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ORIGINAL ARTICLE

Craig Moskowitz

Risk-adapted therapy for relapsed and refractory lymphoma using ICE chemotherapy

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Abstract At Memorial Sloan Kettering Cancer Center, New York, we have treated over 400 patients with ICE chemotherapy after failure of upfront anthracycline-based therapy with a response rate of 72% in aggressive non-Hodgkin's lymphoma (NHL) and 84% in Hodgkin's disease. Utilizing this database, we have identified pretreatment prognostic markers capable of predicting the quality of response (complete response vs partial response vs failure) to second-line cytoreductive ICE chemotherapy and consequently autologous stem cell transplantation. We have shown that in aggressive NHL, patients achieving a complete response have superior survival when compared to those achieving only a partial response. By identifying a priori those patients destined to have only a partial response to ICE, we will be able to target a group of chemosensitive patients who are most likely to benefit from improved treatment. Novel treatment strategies designed to increase their complete response rate would be anticipated to improve their long-term survival.

Keywords Risk-adapted therapy · Refractory lymphoma · ICE chemotherapy · Ifosfamide

The incidence of lymphoma is increasing at a rate faster than any non-cutaneous malignancy with 70,000 cases expected in 2001. Despite advances in the therapy of intermediate grade non-Hodgkin's lymphoma (NHL) and advanced Hodgkin's disease, treatment failure remains a clinical challenge. Results indicate that 40–60% of patients either fail to achieve a complete remission or relapse after receiving standard front-line therapy. Two prospective randomized trials have determined that high-dose chemoradiotherapy (HDT) and autologous stem cell transplantation (ASCT) is the most successful therapeutic modality for relapsed patients with chemosensitive disease. In 1993, we developed the ICE (ifosfamide, carboplatin, etoposide)/G-CSF regimen for cytoreduction and mobilization in patients with primary refractory, and relapsed NHL (Fig. 1). The results were analyzed by treatment intention, with HDT/ASCT anticipated for all patients entering the program. The results have been reported elsewhere [1]. A total of 163 patients with NHL were treated from October 1993 to December 1997 and the overall response rate was 67% with one-third of the responses complete. Peripheral blood progenitor cell collection was successful and only 14% of patients failed to mobilize at least 2×10^6 $CD34^+$ cells per kilogram. Importantly, there was minimal non-hematologic toxicity and no patient was ineligible for high-dose therapy secondary to ICE-related toxicity.

As of September 2001, 270 patients with relapsed or primary refractory aggressive NHL have been treated with three cycles of ICE with cytokine support. Utilizing this database, we have identified pretreatment prognostic markers capable of predicting the quality of response (complete response vs partial response vs failure) to second-line cytoreductive ICE chemotherapy and consequently ASCT. We have shown that in aggressive NHL, patients achieving a complete response have superior survival to those achieving only a partial response. By identifying a priori those patients destined to have only a partial response to ICE, we will be able to target a group of chemosensitive patients who are most likely to benefit from improved treatment. Applying this concept, we have combined rituximab with the ICE regimen at Memorial Sloan Kettering Cancer Center (MSKCC) for patients with B-cell aggressive relapsed or primary refractory disease. Preliminary results are encouraging and were presented at the American Society of Hematology 2001 Annual Meeting [2] (Fig. 2).

More novel treatment strategies designed to increase the complete response rate would be anticipated to

This work was presented at the Satellite Symposium "Introducing Ifosfamide in Innovative Treatment Modalities" of the ECCO 11 meeting, Lisbon, Portugal, 21 October 2001.

