Randomized Study to Evaluate the Use of High-Dose Therapy as Part of Primary Treatment for “Aggressive” Lymphoma


Purpose: This trial of the German High-Grade Non-Hodgkin’s Lymphoma Study Group compares the use of high-dose therapy (HDT) as part of primary treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus etoposide followed by involved-field (IF) radiotherapy in a randomized, multicenter, phase III study.

Patients and Methods: Three hundred twelve patients with “aggressive” non-Hodgkin’s lymphoma aged ≤ 60 years with elevated serum lactate dehydrogenase levels were included from 1990 to 1997. Patients with at least a minor response after two cycles of CHOEP (CHOP + etoposide 3 × 100 mg/m²) were to receive three further cycles of CHOEP followed by IF radiotherapy (arm A) or one further cycle of CHOEP followed by autologous stem-cell transplantation and IF radiotherapy (arm B).

Results: Among 158 patients randomized to arm B, 103 (65%) received HDT. The complete remission rate at the end of treatment was 62.9% in arm A and 69.9% in arm B. With a median observation time of 45.5 months, overall survival for all 312 patients was 63% after 3 years (63% for arm A, 62% for arm B; \( P = .68 \)). Event-free survival was 49% for arm A versus 59% for arm B (\( P = .22 \)). Relapse in arm B was associated with a significantly worse survival rate than relapse in arm A (\( P < .05 \)). Relapse after HDT occurred early (median interval, 3 months). Six patients developed secondary neoplasia, three in arm A and three in arm B.

Conclusion: Results of the randomized trial comparing CHOEP-like chemotherapy with early HDT do not support the use of HDT with carmustine, etoposide, cytarabine, and melphalan following shortened standard chemotherapy.

WITHT CONVENTIONAL chemotherapy, long-term remission can be achieved in approximately 50% of patients with disseminated “aggressive” lymphoma. The landmark intergroup study revealed that cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) can still be regarded as the international standard. Since the early 1980s, however, data have appeared that indicate that high-dose therapy (HDT) with autologous stem-cell transplantation may be superior to conventional therapy in selected younger patients with aggressive lymphoma. Phase I/II studies, initially performed with autologous bone marrow transplantation, suggested promising results with stable remissions in 70% to 80% of the patients. Treatment-related mortality was around 5%. The use of autologous peripheral-blood stem cells and improvements in supportive care have further diminished treatment-related mortality. In patients with relapsed lymphoma, results of the trial conducted by the Parma study group have shown that high-dose chemotherapy in sensitive relapse may be superior to conventional salvage treatment. However, in primary aggressive lymphoma, the role of HDT and its optimal timing have still not been determined.

In the German High-Grade Lymphoma Study Group, CHOEP (standard CHOP + etoposide) has been established as an effective regimen. In a phase II study recruiting patients from 1982 to 1985, CHOEP followed by involved-field radiation was shown to induce complete remission (CR) rates in 82% of 60 enrolled patients, leading to a 5-year event-free survival rate of 55%. In the subsequent phase III study launched in 1986, four cycles of CHOEP were compared with a sequential therapy consisting of an escalating CHOEP regimen alternating with ifosfamide, vincristine, etoposide, and prednisone, followed by involved-field radiation in both arms. The CR rate was 85%, and event-free survival rates were 59% and 55% after 2 and 5 years, respectively, for both groups without any statistically significant difference underlining the efficacy of the CHOP regimen. Serum lactate dehydrogenase (LDH) was the strongest prognostic parameter. The 2-year survival rate was 84% for patients with normal LDH versus 55% for patients with elevated LDH (\( P < .001 \)).

These experiences led us to conceive the subsequent trial to determine the value of high-dose chemotherapy followed by...
with granulocyte colony-stimulating factor in a dosage of 10 μg/kg after treatment cycles 2 or 3. There were no recommendations concerning the source of stem cells. At the time of initiation in 1990, most patients received autologous bone marrow. Since 1994, peripheral stem cells have been the source of choice. No purging procedures were required or recommended.

**Evaluation of Response**

Response after two cycles of CHOEP was defined as any reduction in tumor size. CR required the disappearance of all tumors detectable by clinical examination, imaging, biochemical analysis, or biopsy. PR was defined as a reduction of ≥ 50% in all measurable manifestations and the absence of new lesions. Stable disease was defined as less than PR but no signs of progression. Progressive disease required a greater than 50% increase of any previously identified abnormal node for PR or nonresponders or the appearance of any new lesion during or at the end of therapy.

