Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin’s lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience

On behalf of the GEL/TAMO Spanish Group

1Hospital Son Dureta, Palma de Mallorca; 2Hospital Clinico Universitario, Salamanca; 3Hospital Clinico Universitario de Valencia; 4Hospital de la Princesa, Madrid; 5Hospital 12 de Octubre, Madrid; 6Hospital de la Santa Creu i Sant Pau, Barcelona; 7Hospital Marques de Valdecilla, Santander; 8Hospital de la Vall de Hebron, Barcelona; 9Hospital Clinic i Provincial, Barcelona; 10Hospital Ramon y Cajal, Madrid; 11Hospital Nuestra Señora de Aranzazu, San Sebastian; 12Hospital de Cruces, Vizcaya; 13Institut Catala d’Oncologia, Barcelona; 14Clinica Universitaria de Navarra, Pamplona; 15Hospital Juan Canalejo, La Coruña; 16Hospital La Fe, Valencia; 17Hospital Xeral i Cies, Vigo; 18Hospital General de Jerez, Jerez de la Frontera, Spain

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Background: Here we evaluate the results of high-dose chemotherapy and autologous stem-cell transplantation (HDC/ASCT) in 114 patients included in the GEL/TAMO registry between January 1990 and December 1999 with diffuse large B-cell lymphoma who failed to achieve complete remission (CR) with front-line conventional chemotherapy.

Patients and methods: Sixty-eight per cent had a partial response (PR) and 32% failed to respond to front-line therapy. At transplant, 35% were chemoresistant and 29% had two to three adjusted International Prognostic Index (a-IPI) risk factors.

Results: After HDC/ASCT, 57 (54%) of 105 patients evaluable for response achieved a CR, 16 (15%) a PR and 32 (30%) failed. Nine patients were not assessed for response because of early death due to toxicity. With a median follow-up of 29 months for alive patients, the survival at 5 years is 43%, with a disease-free survival for complete responders of 63%. The lethal toxicity was 8%. Multivariate analysis revealed a-IPI and chemoresistance to be predicting factors.

Conclusions: Our results show that one-third of patients who do not obtain a CR to front-line chemotherapy may be cured of their disease with HDC/ASCT. However, most chemoresistant patients pretransplant failed this therapy. For this population, as well as for those who presented with adverse factors of the a-IPI, pretransplant novel therapeutic modalities need to be tested.

Key words: autologous stem-cell transplantation, diffuse large B-cell, non-Hodgkin’s lymphoma

Introduction

Approximately 30–50% of patients with aggressive non-Hodgkin’s lymphoma (NHL) fail to achieve a complete response (CR) with standard anthracycline-based induction chemotherapy [1, 2]. The Parma trial established that high-dose chemotherapy with autologous stem cell transplantation support (HDC/ASCT) is a more effective therapeutic procedure than conventional salvage chemotherapy for patients with chemosensitive relapse [3]. However, the value of this therapy for patients who do not achieve a CR after the induction regimen is less well defined. Initial studies showed a dismal prognosis for patients transplanted with primary refractory disease. In fact, Philip et al. [4] reported an event-free survival of 10–15% with a prolonged follow-up, which is similar to that observed with standard-dose salvage regimens.

However, when the chemosensitive condition was defined, the results in this group of patients who were initially deemed primary failures but chemosensitive were substantially better than the corresponding truly chemoresistant primary failures [5, 6]. Recently, Vose et al. [6] reported data from the ABMTR (Autologous Blood and Marrow Transplant Registry)
pointing out the benefit of HDC procedures in induction failure patients with this group of lymphomas provided that the chemosensitive condition has been established. The Memorial Sloan-Kettering group arrived at the same conclusion in patients with primary refractory aggressive NHL who received salvage regimen with ICE (ifosfamide, carboplatin, etoposide). Only those patients sensitive to the salvage regimen were consolidated with ASCT [7].

Herein, we analyze retrospectively in a collaborative setting the outcome of 114 patients with diffuse large B-cell lymphomas who did not achieve a CR to induction treatment. Secondly, we analyzed those variables at transplant that are associated with outcome, in order to define those patients who will benefit from this therapeutic modality.

