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Diffuse large B-cell lymphoma: the curable disease?

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A B S T R A C T

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL), and accounts for around 30% of new cases. More than half of all patients with DLBCL can be cured with combination chemotherapy, but a substantial proportion of patients fail to respond. For around 30 years, the standard induction therapy for DLBCL has been the CHOP regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone, given once every three weeks, typically for eight cycles.

Recent research has resulted in a greater appreciation of the heterogeneity of patients with DLBCL and this has been defined by the International Prognostic Index (IPI) and gene microarray studies. Moreover, increased understanding of the molecular basis of DLBCL has supported the use of the anti-CD20 monoclonal antibody rituximab in combination with the CHOP regimen, which has led to improved response and survival in patients aged over 60 years. Such therapeutic effects have been demonstrated in two large phase III trials and a more recent trial in younger patients has indicated a similar benefit with the addition of rituximab, particularly in patients with a favourable prognosis. The use of dose-dense (2-weekly) CHOP chemotherapy has also delivered encouraging results in older patients. This approach is under investigation in younger patients with a poor prognosis, a group in which efforts to improve rates of 5-year survival have remained disappointing. As recent results obtained in older patients with DLBCL are the best achieved to date, CHOP in combination with rituximab has become the standard therapy against which other novel regimens should be compared. Intensification of chemotherapy with dose-dense 2-weekly CHOP also holds considerable promise.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most commonly encountered form of non-Hodgkin's lymphoma (NHL), and accounts for around 30% of newly diagnosed cases.[1] Broadly, NHL is made up of a heterogeneous group of lymphoproliferative malignancies with varying patterns of behaviour and response to treatment that originate in lymphoid tissue and can spread to other tissues. NHL has a greater propensity than Hodgkin's disease to disseminate to extranodal sites.[2]

Diagnosis and classification

Prognostically, NHL can be divided into two types: indolent and aggressive. Aggressive NHL, of which DLBCL is a subtype, has a shorter natural history, but many patients (30% to 60%) can be cured with intensive combination chemotherapy. Indolent NHL has a relatively good prognosis, with median survival up to 10 years, but is not usually curable in its advanced stages.[3]

Most patients with DLBCL present with rapidly enlarging masses, often with both local and systemic symptoms (e.g. fever, recurrent night sweats, or weight loss). However, most patients with localised disease have been shown to be curable with either combined modality therapy or chemotherapy alone (Figure 1). Miller et al.[4] randomised 401 eligible patients with localised intermediate or high grade NHL to treatment with either eight cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or three cycles of CHOP followed by radiotherapy. Although patients who received combined modality therapy had significantly better progression-free survival (PFS) than those who received chemotherapy alone, 5-year estimates of PFS were encouraging for both groups (77% for CHOP plus radiotherapy and 64% for CHOP alone). Corresponding estimates of overall 5-year survival were 82% and 72%, respectively.

Difficulties in identifying prognostic subgroups of patients with aggressive NHL with the widely accepted Ann Arbor system,[5,6] which was originally developed for patients with Hodgkin's disease and emphasizes the distribution of nodal disease sites, has led to the development of an International Prognostic Index (IPI) for DLBCL.[7] The IPI was based on observations in 2031 patients from 16 sites across the US, Europe, and Canada who were treated between 1982 and 1987 with combination chemotherapy regimens containing doxorubicin. After evaluation for clinical features predictive of overall and relapse-free survival, and step-down regression analysis, five significant risk factors that predicted overall survival were found to be:

1. age (≤60 years versus >60 years)
2. serum level of lactate dehydrogenase (normal versus elevated)
3. performance status (0 or 1 versus 2 to 4)
4. disease stage (I or II versus III or IV)
5. extranodal site involvement (0 or 1 versus 2 to 4).

Patients with two or more of these risk factors have a less than 50% chance of relapse-free or overall survival at 5 years.[7] The study also identified patients at risk of relapse on the basis of specific sites of disease involvement, such as bone marrow, central nervous system, liver, lung, and spleen.

