Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin’s lymphoma


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Introduction

Aggressive non-Hodgkin’s lymphoma is potentially curable, with doxorubicin-based chemotherapy resulting in long-term failure-free survival rates of 40–45%, as demonstrated by the National High-Priority Lymphoma study [1]. Recent advances, such as the addition of rituximab to CHOP for diffuse large B-cell lymphoma (DLBCL) or the use of an accelerated dosing regimen, may increase the overall survival (OS) by an additional 10–15%, although the follow-up is relatively short [2]. Unfortunately, despite these advances about half of all diffuse large-cell lymphoma (DLCL) patients will have either persistence of tumor following initial therapy (primary refractory disease) or a relapse after a complete remission. For these patients, stem cell transplantation (SCT) has been demonstrated to have the greatest potential for a curative outcome [3]. However, this treatment approach has typically been restricted to patients with disease sensitive to second-line chemotherapy (Figure 1). Consequently, the effectiveness of the second-line regimen is of paramount importance.

To be suitable as pre-transplant therapy, a second-line regimen should have the following features: effective cytoreduction, a low incidence of non-hematological toxicity and a brief duration of therapy [4–7]. Some of the most commonly used regimens, etoposide/high-dose cytarabine/cisplatinum (ESHAP), dexamethasone/cisplatin/cytarabine (DHAP) and BCNU (bis-chloroethyl/nirotosourea)/etoposide/cytarabine/melphalan (mini-BEAM), have inherent limitations which may preclude SCT, including poor stem cell mobilization and non-hematological toxicities such as nephrotoxicity (DHAP and ESHAP) and pulmonary toxicity (mini-BEAM). To address these limitations, we developed the ifosfamide, carboplatin and etoposide (ICE) regimen as a short-course, dose-intensive regimen for cytoreduction and stem cell mobilization [8]. Though the results with the ICE regimen were good, only 45% of patients with chemosensitive disease are cured with SCT; therefore, to improve these results, combination of ICE with immunotherapy was studied.

Among the evolving therapies for NHL, anti-CD20 monoclonal antibodies (mAb) have shown significant promise [9, 10]. CD20 is a membrane-bound phosphoprotein with expression restricted to B-cell precursors and mature B-cells; it is not expressed on plasma cells or stem cells [11]. Approximately 93% of B-cell lymphomas express CD20, which has many features (e.g. it is not rapidly internalized, nor is it shed) that make it an attractive target for immunotherapy. Rituximab is a chimeric anti-CD20 IgG1κ mAb, which is comprised of murine variable regions and human constant regions. In vitro studies show that rituximab can lyse human B-cells via antibody-dependent cellu-
lary cytotoxicity (ADCC) and complement mediated lysis [12]. We have sought to improve on the ICE regimen by the addition of rituximab (R-ICE).

In the following update, the results of the ICE regimen for 222 patients treated over 7 years, now with 5 years median follow-up for surviving patients, are presented. The ICE regimen remains an excellent second-line chemotherapy approach, with short-duration, dose-intense chemotherapy capable of highly effective cytoreduction and peripheral blood progenitor cell (PBPC) mobilization. Given the importance of stem cell mobilization to proceed with the potentially curative high-dose therapy (HDT)/autologous stem cell transplantation (ASCT), we propose a new method of evaluating second-line chemotherapy programs which accounts for mobilization failures in the response rate—the mobilization-adjusted response rate (MARR). This will facilitate future comparisons of new and existing second-line regimens. Finally, we report preliminary results from the R-ICE regimen, demonstrating an improvement in complete response rates.

Patients and methods

Patients

Two hundred and twenty-two patients were enrolled on consecutive Institutional Review Board (IRB) approved protocols for relapsed and primary refractory NHL lymphoma at Memorial Sloan-Kettering Cancer Center (MSKCC) from 28 January 1993 to 1 August 2000. An additional 31 patients were treated on the R-ICE chemotherapy regimen and a preliminary report of these results was presented at the Annual Meeting of the American Society of Hematology in December 2001. The results of these two populations (ICE and R-ICE) are reported separately. Those study patients receiving protocol-directed investigational cytokines for the mobilization of stem cells were excluded from the analysis of PBPC mobilization—for this analysis the granulocyte colony-stimulating factor (G-CSF) mobilization data from the 163 patients reported in the initial ICE paper are utilized [8].