Patients and methods

Patients

Between July 1990 and December 1999, the hospitals participating in the Spanish Group for Lymphoma and Autologous Transplantation (GEL/TAMO) included 452 patients with diffuse large cell lymphoma who underwent HDC/ASCT. In this report we retrospectively selected the 114 (25%) cases from the registry with B-cell phenotype who failed to respond to first-line induction treatment and who received HDC/ASCT as part of their salvage treatment. Other types of aggressive lymphoma, including those cases with T-cell immunophenotype, were excluded from the analysis.

Patients were eligible for ASCT according to standard bone marrow transplant guidelines, including the lack of severe concomitant medical or psychiatric illness, active central nervous system involvement or HIV seropositivity. Other criteria for ineligibility included a bilirubin level >2 mg/dl, creatinine level >1.5 mg/dl, low cardiac ejection fraction (<50%) and a forced expiratory volume in 1 second <60% and/or carbon monoxide diffusion test <50% of predicted level. Patients were staged according to standard procedures, with a physical examination, serum chemistry assays, chest X-rays, and computed tomography of the neck, chest, abdomen and pelvis. Bone marrow aspirates and biopsies were obtained prior to HDC, as well as the other staging procedures performed at diagnosis. All patients were staged according to the Ann Arbor staging system and standard variables of the International Prognostic Index (IPI) [8] were evaluated, as well as others of prognostic value (i.e. B-symptoms and β2-microglobulin). Table 1 depicts the clinical characteristics at diagnosis. Information on these variables was also collected pretransplant to determine their prognostic importance. The histological diagnosis was performed by the local pathologist in each center, with no central pathologist review. However, the policy of the Group is to consult cases of difficult diagnosis, which are reviewed by two or more expert histopathologists.

Patients were assessed for response ~90 days after the infusion procedure with standard physical examination and radiological procedures. Evaluation of response was performed by the investigator responsible in each center. Patients were classified according to response to front-line regimen as partial responders if the reduction in the sum of the products of each center. Patients were classified according to response to front-line treatment with no central pathologist involvement. Two or more expert histopathologists.

The different treatment regimens received as front-line therapy were as follows: 67 (59%) CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), 28 (25%) third-generation regimens, nine (8%) second-generation regimens and 10 (9%) others. Forty-four per cent of the patients received one regimen and 56% two or more regimens prior to transplant. Conditioning regimens are depicted in Table 2. Most patients (72%) received BEAM (carmustine, etoposide, cytarabine, melphalan) (44%) or BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) (28%) regimens. Twenty-one patients received radiotherapy post-transplantation, of whom 17 presented with bulky disease at diagnosis. Two patients received interferon-α as adjuvant treatment post-transplant and one patient received rituximab.

Thirty-four patients (30%) received bone marrow as stem-cell product, 72 patients (65%) peripheral stem cells and eight patients (7%) both bone marrow and peripheral stem cells. The median number of aphereses was two (range one to nine), and the 80 patients who received peripheral blood were mobilized with granulocyte colony stimulating factor (G-CSF).
alone in 44% of cases and G-CSF plus chemotherapy in 49% of cases. No purging was used except for three patients who underwent CD34+ selection; 77 patients received G-CSF \((n=66)\) or granulocyte–macrophage colony stimulating factor \((n=11)\) post-transplant.

### Table 2. Patients’ characteristics at transplant \((n=114)\)

<table>
<thead>
<tr>
<th>Characteristics at transplant</th>
<th>(n)</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>74</td>
<td>65</td>
</tr>
<tr>
<td>FT</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>B symptoms</td>
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<td>20</td>
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<tr>
<td>Extramedal sites</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>&gt;1</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>NA</td>
<td>2</td>
<td></td>
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<tr>
<td>Bone marrow involvement</td>
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<td>7</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
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<td>97</td>
<td>87</td>
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<tr>
<td>&gt;1</td>
<td>15</td>
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</tr>
<tr>
<td>NA</td>
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<td></td>
</tr>
<tr>
<td>Bulky mass</td>
<td>18</td>
<td>17</td>
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<tr>
<td>High LDH</td>
<td>37</td>
<td>35</td>
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<tr>
<td>Age-adjusted IPI</td>
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<td></td>
</tr>
<tr>
<td>0–1</td>
<td>73</td>
<td>72</td>
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<tr>
<td>2–3</td>
<td>29</td>
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<tr>
<td>Stem cell source</td>
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<tr>
<td>BM</td>
<td>34</td>
<td>30</td>
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<tr>
<td>PB</td>
<td>72</td>
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<tr>
<td>Conditioning regimen</td>
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</tr>
<tr>
<td>BEAM</td>
<td>50</td>
<td>44</td>
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<tr>
<td>BEAC</td>
<td>32</td>
<td>28</td>
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<tr>
<td>TBI/cyclophosphamide</td>
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<td>12</td>
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<tr>
<td>CVB</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Cytokines post-infusion ((77) patients)</td>
<td></td>
<td></td>
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<tr>
<td>G-CSF</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