C. Moskowitz
Lymphoma Service,
Memorial Sloan Kettering Cancer Center, New York, NY, USA
E-mail: moskowic@mskcc.org

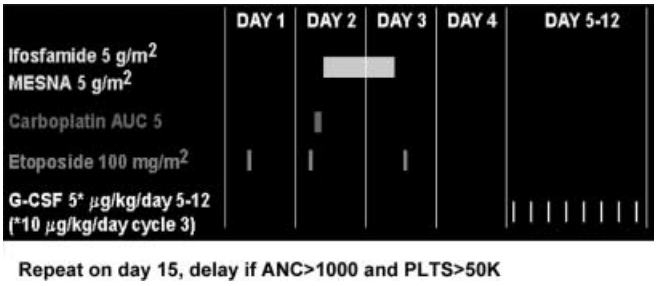

Fig. 1. ICE as second-line therapy

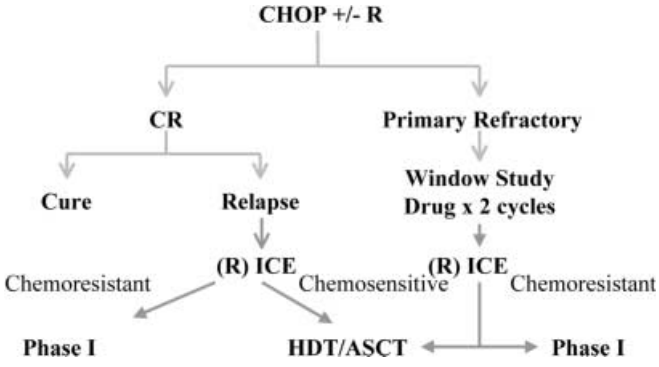

Fig. 3. MSKCC strategy for diffuse large B-cell lymphoma

improve long-term survival [3]. A window study model has been created for the introduction of novel phase I/II drugs prior to administration of standard ICE, with the intention to bring all chemoresponsive patients to ASCT. The phase I/II drugs will be selected based on preclinical evidence of activity in a dog lymphoma model and phase I data regarding activity in lymphomatous tumors if available. Their safety with regard to stem cell collection will be assessed. After two or three cycles of the study drug, response to therapy will be assessed with the possibility of additional cycles if response is demonstrated. All patients would subsequently receive ICE chemotherapy with the intention to perform ASCT (Fig. 3).

In Hodgkin's disease, the design of our initial high-dose combined modality protocols, which consisted of total lymphoid irradiation rather than total body irradiation, limited the radiation exposure to nodal sites that are the most likely to be involved with Hodgkin's disease. Furthermore, avoiding exposure of dose-limiting organs such as the liver and lungs allowed the use of higher radiation doses (1800 cGy within 5 days) without increasing the risk of toxicity. We further increased the dose to relapsed or refractory sites by adding a booster dose of radiation prior to total lymphoid irradiation thus escalating the radiation dose to high-risk sites to 3600 cGy. A group of 68 consecutive patients with unirradiated refractory/relapsed Hodgkin's disease were treated on this protocol from 1985 to 1994. This group included a significantly higher proportion of patients with advanced-stage presentation (82%), refractory to initial chemotherapy (57%) and to standard-dose salvage therapy (35%), compared to a concurrent group of 78 previously irradiated patients treated at MSKCC with HDT alone. At a median follow-up of 9 years the event-free survival (EFS) was $49 \pm 6\%$ with no relapses or toxicity occurring after 3.3 years [4]. Multivariate analysis showed that poor response to the standard-dose salvage chemotherapy adversely affected survival, and this concept was tested in our second-generation program.

We evaluated the ICE regimen in our second-generation protocol using HDT for relapsed and refractory Hodgkin's disease [5]. This was a two-step salvage program that included uniform cytoreduction with ICE. The response rate (complete/partial response) to ICE was 86%. Seven of the eight ICE failures died of Hodgkin's disease at a median follow-up of 5 months and 56 of 57 responders to ICE underwent ASCT. Therefore the ICE regimen is a highly effective cytoreductive/mobilization regimen in lymphoma. The EFS of the transplanted patients was 71.4%. These results compare very favorably with other series and indicate the feasibility and efficacy of (1) giving standard intensive cytoreductive chemotherapy, and (2) integrating higher dose radiotherapy into an ASCT treatment program [6]. The results of this trial also compare well with our historical results.