Eligibility for second-line therapy and HDT/ASCT

All patients were staged according to the Cotswold modification of the Ann Arbor system [13]. Hematopathologists at MSKCC performed histological reviews of the original and pre-ICE biopsy specimens. Histopathology, initially classified according to the International Working Formulation [14], was retrospectively reclassified according to the World Health Organization (WHO) classification scheme [15]. In general, patients with aggressive histology (DLBCL, mantle cell lymphoma, transformed indolent lymphoma, peripheral T-cell lymphoma and anaplastic large-cell lymphoma) were eligible, although depending on protocol availability other histologies may have been allowed. All patients had biopsy confirmation of relapsed or primary refractory disease prior to the initiation of ICE-based chemotherapy and had previously received only one doxorubicin-based chemotherapy program. Patients were required to have a corrected carbon monoxide diffusion capacity >50% of predicted and serum creatinine ≤1.5 mg/dl (or creatinine clearance 260 ml/min). Patients achieving a complete or partial response (CR or PR) to (R)-ICE were eligible for HDT with ASCT, provided a bone marrow biopsy revealed adequate cellularity and no involvement with large-cell lymphoma at the conclusion of ICE-based chemotherapy. Patients with small cleaved cells in the bone marrow were eligible. Finally, all patients had to have collected a minimum of 2 × 10^6 CD34+ cells/kg.

Modified International Working Group response criteria

The International Working Group response criteria [16] were modified to include the results of functional imaging with Gallium or 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scan. A complete response was defined as no evidence of disease by computed tomography (CT) scan and a normal functional imaging study (Gallium or PET) as documented by restaging ~2 weeks after completion of ICE. A conditional complete response was defined as no clinical signs or symptoms of lymphoma, but residual radiographical abnormalities <2 cm which were inaccessible to biopsy, and showed at least a 75% regression in size from the original radiographical study with negative functional imaging (gallium or PET). A partial response was defined as a >50% decrease in the sum of the products of the diameters of each measurable lesion with or without a positive functional imaging result.

ICE second-line chemotherapy treatment program

Three cycles of ICE chemotherapy were planned to be administered at 2 week intervals, as previously reported [8]. A brief summary of the treatment program is as follows: patients were treated as inpatients. On admission, a 12-h creatinine clearance was measured for subsequent carboplatin dosing. Chemotherapy was administered as follows: etoposide 100 mg/m² by intravenous bolus on days 1–3; carboplatin area under the curve (AUC) 5 (5 × [25 + CrCl]); maximum dose 800 mg) by intravenous bolus on day 2; and ifosfamide admixed with mesna both at a dose of 5 g/m² by 24-h continuous infusion beginning on day 2. Patients were treated with filgrastim 5 mcg/kg/day on days 5–12 for cycles 1 and 2. Filgrastim was increased to 10 mcg/kg/day following the third cycle until the completion of peripheral blood stem cell collection. Chemotherapy was ideally repeated every 14 days or when the absolute neutrophil count was ≥1000 cells/ml and the platelet count was ≥50,000/ml. Patients receiving R-ICE chemotherapy had rituximab 375 mg/m² administered as an intravenous bolus on day 1 and commenced ICE on day 3. The first cycle of R-ICE was preceded by an additional dose of rituximab 375 mg/m² on day −2.

Peripheral blood progenitor cells were collected as previously described [8] following the third cycle of R-ICE when the total white blood cell count
WBC) had risen to ≥5000 cells/mcl (most commonly on days 11 or 12 post day 1 of ICE). Collection continued until >6 × 10^6 CD34+ cells/kg body wt had been collected or for a maximum of five apheresis procedures. During apheresis 10 l of whole blood was processed over 2.5–3 h. A minimum of 2.0 × 10^6 CD34+ cells/kg body wt was considered a successful collection.

