Symposium article

Annals of Oncology 14 (Supplement 1): i1–i3, 2003
DOI: 10.1093/annonc/mdg701

Current role and future perspectives for ifosfamide in the treatment of malignant non-Hodgkin's lymphoma—results from an expert meeting

V. Sneller[1] & J. Armitage[2]*

[1]*Baxter-Oncology GmbH, Frankfurt, Germany;* [2]*University of Nebraska Medical Center, Omaha, NE, USA*

In this supplemental issue of *Annals of Oncology*, leading experts from Australia, Europe and the USA present results from their trials using ifosfamide-containing chemotherapy regimens for the treatment of malignant non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). The relative merits of the established regimens, achievable treatment results and future perspectives for ifosfamide regimens were discussed during a workshop, held in October 2002 at Cap Ferrat, France. The expert faculty discussed practical issues related to the use of ifosfamide and mesna including suggestions for inpatient and outpatient ifosfamide regimens in combination with rituximab and guidelines for the management of possible side-effects. The practical guidelines for outpatient ifosfamide-based regimens, by fractionating the administration of ifosfamide, infusomates or oral mesna, were discussed as well.

Many patients with aggressive NHL can be cured with anthracycline-containing chemotherapy regimens. The benefit of adding rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy for non-pretreated elderly patients with aggressive NHL was demonstrated in a recently published randomized trial performed by Groupe d'Étude des Lymphomes de l'Adulte (GELA) [1]. Despite this, more than half of the patients are primarily refractory or relapse and require salvage therapy. A certain subset of patients with chemosensitive disease can be cured with high-dose therapy and stem cell transplantation. Before high-dose therapy, patients usually receive combination chemotherapy regimens to establish tumor chemosensitivity and to reduce tumor bulk. It is critical that a cytoreductive regimen has a high response rate with minimal organ-related toxicities, while at the same time providing adequate collection of peripheral blood stem cells (PBSC).

Zelenetz et al. report an update on their long experience with a cytoreductive and mobilization regimen consisting of ifosfamide, carboplatin and etoposide (ICE), previously published by Moskowitz et al. [2]. In the Memorial Sloan Kettering Cancer Center, New York, this regimen has been used in more than 220 patients so far with relapsed and refractory aggressive NHL and in more than 100 patients with HD. In order to attain high response rates, the ICE regimen was administered every 2 weeks with concomitant use of growth factors. A similar dose-dense approach with 2-weekly CHOP-14 as initial therapy for aggressive NHL was recently reported by the German High-Grade NHL group [3]. The results in elderly patients showed the superiority of 2-weekly CHOP in terms of event-free and overall survival compared with standard 3-weekly CHOP. Zelenetz et al. conclude that 2-weekly ICE has significant antitumor activity, minimal non-hematological toxicity and results in a high stem cell yield. Primary refractory patients who responded to second-line chemotherapy and were able to receive autologous stem cell transplantation (ASCT) showed a progression-free survival rate as good as that in chemosensitive relapsed patients. Furthermore, the quality of the clinical response to ICE is predictive of post-transplant outcome.

Hertzberg et al. present their experiences with outpatient ICE in 38 patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), HD and mantle cell lymphoma (MCL). Their data confirm the high efficacy and good tolerability of fractionated ICE as both a salvage and a mobilization regimen; a finding which was found to be consistent in the different histological types of lymphoma. This combination can be safely given on an outpatient basis every 21 days by administering ifosfamide in short 1-h infusions over 3 consecutive days and by using mesna tablets. Hertzberg et al. suggest that the few studies comparing short versus long infusional ifosfamide regimens in cancer patients have failed to show convincing evidence of a significant difference in either pharmacokinetics, response rates or hematological toxicity.

As previously shown by Hamlin et al. [4], patients with good-risk disease [Second-line age-adjusted international prognostic index (sAAIPI) I/II] are highly curable with an ICE-based high-dose therapy (HDT) approach. Another important finding was that patients who achieved complete remission following therapy with ICE had significantly improved survival compared with patients achieving partial remission [2]. Outcome for patients with poor-risk disease (sAAIPI III/IV) was still not satisfactory and they might therefore benefit from novel treatment strategies, such as inclusion of new agents with the goal of increasing the complete remission rate prior to HDT. One of these promising agents is the monoclonal antibody rituximab, which has been recently introduced for the initial treatment of aggressive lymphomas in combination with CHOP-like regimens. There are also promising data in relapsed and refractory disease, as well as in follicular and mantle cell lymphomas.