DLBCL therefore belongs to a group of potentially manageable lymphomas, although recent research has identified issues pertaining to patient risk factors and treatment strategies that are likely to influence outcomes in persons with this disorder. The present review discusses the current management of DLBCL, together with recent advances in therapy that are

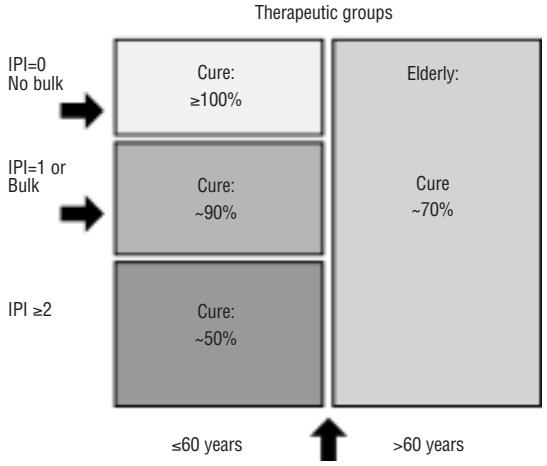

Figure 1: Treatment of aggressive lymphomas. Cure rates in patients with DLBCL and varying risk factors.

likely to benefit patients in both younger and older age groups.

Current treatment of DLBCL

The CHOP regimen (cyclophosphamide 750 mg/m^2, doxorubicin [Adriamycin] 50 mg/m^2, and vincristine 1.4 mg/m^2 [to a maximum of 2 mg] on day 1, with prednisone 100 mg daily from days 1 to 5)[8] remains the standard of care for patients with aggressive NHL, and it has transformed aggressive NHL from a fatal disease to one that is often curable. However, many patients continue to die from this disease, especially when additional risk factors are involved. For example, 5 years after treatment, only one third of patients aged over 60 years are alive and disease-free, as shown by a study in 195 Korean patients with DLBCL who received CHOP or CHOP plus bleomycin and procarbazine.[9] Likewise, review of two earlier clinical studies carried out by the Southwest Oncology Group (SWOG) showed an adverse influence of age on outcomes in patients with DLBCL treated with CHOP or a modification thereof.[10] In 307 patients treated between 1974 and 1982, complete response rates fell from 65% in those aged under 40 to 37% in those aged 65 years and over. Corresponding median survival times were in excess of 101 months versus only 16 months. The investigators suggested that the inferior outcomes in older patients may have been related to the use of less intensive induction chemotherapy because of these individuals' perceived inability to tolerate aggressive treatment.

Other chemotherapy regimens have been tried in aggressive lymphoma, but without demonstration of consistent benefit. The SWOG and Eastern Cooperative Oncology Group (ECOG) compared CHOP with three so-called *third generation* regimens: m-BACOD (low-dose methotrexate with folate rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone),[11] ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide and etoposide followed by cytarabine, bleomycin, vincristine, and methotrexate with folate rescue)[12] and MACOP-B (methotrexate with folate rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin).[13] These regimens were associated in earlier studies with increased rates of complete remission and survivals of 55 to 65%, but follow-up was limited and the new schedules were found to be more difficult to administer, toxic, and costly. Furthermore, there was no subgroup of patients in which survival was improved by one of the third generation regimens. The authors concluded that it was unlikely that the use of different combinations of existing drugs would improve the results of therapy to any meaningful extent.

The cause of most cases of DLBCL remains unknown; variability in response to therapy suggests an underlying heterogeneity in the disease, and this has prompted research into the molecular biology of DLBCL.[14] As such, there remains a need for ongoing research and refinement of chemo- and combination therapy regimens.

Recent advances in the treatment of DLBCL

Current thinking on the best treatment for DLBCL has been influenced by the above experience of chemotherapy and more recent advances in the field of combination treatment and molecular pathology. In France, the Groupe d'Étude des Lymphomes de l'Adulte (GELA) has carried out a number of phase II and III trials over the past 20 years, with the suggestion that it may be possible to improve

results seen with the standard CHOP regimen by using dose-intense treatment with additional bleomycin, and by using high-dose therapy with autotransplantation in young poor-risk patients.[15] German researchers have achieved some improvement by adding etoposide and shortening treatment intervals from 3 to 2 weeks (the CHOEP-14 regimen), and have optimized outcomes in young patients with good prognosis by giving six cycles of CHOP or a variant of this in combination with the recombinant humanized anti-CD20 antibody rituximab (CD20 is a pan-B-cell marker).[16] Indeed, the use of this monoclonal antibody is being investigated by groups in several countries: for example, French researchers have shown benefit of adding rituximab to CHOP (R-CHOP) for up to 5 years in elderly patients with aggressive B-cell lymphoma.[17,18]