Transplant conditioning regimens
One hundred and fifty-three patients underwent ASCT. Conditioning regimens were determined based on prior radiotherapy and protocol availability at the time of transplantation. Eighty-two patients (54%) received a chemotherapy only conditioning regimen, while 71 patients (46%) received a total body irradiation (TBI)-based conditioning regimen. Involved field radiotherapy (boost radiotherapy) was administered to 87 patients prior to the high-dose conditioning regimen in patients whose residual disease after ICE-based therapy was limited to less than or equal to two anatomical regions. Boost radiotherapy was delivered at 150 cGy twice daily fractions administered over 6 days in patients who received TBI to a total dose of 1800 cGy, or 3000 cGy given over 10 days in patients receiving high-dose chemotherapy alone.

Mobilization-adjusted response rate
The mobilization-adjusted response rate (MARR) was defined as the [overall response rate (ORR) (%) minus mobilization failure rate (%)]. This response rate was calculated for the 163 patients included in the original ICE database, who received G-CSF mobilization as noted above. Additionally, this response rate was calculated for the R-ICE patients, who also received uniform G-CSF mobilization. Patients enrolled on protocols investigating novel cytokines were excluded from this analysis.

Statistics
Progression-free survival (PFS) and OS were assessed from the first day of (R)-ICE chemotherapy. Progression-free survival events were defined as disease progression or death from NHL. Survival analyses were performed to obtain estimates of median survival for the various second-line age-adjusted International Prognostic Index (AAIPI) groups using the methods of Kaplan and Meier [17]. The log-rank test [18] was used to compare survival distributions for the AAIPI groups.

Results
Patients
The characteristics of 222 patients treated with ICE are described in Table 1. The characteristics of 31 patients treated with R-ICE are summarized below (see ‘Improving the outcome of ICE with Rituximab’). The median age of the population was 46 years (range 14–71), reflecting the patient population referred to MSKCC for treatment of relapsed and refractory disease. Unfavorable characteristics including elevated lactate dehydrogenase (LDH), poor performance status (ECOG <2 or Karnofsky ≤70%) and advanced stage were seen in 53%, 30% and 79% of patients, respectively.

Response to ICE
One hundred and fifty-nine patients responded to ICE for an ORR of 71.6%, with 63 patients achieving a CR (28.4%) and 96 patients achieving a PR (43.2%) (Table 2). DLBCL comprised the majority of these patients (79%) with 28% achieving a CR and 41% a PR. Neither peripheral T-cell lymphoma (PTCL) nor peripheral T-cell lymphoma (PTCL)
(PR 23%, CR 31%) nor mantle cell lymphoma (MCL) (PR 63%, CR 0) responded particularly well.

**Stem cell mobilization**

One hundred of the 163 patients who received standard G-CSF mobilization as described above underwent leukapheresis. Ninety-one per cent began stem cell collection on day 11 or day 12 following day 1 of ICE. The median stem cell collection was $8.4 \times 10^6$ CD34+ cells/kg body wt in a median of three apheresis procedures (range 1–5). Fourteen per cent of patients failed to mobilize the minimum of $2 \times 10^6$ CD34+ cells/kg body wt.

In the initial 31 patients treated with R-ICE, a median of $6.3 \times 10^6$ CD34+ cells/kg body wt were harvested (range 0.3–15.6) in a median of three aphereses (range 1–5). Less than $2 \times 10^6$ CD34+ cells/kg body wt were collected in five patients (16%).

**Mobilization-adjusted response rate**

For the 163 patients evaluable for stem cell mobilization treated with ICE and G-CSF mobilization and for the 31 patients treated with R-ICE, MARR was calculated as described in the Patients and methods section. The MARR for the ICE regimen was 52% by intention-to-treat analysis. For the R-ICE regimen, MARR in evaluable patients reported at ASH 2001 was 61% by intention-to-treat.

