Impact of high-dose salvage therapy (BEAM) on overall survival in younger patients with advanced large-cell lymphomas entered into BNLI trials

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Summary

The survival of two cohorts of patients with stage III/IV large-cell lymphomas treated by CHOP has been compared. In the first cohort of 88 patients (1974-1982), high-dose therapy with autologous bone marrow transplantation (ABMT) was not available as salvage therapy and in the second cohort of 87 patients (1987-1992), this was the recommended salvage for patients with disease that was still chemosensitive to conventional-dose therapy. The actuarial overall survivals at five years were 40% and 44% in the first and second cohorts, respectively, indicating that the availability of ABMT had made little impact.

Of the 62 patients in the second cohort who failed CHOP therapy, 8 died before second-line chemotherapy could be given, 1 refused more therapy, and 8 were considered unsuitable for further combination chemotherapy. Seven patients with localized disease remained received local radiotherapy. Of the 38 patients given salvage therapy, 14 had chemoresistant disease. Only 9 patients received high-dose BEAM chemotherapy and ABMT, and 7 remain disease-free. ABMT was restricted to a highly select patient group, and as a result more widespread application of this strategy might result in only a modest further improvement.

Key words: autograft, large-cell lymphomas, survival impact

Background

Chemotherapy with the CHOP regimen was introduced for the treatment of large-cell lymphomas over 20 years ago [1]. More recent regimens which include an increased number of drugs and modestly increased dose intensity do not appear to convey a significant overall benefit [2].

In patients failing standard chemotherapy, very high-dose therapy facilitated by autologous hematopoetic stem-cell transplantation can improve survival [3]. The role of high-dose therapy is restricted to younger patients and those with chemosensitive disease [4, 5], either those achieving a partial response (PR) on frontline therapy or those responding to conventional-dose salvage therapy after relapse from complete remission (CR). In view of this high level of selectivity of patients receiving high-dose therapy, it is not readily possible to ascertain the overall impact of this form of salvage treatment in the management of large-cell lymphomas.

To provide insight into the potential contributions of high-dose salvage therapy to survival in younger patients, we have analyzed the outcome of a cohort of stage III/IV patients with diffuse large-cell and diffuse mixed cell lymphomas under the age of 60 years treated with CHOP between 1987 and 1992. At this time, high-dose therapy and autologous bone marrow transplantation was the recommended form of salvage treatment for 'suitable' patients within the BNLI. The overall results of this cohort of patients are compared with a similar cohort of patients treated with CHOP between 1974 and 1982, before high-dose salvage therapy became established.

Patients

Between 1974 and 1982, 88 patients between the ages of 16 and 59 years presenting with stage III/IV diffuse large-cell (including immunoblastic) and diffuse mixed-cell lymphomas were treated with a weekly CHOP regimen for four weeks (cyclophosphamide 750 mg/m² day 1 and day 8; hydroxydaunorubicin 25 mg/m² day 1 and day 8; vincristine 1.4 mg/m² [max 2 mg] day 1 and day 8; prednisolone days 1–10). In responding patients, at least two cycles were given after attainment of CR with a minimum of six cycles administered. For patients failing first-line therapy, further therapy was given at the discretion and choice of the individual physicians. No patient in this cohort received salvage treatment with high-dose therapy and autologous bone marrow transplantation (ABMT). A second cohort of similar patients (Table 1) received identical therapy between 1987 and 1992 in a trial in which patients were randomized between CHOP and PACEBOM, an 11-week multiagent weekly regimen [6]. In this cohort, high-dose therapy with BEAM (BCNU 300 mg/m² day −6; etoposide 200 or 400 mg/m² day −5 to day −2; cytosine arabinoside 200 mg/m² twice daily day −5 to day −2; melphalan 140 mg/m² day −1) and ABMT (day 0) [5] was recommended as salvage therapy for those patients with chemosensitive disease but was not mandatory.
### Table 1. Patient characteristics.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Median age (range)</td>
<td>49.5 years (17–59)</td>
<td>44 years (17–59)</td>
</tr>
<tr>
<td>Sex M:F (%)</td>
<td>58:42</td>
<td>71:29</td>
</tr>
<tr>
<td>Stage III</td>
<td>38%</td>
<td>36%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>62%</td>
<td>64%</td>
</tr>
<tr>
<td>B symptoms</td>
<td>55%</td>
<td>58%</td>
</tr>
<tr>
<td>ESR &gt;39 mm/h</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>Albumin &lt; 36 g/l</td>
<td>38%</td>
<td>30%</td>
</tr>
</tbody>
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### Results

The outcome of the two patient cohorts is shown in Table 2. In the 1974–1982 cohort, 65/88 (74%) of patients either failed to achieve CR or relapsed from CR compared to 62/87 (71%) in the 1987–1992 cohort. The fact that the actuarial overall survival at five years was only marginally better in the second cohort suggests that there has been little improvement in salvage therapy.