US treatment guidelines point out that treatment depends on histology and stage, and that many improvements in survival have been attained by the use of experimental therapy in clinical trials.[3] The overall North American perspective has recently been summarized by Canadian authors who state that approximately 25% of patients with DLBCL present with limited-stage disease and are candidates for combined modality therapy (brief chemotherapy with involved-field irradiation).[19] However, most patients present with advanced disease and require extended chemotherapy, usually based on CHOP, with targeting of CD20 as a promising new treatment approach. Insights gained from molecular techniques such as gene expression profiling are expected to allow identification of other lymphoma-specific targets and better individualization of therapy.

Recent developments in young patients with DLBCL

Anti-CD20 therapy with rituximab added to six cycles of CHOP has recently been shown to be effective in younger (aged up to 60 years) patients with prognostically favourable DLBCL.[20] This study, which was carried out by the MabThera International Trial (MInT) group, followed on from observations by SWOG that three cycles of CHOP before involved-field radiotherapy appears more effective than eight cycles of CHOP alone in patients with limited-stage DLBCL,[4] and a report by the Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome (DSHNHL) to indicate that the addition of etoposide to CHOP prolongs event-free survival.[21]

The MInT group enrolled 824 patients from 18 countries who had no risk factors or one risk factor according to the age-adjusted IPI, stage II to IV disease, or stage I disease with bulk. Randomisation was to six cycles of CHOP-like chemotherapy alone (n=411) or with rituximab 375 mg/m^2 on days 1, 22, 43, 64, 85, and 106 (n=413). Chemotherapy regimens used were CHOP-21 (3-weekly CHOP), CHOEP-21 (CHOP-21 with etoposide), MACOP-B (described earlier), and PMitCEBO (mitoxantrone, cyclophosphamide, etoposide alternating weekly with bleomycin and vincristine, and oral prednisone throughout).

Significantly more patients assigned to chemotherapy plus rituximab than to chemotherapy alone had a complete remission or unconfirmed complete remission 155 days after starting treatment (86% versus 68%; $p<0.0001$). After a median follow-up of 34 months, respective 3-year event-free survival rates were 79% and 59% ($p<0.0001$), and progression-free survival rates were 85% and 68% ($p<0.0001$). Thus, overall 3-year survival was significantly better in the group receiving rituximab (93% versus 84%; $p=0.0001$) (Figure 1). Moreover, in a favourable subgroup of patients (age-adjusted IPI=1 with no bulky dis-

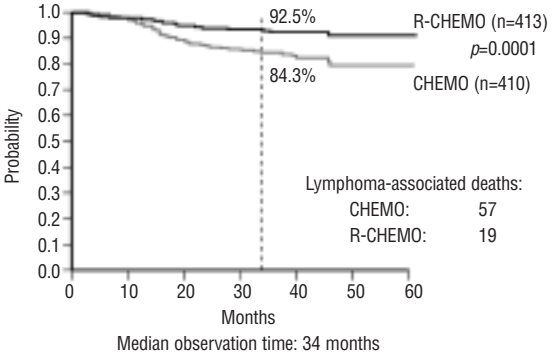

Figure 2: Overall survival in the MabThera International Trial (MInT) in patients aged 18 to 60 years with DLBCL.[20] Patients were randomized to six cycles of CHOP-like chemotherapy with or without the anti-CD20 monoclonal antibody rituximab. Reproduced with permission from Elsevier (*Lancet Oncol 2006;7:379–91*).