PR, partial response; FT, failure treatment; NA, not available; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; BM, bone marrow; PB, peripheral blood; BEAM, carmustine, etoposide, cytarabine, melphalan; BEAC; carmustine, etoposide, cytarabine, cyclophosphamide; TBI, total-body irradiation; CVB, carmustine, etoposide, cyclophosphamide; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte–macrophage colony stimulating factor.

### Statistical methods

For calculation of overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS), patients were evaluated at the time of last follow-up. OS was measured from the date of transplantation and was estimated according to the Kaplan–Meier method \([9]\). DFS for patients who attained a CR post-transplant was estimated by the Kaplan–Meier method. Comparison among those variables of interest was performed by the log-rank test \([10]\). A forward stepwise Cox proportional hazards regression model was used for multivariate analysis, including those variables that were found by univariate analysis to be associated with outcome (Table 3).

### Results

#### Clinical characteristics at diagnosis

As shown in Table 1, median age at diagnosis was 40 years \((range\ 13–73)\). Twenty-two patients \((19%)\) presented with bone marrow involvement by the lymphoma. According to the adjusted IPI \((a-IPI)\) for 104 patients <60 years old, 73% of these patients had two \((41%)\) or three \((32%)\) adverse factors at diagnosis.

#### Response to front-line induction therapy

Seventy-eight patients \((68%)\) attained a maximal response of PR and 36 patients \((32%)\) failed to respond to induction treatment. The median time from diagnosis to transplant was 8 months \((range\ 2–36)\), and four patients who attained a PR to front-line treatment progressed prior to transplant. Overall, 74 patients \((65%)\) were deemed chemosensitive and 40 patients \((35%)\) chemoresistant at the moment of transplant.

#### Clinical characteristics pretransplant

Table 2 depicts the clinical characteristics of the patients pretransplant. Briefly, 20% of the patients presented with B symptoms and eight patients \((7%)\) had bone marrow involvement. Fifteen patients \((13%)\) had an Eastern Cooperative Oncology Group performance status of >=2 and 18 patients \((16%)\) presented with a bulky mass \((>10\ cm)\) pretransplant. Of the 58 patients for whom \(B_2\)-microglobulin data were available pretransplant, 26 \((45%)\) had a high level \((\geq3\ mg/dl)\). According to the a-IPI pretransplant, in 102 informative cases 73 patients \((72%)\) presented with no or one risk factors, 23 \((22%)\) with two and six \((6%)\) with three risk factors. The median age of patients with induction failure was 35 years \((range\ 13–59)\), and for the PR patients was 44 years \((range\ 14–73)\).

#### Response to transplant

Nine patients died of toxicity early post-transplant and 105 patients were evaluable for response. Fifty-seven \((54%)\) achieved a CR post-transplant, 16 patients \((15%)\) a PR and 32 patients \((30%)\) failed. Of 40 patients transplanted in chemoresistant disease, only six \((15%)\) achieved a CR with the transplant. However, 51 patients \((69%)\) of the 74 transplanted in chemosensitive disease achieved a CR \((P<0.001)\).
With a median follow-up of 29 months (range 1–80), 56 patients are alive (49%) and 58 patients have died. Forty-seven patients (81%) died of disease progression. Nine patients (8%) died of toxicity and two patients died of a second neoplasia, one of whom was in unmaintained CR. The actuarial OS at 5 years is 43% and the actuarial DFS at 5 years for patients who attained a CR is 63% (Figures 1 and 2).