A more detailed analysis of outcome has been performed in those patients failing first-line therapy in cohort 2. Eight patients died before receiving any second-line therapy, 7 dying while receiving or within 1 month of receiving CHOP, and 1 dying at relapse before any further treatment was administered (Figure 1). Of the 45 patients who achieved a CR, 20 relapsed, with 19 alive and eligible for second-line therapy, which together with the 35 patients who survived first-line chemotherapy but did not achieve CR, adds up to 54 patients eligible for further chemotherapy. Of these, 1 patient refused further treatment and died, and 8 were considered unsuitable for intensive therapy and received 'palliative' treatment only. This included 1 patient found at the end of treatment to have residual 'low-grade lymphoma' in the bone marrow, who subsequently received oral chlorambucil. This patient remains alive 79 months from diagnosis, and the other 7 patients treated with palliative therapy have all died. Six patients had only localized residual masses at the end of treatment and were consolidated with radiotherapy. Three achieved a CR which has been maintained at 47–61 months from diagnosis. The other 3 died despite further chemotherapy in 2. One patient with a localized relapse also received radiotherapy as initial second-line therapy, but the disease progressed and he died despite further standard-dose chemotherapy.

Only 38 patients (61% of all treatment failures) thus received nonpalliative chemotherapy as second-line treatment. Three of these with a partial response to CHOP went on directly to BEAM plus ABMT, and all remain in continued complete remission (CCR) at 20, 54, and 57 months from the time of the high-dose therapy. Thirty-five patients received a variety of standard-dose second-line therapies, including IMVP16 [7], PACEBOM [6], DHAP [8], and mini-BEAM [9]. Five achieved a CR (14%) and 2 remain in CCR. None of these patients had their remission consolidated with an autograft. Sixteen patients had a PR and 4 went on to a BEAM autograft. Three remain in CCR at 19, 20, and 22 months since the autograft, and 1 died of disease. Of the remaining 12 patients, 1 was alive with disease at 23 months from diagnosis when he emigrated and was lost from follow-up. Fourteen patients had no response to second-line chemotherapy. Despite this chemoresistance, 2 received BEAM and ABMT and 1 remains in CCR at 31 months from the time of transplant. The other 13 patients have all died of disease.

In total, 9 patients received BEAM plus ABMT salvage therapy and 7 remain in CCR at 19–57 months from the time of the BEAM therapy.

### Conclusions

Comparison of the two cohorts of patients < 60 years of age with stage III/IV diffuse large-cell or diffuse mixed-cell lymphoma treated initially with an identical CHOP chemotherapy resulted in a lower complete remission rate and a higher actuarial relapse rate at 5 years in the 1974–1982 cohort. The actuarial overall survival at 5 years was also only marginally better in the second cohort, suggesting that there has been little improvement in salvage therapy.

![Figure 1. Outcome of 87 patients with stage III/IV disease under the age of 60 years treated with CHOP.](image-url)
regimen suggests there has been little improvement in outcome over nearly two decades, despite the development of more effective high-dose salvage regimens. The actuarial overall survival at five years of 40% and 44% is in accord with other series of stage III/IV patients. There is widespread agreement that only patients with chemosensitive disease have a sufficiently good chance of a satisfactory outcome to justify very intensive therapy. In the 1987–1992 cohort reported here, of the 62 patients who failed first-line therapy, 8 (13%) died before salvage therapy could be given and 8 (13%) were considered at the time of treatment failure to be unsuitable for salvage treatment with curative intent.

Six of the remaining patients had persistent disease readily encompassable within a limited radiation field, and 1 patient relapsed in a single site and was treated with local radiotherapy. Three of these patients remain in CCR since the irradiation, emphasizing the fact that selected patients receiving this form of consolidation can be cured. It is frequently not possible, however, to be sure whether the residual masses irradiated, which are often mediastinal or intra abdominal, were disease or fibrosis, although this caveat also applies to the good results reported for high-dose therapy in patients with residual small masses after standard therapy [5]. The 3 patients in this series who had a good PR with CHOP and went on directly to a BEAM autograft all remain alive and well.

Of those 21 patients achieving a CR or PR to second-line therapy it is perhaps surprising that so few received an autograft despite widespread availability during this period. This clearly indicates that there has been considerable patient selection, which may account in part for the excellent results in the small group of patients who received this modality of treatment. Six out of 7 patients with chemosensitive disease and 1 out of 2 patients with chemoresistant disease have achieved a durable complete remission.

It can be argued that the overall outcome would have been better had more patients received high-dose therapy at an appropriate time. If all of the 31 patients with localized residual disease or chemosensitivity to second-line therapy had received high-dose therapy, and assuming that 60% were cured, this would represent 7 extra lives saved compared to actual outcome. A 60% long-term survival is, however, optimistic when the level of selection is minimized. And if the long-term survival was only 50% following high-dose therapy, which accords with the UCLH data [5] and the Parma trial [3], then the number of additional lives saved by a more widespread autografting policy might only be 3 or 4.

In conclusion, this study indicates that the outcome of high-dose salvage therapy was excellent, but was only performed in a highly selected subgroup of patients. A more widespread use of high-dose therapy might benefit additional patients, but the overall impact on survival in the total patient cohort is likely to be small. Furthermore, this cohort study was restricted to patients under 60 years of age, and this is likely to be below the median age for this disease. High-dose salvage therapy was thus a clear benefit to selected patients who received it, but major advances in this disease must come from improved front-line therapy.

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References


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