oncol 2004; 5:1.
342. Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003; 362:1255-60.
343. Leyland-Jones B, BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 2003; 4:459-60.
344. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol 2003; 122: 10-23.
345. Reynolds CH. Clinical efficacy of rhIL-11. Oncology (Huntingt) 2000;14(9 Suppl 8):32-40.
346. Cairo MS, Davenport V, Bessmertny O, Goldman SC, Berg SL, Kreissman SG, et al. Phase I/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. Br J Haematol 2005; 128:49-58.
347. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. Blood 2002; 100:3457-69.
348. Broudy VC, Lin NL. AMG531 stimulates megakaryopoiesis *in vitro* by binding to Mpl. Cytokine 2004; 25:52-60.
349. Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther 2004; 76:628-38.
350. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004; 127: 3-11.
351. Coiffier B, Mounier N, Bologna S, Ferme C, Tilly H, Sonet A, et al Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes del'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol 2003: 21:4402-6.
352. Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 2004; 351:2590-8.
353. Stebbing J, Marvin V, Bower M. The evidence-based treatment of AIDS-related non-Hodgkin's lymphoma. Cancer Treat Rev 2004; 30:249-53.
354. Persico M, De Marino F, Russo GD, Morante A, Rotoli B, Torella R, et al. Efficacy of lamivudine to prevent hepatitis reactivation in hepatitis B virus-infected patients treated for non-Hodgkin lymphoma. Blood 2002; 99:724-5.
355. Leaw SJ, Yen CJ, Huang WT, Chen TY, Su WC, Tsao CJ. Preemptive use of interferon or lamivudine for hepatitis B reactivation in patients with aggressive lymphoma receiving chemotherapy. Ann Hematol 2004; 83:270-5.
356. Hermine O, Lefrere F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002; 347:89-94.
357. Kelaidi C, Rollot F, Park S, Tulliez M, Christoforov B, Calmus Y, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphoma. Leukemia 2004; 18:1711-6.
358. Vallisa D, Bernuzzi P, Arcaini L, Sacchi S, Callea V, Marasca R, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005; 23: 468-73.