**Autologous stem cell transplantation**

One hundred and forty-six of 159 patients responding to ICE underwent ASCT. The 13 patients who did not proceed to stem cell transplantation refused ASCT, failed to mobilize adequate numbers of stem cells or had rapid disease progression prior to the initiation of stem cell transplantation. Seven patients who failed ICE chemotherapy received additional treatment and went on to receive ASCT, these patients were considered ICE failures. A total of 153 patients received ASCT.

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**Table 2. Response to ICE chemotherapy by histology**

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of patients</th>
<th>CR n</th>
<th>CR %</th>
<th>PR n</th>
<th>PR %</th>
<th>F n</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>222</td>
<td>63</td>
<td>28.4</td>
<td>96</td>
<td>43.2</td>
<td>63</td>
<td>28.4</td>
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<tr>
<td>DLCL</td>
<td>176</td>
<td>50</td>
<td>28.4</td>
<td>72</td>
<td>40.9</td>
<td>54</td>
<td>30.7</td>
</tr>
<tr>
<td>B-cell</td>
<td>150</td>
<td>42</td>
<td>28</td>
<td>66</td>
<td>44</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>T-cell</td>
<td>26</td>
<td>8</td>
<td>30.8</td>
<td>6</td>
<td>23</td>
<td>12</td>
<td>46.2</td>
</tr>
<tr>
<td>ALCL</td>
<td>17</td>
<td>4</td>
<td>23.5</td>
<td>9</td>
<td>53</td>
<td>4</td>
<td>23.5</td>
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<tr>
<td>MCL</td>
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<td>0</td>
<td>7</td>
<td>63</td>
<td>4</td>
<td>37</td>
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<td>FCL 1–3</td>
<td>12</td>
<td>5</td>
<td>41.7</td>
<td>6</td>
<td>50</td>
<td>1</td>
<td>8.3</td>
</tr>
<tr>
<td>Othera</td>
<td>6</td>
<td>4</td>
<td>67</td>
<td>2</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*LPHD = 4 and SLL = 2.*

ALCL, anaplastic large cell lymphoma; DLCL, diffuse large-cell lymphoma; FCL, follicular cell lymphoma; ICE, ifosfamide, carboplatin, etoposide; LPHD, lymphocyte predominant Hodgkin’s disease; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

**(PR 23%, CR 31%) nor mantle cell lymphoma (MCL) (PR 63%, CR 0) responded particularly well.**

![Figure 2. Results of the overall experience with ifosfamide, carboplatin and etoposide (ICE). (A and B) Progression-free survival and overall survival for 222 patients treated with ICE as cytoreduction with intent to proceed to autologous stem cell transplantation (ASCT). (C) Progression-free survival of patients stratified by response to ICE (excluding treatment failures). There is a significant difference in progression-free survival between patients achieving a complete response (CR) versus partial response (PR) to the ICE cytoreduction.](image-url)
At a median follow-up of 5 years (64.6 months) for surviving patients, the PFS and OS are 29.2% and 38.4% by intention-to-treat analysis and 38.9% and 48.6% for chemosensitive patients (Figure 2A and B). Chemosensitive patients in a CR had a median time between treatments to 19 days. Attempts were made to improve the pretransplant cytoreduction by increasing the CR rate with the addition of rituximab to ICE (the goal was an increase from 24% to 45%). Preliminary results of our trial of rituximab combined with ICE chemotherapy have been reported [19]. Briefly, at the time of the initial report 31 patients with relapsed or refractory aggressive NHL will proceed to ASCT with ICE-based cytoreduction. We developed the ICE regimen specifically for pre-ASCT cytoreduction. We proposed using the MARR parameter as a primary end point in comparative studies of cytoreductive regimens. Clearly, efforts to improve the outcome of ICE with rituximab (R-ICE)