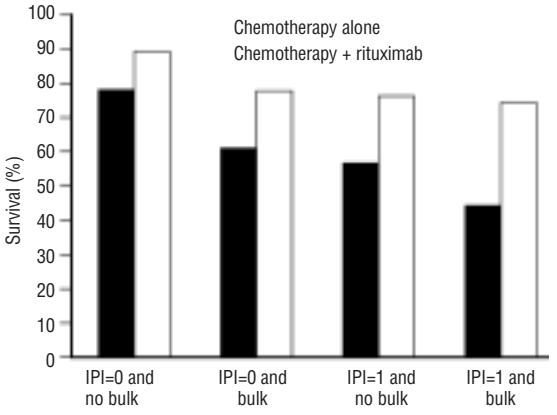

Figure 3: Three-year event-free survival in patients stratified according to International Prognostic Index and disease bulk in the MInT study.[20] Reproduced with permission from Elsevier (*Lancet Oncol 2006;7:379-91*).

ease), 3-year event free survival was an encouraging 89% with chemotherapy plus rituximab, which was compared with only 76% across three other stratified subgroups (IPI=1 or bulk or both; p=0.0162) (Figure 2). The effect of risk stratification on overall survival with chemotherapy plus rituximab was not as marked, however: overall 3-year survival in the favourable subgroup was 98%, which was compared with 91% across the less prognostically favourable patients (p=0.08). Figure 3 shows overall survival curves for favourable and less favourable patients receiving two types of chemotherapy with rituximab.

As noted earlier, patients with a poor prognosis as indicated by the presence of at least two IPI risk factors have a 5-year survival of only around 50%,7 and progress has been lacking in these individuals. Moreover, the 76% 3-year event-free survival seen after chemotherapy plus rituximab in less prognostically favourable patients in the MInT study warrants further improvement.[20]

Studies are in progress to determine whether dose-dense conventional or high-dose chemotherapy regimens requiring stem cell support in addition to rituximab will result in improved response and survival rates in younger patients with a poor outlook. Sixty-seven patients aged 18–60 years were randomised to receive an intensified regimen of CHOEP in the MegaCHOEP study.[22] The study was designed with two treatment arms; arm A (n=41; IPI ≥2=80%) had four courses of treatment consisting of a first course of cyclophosphamide 750 mg/m^2 and doxorubicin 35 mg/m2 on days 1 and 2, vincristine 2 mg on day 1, etoposide 100 mg/m^2 administered 12-hourly on days 1-3, and prednisone 100 mg on days 1-5, followed by three courses of cyclophosphamide 3000 mg/m^2 and doxorubicin 35 mg/m^2 on days 1 and 2, vincristine 2 mg on day 1, etoposide 185 mg/m^2 administered 12-hourly on days 1–4, and prednisone 100 mg on days 1-5. The first three courses in arm B (n=26; IPI≥2=85%) consisted of increased doses of chemotherapy: cyclophosphamide 800 mg/m^2 and doxorubicin 35 mg/m^2 on days 1 and 2, vincristine 2 mg on day 1, etoposide 100 mg/m^2 administered 12-hourly on days 1–3, and prednisone 100 mg on days 1–5. Courses 4–6 retained the same dosing schedule as courses 1–3, but contained increased doses of cyclophosphamide (2250 mg/m^2 and etoposide (160 mg /m^2). Courses were scheduled 21 days apart.

Complete recovery was achieved by 65.9% of patients in arm A and 50% of patients in arm B of the MegaCHOEP study.[22] A partial recovery was achieved by 9.8% and 15.4% of patients in arm A and B; progression was seen in 22% of arm A patients in 2.7–5.6 months, and in 31% of arm B patients in 1.4–6.8 months. Patients that had progressive disease or recurrence at 2 years had an overall survival rate of 47.5% and 74% in arms A and B respectively (p=0.036). The overall survival rate at 2 years was 70% in arm A and 46% in arm B (p=0.037). This study clearly shows that in patients with aggressive lymphoma and a poor prognosis, high-intensity therapy confers a significant survival advantage.

