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Chemotherapy in cutaneous T-cell lymphoma

S. Rupoli
M.G. Bernengo[1]
R. Alterini[2]
M. Cantonetti[3]
P.L. Zinzani[4]
N. Pimpinelli[5]

for the GILC (Gruppo Italiano Linfomi Cutanei)

Dept. of Hematology, Politechnical University of Marche Medical School, Ospedali Riuniti, Ancona, Italy; [1]Dept. of Dermatology, University of Turin Medical School, Turin, Italy; [2]Dept. of Haematology, University of Florence Medical School, Florence, Italy; [3]Dept. of Haematology, University of Rome Tor Vergata Medical School, Rome Italy; [4]Inst. of Haematology and Oncology L. And A. Seragnoli, University of Bologna Medical School, Bologna, Italy; [5]Department of Dermatological Sciences, University of Florence Medical School, Florence, Italy

Which and when aggressive treatment in cutaneous T-cell lymphoma (CTCL)? When approaching the topic of chemotherapy in different subtypes of CTCL,[1] the first issue to be made clear is the target of this type of treatment. The use of systemic chemotherapy as a first line treatment should be restricted with few exceptions to advanced/aggressive forms of CTCL: advanced mycosis fungoides (MF, stage IIB-IV), Sézary syndrome (SS), primary cutaneous CD30$^+$ anaplastic large cell lymphoma with disseminated lesions, subcutaneous panniculitis-like T-cell lymphoma with progressive lesions, and peripheral T-cell lymphoma, unspecified.[2-6] Of course, chemotherapy is one of the options in any refractory CTCL. The second issue concerns the selection of chemotherapy regimens. The choice of treatment is often determined by institutional experience, particularly as there is a paucity of data from phase III trials and a lack of consensus concerning treatment for the later stages of MF/SS. A strict rule is definitely non-appropriate in this regard. A careful and balanced evaluation of specific diagnosis, tumour load, cutaneous lesions' features, age, general conditions, and immune status of the patients is obviously the standard to date. According to the EORTC recommendations,[6] monochemotherapy is one of the options indicated in MF patients stage IIB and III refractory to or relapsing after first line treatments. Gemcitabine[7] and pegylated liposomal doxorubicin (Peg-Doxo)[8] should be considered among the most suitable options to date, with an overall response rate (ORR) of 70% and 88%, respectively, and a median progression-free survival (PFS) of 15 and 12 months, respectively (see other chapters in this issue). A recent phase II pilot study from the GILC (*Gruppo Italiano Linfomi Cutanei*) with Peg-Doxo monotherapy (manuscript in preparation) showed an ORR of 86% and a PFS of 20 months, with a very good benefit/risk profile (efficacy vs. side effects and immunodepression), although with significantly less brilliant figures in stage III MF patients.

Other regimens, like 2-chlorodeoxyadenosine [9,10] and pentostatin (deoxycoformycin),[11] although with the limitation of small patients' series, showed lower ORR and PFS. Monochemotherapy should also be considered a valuable first-line therapeutic option for patients with MF stage IIB/III. In this regard, gemcitabine showed very interesting results (ORR 75%, PFS 10 months) as a front-line treatment.[12] Polychemotherapy regimens, among which VICOP-B (idarubicin, etoposide, cyclophosphamide, vincristine, prednisone, bleomycin)[13] and ABVD with Peg-Doxo[14] showed comparable results in terms of ORR (84% and 75%, respectively), did not show better figures in terms of PFS (9 and 11 months, respectively), and obviously have a worse benefit/risk profile. Therefore, polychemotherapy should be recommended in patients with high tumor load and elevated serum LDH, and generally in stage IV MF patients.[15] It should be emphasized that treatment at this stage is palliative, and a careful monitoring of clinical response, side effects, and quality of life is mandatory. Patients who are refractory to or relapsing after at least two lines of systemic treatment should be considered for high-dose chemotherapy and stem cell transplantation (SCT), possibly within clinical trials due to the contradictory results in small series to date.[2-6]

In Sézary syndrome (SS), low-dose metothrexate[16] and oral chlorambucil plus prednisone[17] are possible treatment alternatives to extracorporeal photochemotherapy (ECP) in patients

with a low tumour load. Patients with high tumor load and those refractory to/relapsing after a first line treatment should be treated with chemotherapy. In this regard, EPOCH (etoposide, vincristine, doxorubicin, bolus cyclophosphamide, oral prednisone) regimen[18] and fludarabine + cyclophosphamide[19] achieved a considerable ORR (80% and 62%, respectively), yet with considerable bone marrow toxicity and immunosuppression and no improved survival. Therefore, monochemotherapy with gemcitabine[7] or fludarabine – possibily associated with IFNα[20] or sequential ECP[21] – or pentostatin (associated with pulse high dose IFNα)[22] is a reasonable option, alternative to alemtuzumab and oral bexarotene (see other chapters in this issue). Patients who are refractory to or relapsing after at least two lines of systemic treatment should be considered for high-dose chemotherapy and SCT within clinical trials due to the contradictory results in small series to date.[2-6]

Finally, polychemotherapy (CHOP-like regimens) should be recommended in CD30+ anaplastic large cell lymphoma patients with progressing, multiple lesions in non-contiguous sites, with a considerable cure rate, and in primary cutaneous peripheral T-cell lymphoma, NOS, notwithstanding this type of treatment does not significantly affect their by far generally aggressive course.[1] The only exception in this regard are patients with isolated or localized lesions and $CD4^+$ small/medium pleomorphic T-cell histology (provisional entity of the WHO-WEORTC classification),[1] who should be treated non-aggressively at presentation (radiotherapy, surgical excision in unilesional cases).

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