In the data reviewed above, ICE achieves these goals with a high ORR in patients with relapsed and refractory disease (72%) as well as a low rate of failure to mobilize stem cells (14%). We feel that these are the two most significant parameters in evaluating the effectiveness of a pre-transplant cytoreductive regimen. These parameters can be incorporated into a single value, the mobilization-adjusted response rate [MARR = ORR (%) — mobilization failures (%)] to evaluate the effectiveness of a cytoreductive regimen. In the data reviewed above for ICE, MARR is 52%. The MARR for R-ICE is 64%. Table 3 illustrates the potential utility of MARR. For example, ORR for HD with mini-Beam for HD is 84% which would appear to be an excellent regimen. However, with a 43% rate of mobilization failure, MARR is only 41%. In contrast, ESHAP for HD and NHL has an ORR of 64%, but because of the much lower mobilization failure rate of 15%, it has a similar MARR despite the inferior ORR. We propose using the MARR parameter as a primary end point in comparative studies of cytoreductive regimens. It is clear from this result that there is substantial room for improvement in the cytoreductive regimens. Clearly, efforts to

Discussion

The role of high-dose therapy and ASCT in the treatment of recurrent aggressive lymphoma has been well described, including the randomized Parma trial [3]. However, the Parma trial was limited by the fact that it only included patients with chemosensitive, relapsed disease. Thus, the critical role of cytoreductive therapy for primary refractory patients was not addressed. Numerous regimens have been used for cytoreduction prior to ASCT including DHAP, ESHAP, mini-Beam and dexamethasone (500 mg/m2) and etoposide (300 mg/m2) for HD and NHL with a high-dose dexamethasone [5–7, 25]. While these regimens have been effective, they were not specifically designed for pre-ASCT cytoreduction. We developed the ICE regimen specifically for pre-ASCT cytoreduction with the following goals: effective cytoreduction; minimal non-hematological toxicity; and ability to mobilize adequate numbers of peripheral progenitor stem cells. Based on intention-to-treat, slightly more than half of the patients with relapsed or refractory aggressive NHL will proceed to ASCT with ICE-based cytoreduction.

Progression-free and overall survival

At a median follow-up of 5 years (64.6 months) for surviving patients, the PFS and OS are 29.2% and 38.4% by intention-to-treat analysis and 38.9% and 48.6% for chemosensitive patients (Figure 2A and B). Chemosensitive patients in a CR had a superior 5-year survival compared with those transplanted in a PR for both PFS (52.2% versus 30.1%; P = 0.012) (Figure 2C) and OS (59.3% versus 41.7%; P = 0.03) (data not shown). Patients who did not respond to ICE had a median survival of only 4.8 months.

Improving the outcome of ICE with rituximab (R-ICE)

Attempts were made to improve the pretransplant cytoreduction by increasing the CR rate with the addition of rituximab to ICE (the goal was an increase from 24% to 45%). Preliminary results of our trial of rituximab combined with ICE chemotherapy have been reported [19]. Briefly, at the time of the initial report 31 patients with relapsed or refractory aggressive NHL were evaluable. Rituximab 375 mg/m2 was administered on day 1 of each cycle with ICE administered starting on day 3. In cycle 1 an additional dose of rituximab was administered on day –2. Addition of rituximab increased the incidence of neutropenia and prolonged the median time between treatments to 19 days.

Addition of rituximab did not significantly impact on mobilization failures (17%) and the median number of stem cell collected was 6.3 × 106 CD34+ cells/kg body wt. Though the ORR compared to historical controls was not significantly improved (81% versus 73%), the CR rate was (55% versus 28%). Further analysis of this trial is pending and will be reported separately.