The DSHNHL group developed a similar MegaCHOEP therapy regimen, examining its efficacy in patients 18–60 years of age diagnosed with aggressive lymphoma with (n=72) or without (n=35) rituximab and followed by autologous stem cell transplantation (SCT).[23] The MegaCHOEP regimen consisted of cyclophosphamide 19500 mg/m^2, doxorubicin 280 mg/m^2, vincristine 8 mg, etoposide 5040 mg/m^2 and prednisone 2000 mg, with SCT administered after cycles 2 and 4. Once the feasibility and safety of this regimen had been determined, rituximab was added to the treatment, administered once at a concentration of 375 mg/m^2 before each cycle, and 3 and 6 weeks after the last MegaCHOEP cycle.[23]

There was a trend toward increased survival in patients receiving MegaCHOEP plus rituximab compared with recipients of MegaCHOEP alone (75% *vs*. 57%; p=0.168), as well as a trend toward an increased relative risk of treatment failure in patients receiving MegaCHOEP alone (RR 1.8; p 0.087). FFTF at 3 years was significantly better in patients receiving MegaCHOEP plus rituximab, compared with those receiving MegaCHOEP alone (70% *vs*. 50%; p=0.040). These results suggest that rituximab contributes positively to lymphoma control in this subgroup of patients; however, the higher incidence of serious infections seen in patients receiving rituximab in combination with MegaCHOEP compared with MegaCHOEP alone has the potential to alter the dose intensity of the regimen.[23]

Recent developments in older patients with DLBCL

More than half of all patients with DLBCL are aged over 60 years,[7,24,25] and the management of these individuals is a challenge for clinicians. Intensified chemotherapy regimens may improve outcomes in younger patients, but they are not well tolerated by older persons, in whom even CHOP itself may be excessively toxic.[26,27] Nevertheless, some progress has been made recently with therapy in this group of patients: reduction of the treatment interval from 3 weeks (CHOP-21) to two (CHOP-14) with the addition of stem cell support was associated with improved event-free and overall survival in a study in 689 patients aged from 61 to 75 years.[28] Relative risks were 0.66 (p=0.003) for event-free and 0.58 (p<0.001) for overall survival with CHOP-14 relative to CHOP-21, with no significant increase in toxicity.

Similarly encouraging results have been reported after addition of rituximab to CHOP chemotherapy in older patients. Previously untreated patients aged 60 to 80 years with DLBCL were randomised to treatment with eight cycles of 3-weekly CHOP alone (n=197) or CHOP plus rituximab on the first day of each cycle (n=202).[17] The rate of complete response was significantly higher in the group receiving rituximab (76% *vs*. 63%; p=0.005), and event-free (57% *vs*. 38%; p<0.001) and overall (70% *vs*. 57%; p=0.007) survival times were significantly greater after a median follow-up of 2 years. Thus, the addition of ritux-

imab to CHOP reduced the risk of treatment failure and death significantly (respective risk ratios 0.58 and 0.64), with no clinically relevant increase in toxicity.

Following on from these findings, the next logical step was to investigate the combination of rituximab with dose-dense 2-weekly CHOP, and this has been done by the DSHNHL study group in their RICOVER-60 trial.[29] In this study, patients aged from 61 to 80 years with stage I to IV DLBCL were randomised to treatment with six or eight cycles of CHOP-14 with or without rituximab added on the first day of each cycle. Radiotherapy was applied to sites of initial bulky disease and/or to extranodal sites. RICOVER-60 was powered to show a 9% difference between treatments in the primary endpoint of rate of freedom from treatment failure (FFTF) after 3 years. Results of a planned interim analysis are available for 828 evaluable patients with $CD20^+$ disease, of median age 68 years, and covering a range of prognostic characteristics (IPI 1 to 5). Of evaluable patients, 503 were categorized as having good-prognosis (IPI=1,2) and 325 had poor-prognosis (IPI=3,4).[30]

The interim analysis showed no significant difference in efficacy between six- and eight-cycle regimens, and adherence rates remained high in all groups, with 99% and 96% adherence to protocol seen in 6-cycle CHOP-14 and 8-cycle CHOP-14 respectively, with or without addition of rituximab.[29] However, FFTF after addition of rituximab to CHOP-14 (n=414) was superior to that seen with CHOP-14 alone (n=413; p=0.000025). Most notably, the empirical p value attached to the log rank test underlying the statistical analysis was considerably lower than the critical value of p=0.031 specified for the interim assessment, and RICOVER-60 was therefore terminated early in June 2005. After a median observation period of 26 months, there was a nonsignificant trend toward improved FFTF with eight cycles of CHOP-14 alone over six cycles, but this was lost after addition of rituximab (70% FFTF after both six and eight cycles). Whether there is a survival advantage associated with the addition of rituximab to CHOP-14 in these patients has not yet been shown, but further data are awaited.