**Correspondence to:* Dr James Armitage, University of Nebraska Medical Center, Omaha, NE, USA. Tel: +1-402-559-7290; Fax: +1-402-559-6114; E-mail: joarmita@unmc.edu

Zelenetz et al., with the aim of increasing response rates, added rituximab to the ICE regimen in CD20-positive relapsed and refractory DLBCL patients, as well as in B-cell anaplastic large-cell lymphoma. Rituximab plus ICE (R-ICE) appears to double the complete response rate of ICE alone [5]. This was seen in both relapsed and refractory patients, but is more pronounced in the former group. Furthermore, R-ICE appears to overcome the differences among different prognostic groups of patients, defined by the Second Line International Prognostic Index (sIPI). The addition of rituximab to ICE is safe without significant additive toxicity. Whether the increased complete response rate will translate into prolonged survival following HDT/ASCT remains to be determined.

A similar approach, with the main intention of improving results with currently available salvage regimens, is presented by Vose. R-ICE is administered on an outpatient basis, followed by HDT/ASCT. The University of Nebraska Medical Center strategy is to proceed with the transplant as soon as responses, either complete or partial, can be achieved. Vose reports that R-ICE is effective and well tolerated and can be administered safely in an outpatient setting.

Joyce et al. report the results of an outpatient regimen consisting of rituximab, ifosfamide, mitoxantrone and etoposide (R-IME) for the treatment of B-cell NHL. In this study mitoxantrone was substituted for carboplatin, in an attempt to enhance activity in the follicular and mantle cell sub-types and to reduce the stem cell toxicity. R-IME is effective in mobilizing sufficient yields of stem cells that demonstrate no evidence of tumor cell contamination in the majority of patients. R-IME was effective for cytoreduction in a broad range of B-cell lymphoma, and did not increase HDT/ASCT morbidity.

As already outlined, besides high efficacy and good tolerability, the ability to collect a high number of stem cells is an important feature of an ideal salvage regimen. The number of CD34+ cells must exceed 2×10^6 cells/kg to allow satisfactory long-term recovery of hematopoiesis, but recovery is faster and of better quality if the number is higher. In addition, the data published earlier by Bociek et al. [6] suggest that patients with $>4 \times 10^6$ CD34+ cells/kg may have a superior 2-year probability of survival compared with patients who have cell yields in the range 1.5×10^6 to 4×10^6 cells/kg[6].

Nowrousian et al. report various chemotherapy regimens combined with growth factors to mobilize stem cells in patients with different types of malignant disease. The data suggest that ifosfamide/etoposide-based regimens are highly effective cytoreductive and mobilization regimens, which seem to be superior to cyclophosphamide in combination with growth factor.

Several papers report on the use of ifosfamide-based regimens not only for the treatment of DLBCL, but also for the treatment of anaplastic lymphoma, mantle cell lymphoma, relapsed follicular lymphoma and transformed follicular lymphoma. The management of relapsed indolent lymphomas represents one of the most challenging and controversial areas in hematology due to the many new options available. The use of ASCT in follicular lymphoma is limited by frequent contamination of blood and marrow with the pathological cells, and the inability of even high-dose chemoradiotherapy to eradicate systemic disease in most patients [7]. However, ASCT represents an option for patients without an HLA-identical sibling, particularly if autologous stem cells can be collected that are PCR negative for residual malignant cells. The optimal salvage and intensification regimens have to be determined. First experience with *in vivo* purging with rituximab points to a decrease in the number of tumor cells in stem cell harvest for patients with FL and MCL, but no data are as yet available for relapsed patients.

Of the patients previously reviewed by Zelenetz et al., 17 had follicular center lymphoma, of whom 16 had either CR or PR to ICE, and 11 of 17 were event free at 40 months. Herzberg et al. treated 11 patients with ICE of whom 10 also received rituximab. Joyce et al. report promising responses and 1-year survival achieved by using R-IME in follicular and transformed follicular lymphomas. Similar results for R-ICE are reported by Vose.