### OS and DFS

With a median follow-up of 29 months (range 1–80), 56 patients are alive (49%) and 58 patients have died. Forty-seven patients (81%) died of disease progression. Nine patients (8%) died of toxicity and two patients died of a second neoplasia, one of whom was in unmaintained CR. The actuarial OS at 5 years is 43% and the actuarial DFS at 5 years for patients who attained a CR is 63% (Figures 1 and 2).

### Prognostic factors

Table 3 shows the univariate analysis for OS and DFS. The presence of two or three adverse factors of the a-IPI, extranodal disease and chemoresistance were associated with a worse outcome (Figure 1). However, by multivariate analysis, only chemoresistance [hazard ratio (HR) 0.23; 95% confidence interval (CI) 0.13–0.42; \( P < 0.001 \) for OS; and HR 0.43; 95% CI 0.25–0.74; \( P = 0.002 \) for DFS] and one or more adverse factors of the a-IPI (HR 0.32; 95% CI 0.15–0.70; \( P = 0.004 \) for OS; and HR 0.39; 95% CI 0.21–0.74; \( P = 0.004 \) for DFS) were associated with a dismal outcome. Interestingly, six patients with chemoresistant disease pretransplant who were rendered CR post-transplant still had a statistically significant unfavorable DFS compared with those patients who were chemosensitive pretransplant (\( P < 0.001 \)). This suggests an intrinsic resistance to chemotherapy in these patients (Figure 2).

In addition, those patients with bulky disease at diagnosis who received post-transplant radiotherapy (17 of 79 patients) fared significantly better than patients with bulky disease that were not consolidated after transplant: 82% (95% CI 64% to 100%) versus 31% (95% CI 17% to 45%) (\( P = 0.01 \)) OS at 5 years and 57% (95% CI 33% to 82%) versus 20% (95% CI 8% to 32%) (\( P = 0.02 \)) PFS at 5 years, respectively.

### Table 3. Prognostic factors in univariate analysis

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>% survival at 5 years (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-IPI (0–1 versus &gt;1 risk factors)</td>
<td>53 (41–65) versus 12 (0–26)</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>a-IPI (0 versus ≥1 risk factors)</td>
<td>75 (61–89) versus 18 (7–29)</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Extranodal disease (0 versus ≥1 risk factors)</td>
<td>52 (39–65) versus 25 (10–39)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pretransplant status (PR versus FT)</td>
<td>61 (48–74) versus 10 (0–20)</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-IPI (0–1 versus &gt;1 risk factors)</td>
<td>69 (55–83) versus 19 (0–52)</td>
<td>( &lt;0.02 )</td>
</tr>
<tr>
<td>a-IPI (0 versus ≥1 risk factors)</td>
<td>64 (49–79) versus 11 (3–19)</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Pretransplant status (PR versus FT)</td>
<td>71 (57–84) versus 0</td>
<td>( &lt;0.001 )</td>
</tr>
</tbody>
</table>

CI, confidence interval; a-IPI, adjusted International Prognostic Index; PR, partial response; FT, failure treatment.

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**Figure 1.** Overall survival from transplantation.
Patients with diffuse large B-cell lymphoma who do not achieve a CR after induction treatment do not constitute a uniform population [11, 12]. Indeed, according to most series, the prognosis of patients refractory to induction treatment is worse than that observed in those who obtain a PR [6, 7, 13]. Our results in this group of patients who did not obtain a CR to first-line regimen are similar to most series, including Stiff et al. [5], Prince et al. [14] and Horning et al. [13], who reported a PFS ~40% with a maximum follow-up of 3 years, which is similar to our data. Indeed, with a median follow-up of 29 months, 49% of our patients are alive and 63% of the complete responders remain free of disease at 5 years.

In any case, the prognosis for these patients with conventional salvage regimen is poor [15, 16]. Josting et al. [17] reported 15% of responses for what they call primary progressive aggressive NHL, which included patients who had relapses within 90 days of achieving CR with front-line therapy. Moreover, comparing conventional salvage therapy versus transplant, Martelli et al. [18] found superiority of the transplanted group, with 96% response rate versus 59% for the conventional group. However, probably due to the low power of the study, no differences in the PFS were observed. Regarding toxicity, our 8% lethal toxicity during the first 100 days was similar to recently reported series [6].