Table 3. Mobilization adjusted-response rate for ICE, R-ICE and other regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Disease</th>
<th>n</th>
<th>ORR</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Aphereses [median (range)]</th>
<th>Median CD34+ (× 106 cells/kg)</th>
<th>% Failed mobilization (&lt;2 × 106 cells/kg)</th>
<th>MARR</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>ICE</td>
<td>NHL</td>
<td>163</td>
<td>66.3</td>
<td>24</td>
<td>42</td>
<td>3 (1–5)</td>
<td>8.4</td>
<td>14</td>
<td>52</td>
<td>[8]</td>
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<tr>
<td>R-ICE</td>
<td>NHL</td>
<td>31</td>
<td>81</td>
<td>55</td>
<td>26</td>
<td>6.3</td>
<td>17</td>
<td>64</td>
<td>[19]</td>
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<tr>
<td>Mini-Beam</td>
<td>HD</td>
<td>55</td>
<td>84</td>
<td>51</td>
<td>33</td>
<td>(1–7)</td>
<td>2.7</td>
<td>43</td>
<td>41</td>
<td>[20]</td>
</tr>
<tr>
<td>Ifos/Vino</td>
<td>HD, NHL</td>
<td>10</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>10.9</td>
<td>&lt;11*</td>
<td>29–40</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>MINE</td>
<td>HD, NHL</td>
<td>27</td>
<td>67</td>
<td>38</td>
<td>29</td>
<td>3</td>
<td>13.3</td>
<td>8</td>
<td>59</td>
<td>[22]</td>
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<tr>
<td>VIM</td>
<td>HD, NHL</td>
<td>46</td>
<td>56</td>
<td>39</td>
<td>17</td>
<td>3</td>
<td>10.6</td>
<td>8</td>
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<td>ESHAP</td>
<td>HD, NHL</td>
<td>84</td>
<td>64*</td>
<td>37*</td>
<td>27*</td>
<td>(1–4)</td>
<td>4.9</td>
<td>15</td>
<td>–49</td>
<td>[23]</td>
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<tr>
<td>CY (1.5 g/m2)</td>
<td>HD, NHL</td>
<td>78</td>
<td>64*</td>
<td>37*</td>
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<td>3.3</td>
<td>29</td>
<td>–35</td>
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<tr>
<td>DHAP</td>
<td>NHL</td>
<td>38</td>
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<td>25</td>
<td>38.9</td>
<td>2 (1–3)</td>
<td>5.9</td>
<td>14.7</td>
<td>49.2</td>
<td>[24]</td>
</tr>
<tr>
<td>CY</td>
<td>NHL</td>
<td>34</td>
<td>63.9</td>
<td>25</td>
<td>38.9</td>
<td>2 (1–3)</td>
<td>7.1</td>
<td>10.5</td>
<td>53.4</td>
<td>[24]</td>
</tr>
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</table>

*ESHAP response rate is base on their historic data.

CR, complete response; CY, cyclophosphamide; DHAP, dexamethasone/cisplatin/cytarabine; ESHAP, etoposide/high-dose cytarabine/cisplatinum; ICE, ifosfamide, carboplatin, etoposide; mini-Beam, BCGU (bis-chloro-ethyl) nitrosourea/etoposide/cytarabine/melphalan; Ifos/Vino, ifosfamide and mitoxantrone; MARR, mobilization-adjusted response rate; MINE, ifosfamide, mesna, mitoxantrone and etoposide; ORR, overall response rate; PR, partial response; R-ICE, ICE plus rituximab; VIM, etoposide, ifosfamide and mitoxantrone.
improve the quality of response to second-line chemotherapy may be warranted, given the improvement in PFS and OS with complete responses compared with partial responses. Furthermore, we are currently investigating the utility of prognostic models capable of distinguishing distinct risk groups for whom new therapeutic approaches are necessary.

One novel approach to enhancing ICE chemotherapy is to add the chimeric monoclonal antibody rituximab to the regimen. Preclinical data suggests that the combination of rituximab with certain agents, including platinum derivatives, enhances cell kill compared with chemotherapy alone. Clinical trials have demonstrated that addition of rituximab to conventional chemotherapy results in little additional toxicity. A large randomized trial of rituximab combined with CHOP chemotherapy for elderly patients with DLBCL has shown statistically and clinically meaningful improvements in event-free survival and OS compared to CHOP alone. We have added rituximab to the ICE regimen. Though the combination is well tolerated with no impact on stem cell mobilization, we did see an increase in the myelotoxicity. Preliminary results demonstrate that the CR rate in the patients treated with R-ICE were significantly higher compared with the historical controls but we await further follow-up to determine if this will translate into an improvement in overall outcome.

Disclosure

The authors do not have any financial relationships with companies whose products are mentioned in the text.

References