In addition, a RICOVER-60 subgroup analysis was conducted to investigate the effect of rituximab in combination with CHOP-14 in patients with good- vs poor-prognosis.30 Of 503 patients with good-prognosis, 252 received CHOP-14 alone, and 251 received rituximab in combination with CHOP-14; correspondingly, of 325 patients with poor-prognosis, 161 received CHOP-14 and 163 received combination treatment. It was shown that the addition of rituximab to CHOP-14 resulted in a similar improvement in time-to-treatment failure in both subgroups (good-prognosis: 67% *vs*. 81%, p=0.001; poor-prognosis 36% *vs*. 52%, p=0.004). As with the results for the primary endpoint (FFTF) for 6- versus 8-weekly cycles, the differences between prognosis subgroups in overall survival improvements are not significantly different; patients in the good-prognosis subgroup who received CHOP-14 alone showed an 82% improvement in survival versus 88% in the combination treatment arm (p=0.458). Corresponding improvements in survival for the poor-prognosis group were 58% *vs*. 64% (p=0.146).

Pharmacokinetic findings show a marked nadir in rituximab concentrations after administration of the first rituximab-CHOP-14 cycle, although concentrations of rituximab were observed to increase after each subsequent cycle.[30] Furthermore, the rituximab concentration nadir after administration of the first rituximab-CHOP-14 cycle was expected to be even more marked in a 3-weekly regimen, which is a suggested explanation for the small improvement in the poor-prognosis patient group who received 3-weekly combination treatment.

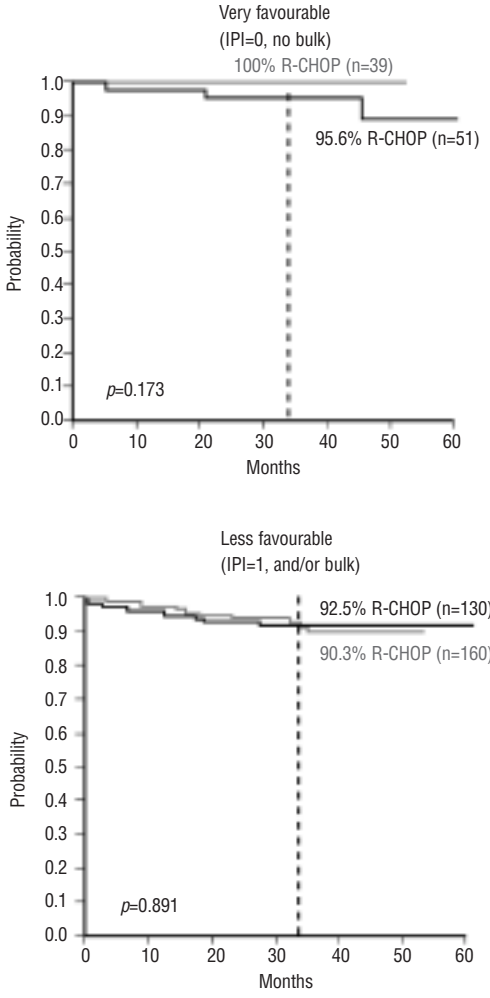

Figure 4: Overall survival in patients stratified by prognostic risk and receiving CHOP plus rituximab (R-CHOP) or the more intensive CHOEP plus rituximab (R-CHOEP) in the MInT study.[20] Stratification was according to IPI status and presence or absence of disease bulk.