The prognosis of chemosensitive patients who undergo a transplant after failing to achieve a CR to front-line regimen, compared with those who respond to salvage regimen after relapse, is a question that needs to be addressed. In the recent report by Kewalramani et al. [7], ~50% of patients failing to achieve CR to front-line therapy were deemed chemosensitive to the salvage regimen, and therefore underwent the ASCT procedure. Interestingly, and as highlighted by the authors, this figure was substantially inferior to the 81% response rate to the same salvage regimen (ICE) observed in patients who had relapsed disease. Although this is not a straightforward comparison, as the risk factors of the two populations were not accounted for, this difference may indicate different intrinsic tumor characteristics in the two scenarios.

We found that ‘truly’ induction-resistant patients had a much worse prognosis than partial responders. In fact, in our study only six of 40 (15%) patients who were transplanted in less than PR attained a CR after transplant, compared with 54% of those deemed PR pretransplant. These differences in response translated in a substantially worse OS and, interestingly, DFS than those in PR (Figures 1 and 2). It is not possible to obtain this information from the Memorial Sloan-Kettering study, as only those patients who responded to the salvage regimen were actually transplanted. In any case, our results confirm prior studies from the ABMTR and Southwest Oncology Group which provided evidence that chemoresistant patients had a poorer survival rate (19%) compared with patients with chemosensitive disease (48%) [5, 6]. These data, as well as those from Prince et al. [14], are similar to those obtained in the Parma study for patients with sensitive relapse [3]. Therefore, provided that chemosensitivity is established, a small difference in outcome after being transplanted seems to exist between relapsed patients and patients failing to achieve CR after induction therapy. This point differs from the report by Mills et al. [19], who evaluated 107 patients with relapsed and refractory NHL treated with ASCT, of whom 26 were identified as first partial responders at the time of transplantation. The authors found an unusually high PFS of 69% at 5 years for this last group of patients, compared with 32% for patients with chemosensitive but relapsed disease.

Our findings that chemoresistance is associated with a poorer survival confirm recent series [7] and highlight the importance of designing new therapeutic modalities for this kind of patient, such as the new monoclonal antibodies.

**Figure 2.** Disease-free survival from transplantation.

**Discussion**

Patients with diffuse large B-cell lymphoma who do not achieve a CR after induction treatment do not constitute a uniform population [11, 12]. Indeed, according to most series, the prognosis of patients refractory to induction treatment is worse than that observed in those who obtain a PR [6, 7, 13]. Our results in this group of patients who did not obtain a CR to first-line regimen are similar to most series, including Stiff et al. [5], Prince et al. [14] and Horning et al. [13], who reported a PFS ~40% with a maximum follow-up of 3 years, which is similar to our data. Indeed, with a median follow-up of 29 months, 49% of our patients are alive and 63% of the complete responders remain free of disease at 5 years.
to initial courses of the induction regimen may have a favor-
tested for this group [21]. Whether early salvage treatment
modality, and therefore other therapeutic strategies need to be
chemoresistant pretransplant or have one or more adverse fac-
can be rescued with HDC followed by ASCT. Patients who are
induction treatment with anthracycline-containing regimens
fuse large B-cell NHL who fail to achieve a CR with front-line
from our data that approximately one-third of patients with dif-
needed to resolve this question. In fact, there is no clear con-
sensus as to whether this approach results in any substantial
benefit. Indeed, the Memorial Sloan-Kettering group did not
find prognostic importance of radiotherapy in their study and
moreover, indirectly, in the Parma study [3], there was no
benefit for those patients who received radiotherapy for conso-
lation of bulky tumor masses. Thus randomized studies are
needed to resolve this question.

Despite the inevitable bias of selection of data associated
with a retrospective cooperative group study, we can conclude
from our data that approximately one-third of patients with dif-
fuse large B-cell NHL who fail to achieve a CR with front-line
induction treatment with anthracycline-containing regimens
can be rescued with HDC followed by ASCT. Patients who are
chemoresistant pretransplant or have one or more adverse fac-
tors according to the a-IPI fare poorly with this therapeutic
modality, and therefore other therapeutic strategies need to be
tested for this group [21]. Whether early salvage treatment
with ASCT consolidation in patients who are slow responders
to initial courses of the induction regimen may have a favor-
able impact on outcome is currently being investigated.

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