Response to salvage chemotherapy (e.g. chemosensitive disease) has been used as the major selection crite-

Fig. 2. Rituximab and ICE

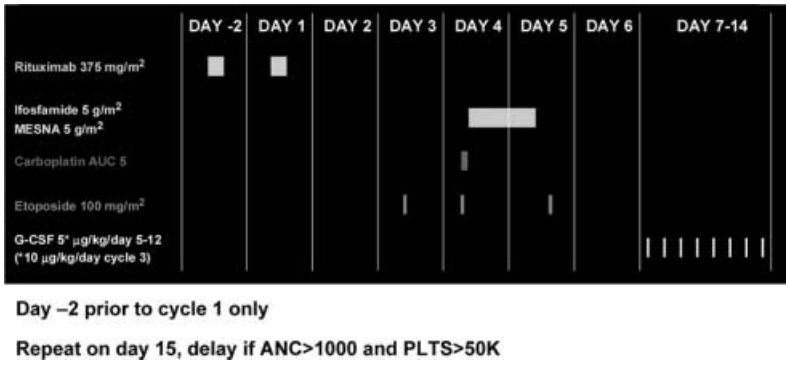

Table 1. Three-factor model

Group	No. of patients	Event-free survival (%)	Overall survival (%)
A (zero or one factor)	40	83	90
B (two factors)	15	27	57
C (three factors)	10	10	25
P values (A vs B vs C)		< 0.001	< 0.001

Table 2. Rationale for the current MSKCC study in Hodgkin's disease with treatment based upon prognostic groups

Group 1 (zero or one factor, 65% of population)	EFS in previous study 83% 97% of patients responded to ICE Improve peripheral blood progenitor cell collection in extensively pretreated patients No change in high-dose chemoradiotherapy regimen
Group 2 (two factors, 25% of population)	EFS in previous study 27% 86% of patients responded to ICE (most responses partial) Improve peripheral blood progenitor cell collection in extensively pretreated patients Dose-escalate ICE such that cycle 2 is ifosfamide 10 g/m^2, etoposide 600 mg/m^2, and same dose carboplatin Increase in dose of cyclophosphamide and etoposide in conditioning regimen to MTD, increase BCNU to 360 mg/m^2
Group 3 (three factors, 15% of population)	EFS in previous study 10% 50% of patients responded to ICE (none complete) Patients will receive a double ASCT (if match ALLO), cyclophosphamide 4.5 g/m^2 will be used for mobilization ASCT no. 1: high-dose ICE (doses are 15 g/m^2). Responders will receive ASCT no. 2 ASCT no. 2: total lymphoid irradiation/boost/etoposide/ara-C/melphalan or BEAM/boost in patients previously irradiated

rion to proceed to ASCT in Hodgkin's disease but other prognostic factors may also predict for long-term EFS in patients with relapsed and refractory Hodgkin's disease. There are several reports describing prognostic factors identifiable prior to the transplant that predict for a poor outcome with this approach [7]. We used a Cox regression analysis to identify prognostic factors prior to the initiation of ICE, not pre-ASCT, that predict for post-transplant outcome. The presence of B symptoms, extranodal disease and primary refractory/complete response duration < 1 year predicted for poor EFS. Patients with zero or one adverse factor had an EFS of 82.5% while those with two factors had an EFS of 33.3%, and patients with all three factors had an EFS of 10% (Table 1). The use of prognostic modeling has enabled us to define prognostic subgroups of patients. However, this is of limited value unless we can utilize this information to select therapy with the appropriate balance of risk and benefit.

The identification of three prognostic groups based on a simple model is the basis for our new program and allows us to tailor the intensity of the salvage regimen to the prognosis of the patients. While we expect that for the favorable subgroup, the excellent EFS will be maintained by delivering a treatment similar to that given in protocol, the second group (intermediate prognosis) will receive an augmented ICE regimen and a moderately escalated high-dose treatment. The unfavorable group, however, will receive two high-dose regimens in tandem. For those patients with an HLA-identical sibling donor the second transplant is a non-myeloablative allotransplant (Table 2).

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