When patients with stage I disease are excluded, the patient population enrolled in RICOVER-60 was similar to that in LNH98-5, a GELA trial that included 399 previously untreated individuals aged 60 to 80 years with DLBCL.[17,18] Patients in LNH98-5 had stage II to IV disease with performance status 0 to 2, and were randomised to 3-weekly CHOP for eight cycles either alone or with rituximab 375 mg/m^2 on day 1 of each cycle. The projected 2.5-year survival rate after 6 cycles of 2-weekly CHOP with rituximab for patients with stage

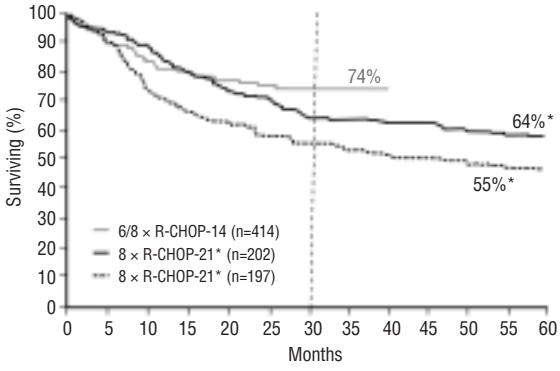

Figure 5: Comparison of 2.5-year overall survival in older patients with DLBCL stages II to IV treated with eight cycles of 3-weekly CHOP with or without rituximab in the GELA LNH98-5 trial[17,18] or with six cycles of 2-weekly CHOP plus rituximab in RICOVER-60.[29]

II to IV disease in RICOVER-60 has been reported as 74%, which compares very favourably with a 2.5-year rate of 64% calculated retrospectively for the LNH98-5 patients who received 3-weekly CHOP with rituximab (Figure 4).[29] This has been attributed to superior survival at 2.5 years of poor-prognosis patients (IPI 3 to 5; 64% in RICOVER-60 versus 54% in LNH98-5).[29]

Five-year results of LNH98-5 are now available, and show the 5-year event-free survival rates with 3-weekly CHOP with and without rituximab to be 47% and 29%, respectively. Median event-free survival times were 3.8 and 1.1 years (p=0.00002).[18] Five-year overall survival rates were 58% with rituximab and 45% without. Progression-free and disease-free survival rates were also statistically significantly increased by the addition of rituximab.

These results demonstrate a distinct advantage, with no apparent clinically significant increase in toxicity, associated with the addition of rituximab to CHOP chemotherapy in older patients. Indeed, results so far with 2-weekly CHOP plus rituximab in RICOVER-60, which is the largest trial carried out to date in patients aged over 60 with DLBCL, are the best reported to date in elderly individuals with DLBCL.

Findings from a two-stage randomised trial in elderly patients (n=632) aged ≥60 years comparing CHOP therapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 2 mg on day 1 and prednisone 100 mg/m^2 on days 1–5 every 21 days) with or without rituximab 375 mg/m^2, followed by rituximab maintenance therapy in responders (n=415; 207 assigned to maintenance, 208 assigned to observation) showed that there were no significant differences in survival with the type of induction therapy or with maintenance therapy.[31] Failure free survival in patients that received maintenance therapy was significantly prolonged after CHOP therapy (p=0.0004), but not after R-CHOP therapy (p=0.81). Rituximab administration during induction therapy did increase 3-year survival significantly, compared with patients who received CHOP therapy alone (53% *vs*. 46%; p=0.04).31

Conclusions

For most patients, DLBCL is a systemic disease at diagnosis and is at bulky stage II, stage III, or stage IV in approximately 75% of cases. Thus, chemotherapy is the mainstay of treatment for the majority of patients, and the standard therapy used has not changed to any appreciable extent for the last 30 years.[32] However, researchers are currently defining prognoses in biologically defined subsets of patients with DLBCL, and techniques such as microarray testing have pointed the way towards molecular therapies aimed at specific cellular targets. The monoclonal antibody rituximab has been combined with CHOP chemotherapy to good effect in both young and old patients, with promising results also being reported after the use of dose-dense 2-weekly regimens of CHOP.

Despite the good outlook for many patients with DLBCL, a considerable proportion of persons with the disease are not cured with conventional therapy. Physicians are therefore encouraged to recognize the limitations of current treatment and to suggest that patients participate in well designed clinical trials where appropriate. Although the best therapy remains to be defined, ongoing advances in molecular characterisation of the disease are pointing the way, and recent clinical experience shows that CHOP with rituximab is now the standard therapy against which new regimens should be compared. Moreover, dose-dense 2-weekly CHOP for six cycles rather than the traditionally accepted eight cycles of CHOP-21 appears to represent a step forward, particularly in older patients. The results of ongoing studies comparing the 14- and 21-day CHOP cycles are awaited with interest.

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