Mantle cell lymphoma is usually not curable with currently available treatment options. The combination of rituximab with chemotherapy before harvesting PBSC (*in vivo* purge) and ASCT with total body irradiation (TBI) gave remarkable results in one study [8], but this has not been confirmed in two other studies [9, 10]. Encouraging survival data from using R-IME in combination with rituximab as a post-transplant therapy suggest that this regimen should be further explored for the treatment of this unfavorable disease.

In conclusion, the addition of rituximab to well-established salvage regimens, such as IME or ICE, further improves results in a broad spectrum of lymphoma. Encouraged by promising data with ifosfamide in the relapse setting, several clinical investigators decided to study the utility of intensification with ifosfamide-based regimens in the first-line setting. One of these trials which started recently in the Memorial Sloan Kettering Cancer Center is testing whether intensification with ICE followed by HDT/ASCT will improve results in patients who are at high risk for relapse after having received CHOP chemotherapy.

Since there is no widely accepted standard regimen for the treatment of relapsed NHL, the Collaborative Trial in Relapsed Aggressive Lymphomas (CORAL) study group has proposed a comparison of rituximab, dexamethasone, cytarabine, cisplatin (R-DHAP) with R-ICE, followed by ASCT in patients with relapsed and primary refractory diffuse large B-cell lymphomas in order to set-up a new standard. This study will address some important questions: 'What is the most efficient salvage regimen associated with rituximab?' 'Will rituximab have an effect in patients previously treated with rituximab?' and 'What is the role of rituximab after transplant?'

The attendant experts agreed that ifosfamide is a valuable drug for the treatment of several types of malignant lymphoma and incorporation of ifosfamide in novel treatment strategies should be explored.

Disclosure

Dr Sneller is an employee of Baxter Oncology GmbH. Professor Armitage received an honorarium for participation in the workshop.

References

1. Coiffier B, Lepage E, Briere J 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: 235–242.
2. Moskowitz CH, Bertino JR, Glassman JR et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 3776–3785.
3. Pfreundschuh M, Trümper L, Kloess M et al. Two-weekly CHOP (CHOP-14): the new standard regimen for patients with aggressive non-Hodgkin's lymphoma (NHL) >60 years of age. Ann Oncol 2002; 13 (Suppl 2): 27 (Abstr 081).
4. Hamlin PA, Zelenetz AS, Nimer SD et al. The age-adjusted international prognostic index (AAIPI) predicts outcome following autologous stem cell transplantation (ASCT) in patients (PTS) with relapsed and primary refractory diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2002; 13 (Suppl 2): 75 (Abstr 250).
5. Kewalramani T, Zelenetz A, Bertino J et al. Rituximab significantly increases the complete response rate in patients with relapsed or primary refractory DLBCL receiving ICE as second-line therapy (SLT). Abstract 1459, American Society of Hematology 43rd Annual Meeting, December 7–11, 2001, Orlando, FL.
6. Bociek RG, Lynch JC, Yee GC et al. Outcome and factors associated with slow mobilization of peripheral blood progenitor cells (PBPC) in patients undergoing autologous transplantation for non-Hodgkin's lymphoma. Abstract 3575, American Society of Hematology 43rd Annual Meeting, December 7–11, 2001, Orlando, FL.
7. Cabanillas F, Horning S, Kaminski M, Champlin R. Managing indolent lymphomas in relapse: working our way through a plethora of options. Educational Book. American Society of Hematology, Washington DC, USA 2000; 166–179.
8. Haas R, Brittinger G, Meusers P et al. Myeloablative therapy with blood stem cell transplantation is effective in mantle cell lymphoma. Leukemia 1996; 10: 1975–1979.
9. Ketterer N, Salles G, Espinouse D et al. Intensive therapy with peripheral blood stem cell transplantation in 16 patients with mantle cell lymphoma. Ann Oncol 1997; 8: 701–704.
10. Freedman AS, Neuberg D, Gribben JG et al. High-dose chemoradiotherapy and anti-B-cell monoclonal antibody purged autologous bone marrow transplantation in mantle-cell lymphoma: no evidence for long-term remission. J Clin Oncol 1998; 16: 13–18.