**Study Design**

The trial was planned as a phase III, randomized, multicenter trial. Seventy-one centers in Germany (n = 68), Switzerland (n = 1), and Sweden (n = 2) participated, among them 25 university hospitals, 37 teaching hospitals, and nine county hospitals. Randomization was carried out centrally by the Institute of Medical Statistics, University of Heidelberg. The patient recruitment was initiated in 1990 and concluded in June 1997. The original protocol called for a sample of 200 patients. In September 1995, based on a review of preliminary results and conditional power calculation, an independent advisory board consisting of four clinicians and biostatisticians not involved in the trial made the decision to extend the recruitment to 300 patients. Neither the interim results nor the reasons for the decision were disclosed to the members of the study group.

**Statistical Analysis**

Data were analyzed using Statistical Analysis System software, version 6.12 (SAS Institute, Cary, NC). For failure-time distributions, such as the survival time or event-free survival time, we generated Kaplan-Meier curves and used log-rank statistics. In agreement with the study protocol, the P values reported for the comparison of survival or event-free survival data were one-tailed. All other P values were two-tailed.

Overall survival was the main end point. As described below, 19 patients were excluded after randomization. We believe the exclusion to be justified because (1) the reasons for exclusion had been specified in advance and did not create an arbitrary imbalance and (2) the exclusion reflected clinical reality, as the treatment protocol of this study, particularly HDT, did not apply to these patients. Therefore, all analyses were restricted to the subset of the remaining 312 patients.

**RESULTS**

**Patient Characteristics**

Between August 1990 and June 1997, 331 patients were registered onto the study. Before the start of therapy or during the first cycle, 19 of the randomized patients were found to violate the entry criteria of the study and were therefore excluded. Of these, 13 patients had been assigned to arm A and six to arm B. The protocol violations were as follows: change of histologic diagnosis by the reference hematopathologist (Hodgkin’s disease, n = 4; solid tumor, n = 4; low-grade lymphoma, n = 1), diagnosis of a secondary high-grade lymphoma (n = 2), bone marrow infiltration greater than 25% (n = 4; diagnosis of secondary malignancies at the time of randomization (n = 1), age less than 18 years (n = 1), withdrawal of consent immediately after registration (n = 1), proven human immunodeficiency virus infection (n = 1), and treatment according to a leukemia protocol after randomization because of extensive bone marrow infiltration (n = 1). Among the remaining 312 patients, 154 were randomized to arm A and 158 to arm B. Patient characteristics are outlined in Table 1. Median age

**PATIENTS AND METHODS**

**Patients**

Eligible patients had to have a histologic diagnosis of a high-grade (aggressive) lymphoma according to the Kiel classification (except for lymphoblastic lymphoma in patients under the age of 35 years; histologic diagnosis had to be confirmed by an expert panel), age 18 to 60 years, stage II to IV disease according to the Ann Arbor classification of malignant lymphomas, and serum LDH level above the normal value. They also had to provide informed consent. Staging included a physical examination, an immunologic examination, an assessment of laboratory status, a chest x-ray, computed tomography scan of the thorax and abdomen, and a bone marrow biopsy. Lumbar puncture was performed in patients with lymphoblastic or Burkitt’s lymphoma or in case of suspected neurologic involvement. Serum LDH level had to be determined within 3 days before staging; hemolytic anemia had to be excluded. Further investigations (eg, bone scan, endoscopy) were to be performed if deemed necessary by the individual investigator.

**Treatment Plan**

Patients were stratified according to age (< 50 years or > 50 years), LDH level (< 400 U/L or > 400 U/L), and disease stage (II/III IV) and randomized before the first cycle to receive either five cycles of CHOEP (arm A) or three cycles of CHOEP plus HDT (arm B). The trial schema is outlined in Fig 1. Because a number of deaths occurred in patients with heavy tumor load during the first cycle, the steering committee recommended in 1994 that patients with serum LDH levels greater than two times normal undergo cytoreduction with vincristine (2 mg) and prednisone (100 mg/d) before the first cycle. CHOEP consisted of cyclophosphamide 750 mg/m² on day 1, doxorubicin 50 mg/m² on day 1, vincristine 2 mg on day 1, etoposide 100 mg/m² on days 1 to 3, and prednisone 100 mg on days 1 to 5. Treatment was repeated on day 22. Patients were restaged after two cycles in each treatment arm. If at least a partial remission had to be confirmed by an expert panel, age 18 to 60 years, stage II to IV disease according to the Ann Arbor classification of malignant lymphomas, and serum LDH level above the normal value. They also had to provide informed consent. Staging included a physical examination, an immunologic examination, an assessment of laboratory status, a chest x-ray, computed tomography scan of the thorax and abdomen, and a bone marrow biopsy. Lumbar puncture was performed in patients with lymphoblastic or Burkitt’s lymphoma or in case of suspected neurologic involvement. Serum LDH level had to be determined within 3 days before staging; hemolytic anemia had to be excluded. Further investigations (eg, bone scan, endoscopy) were to be performed if deemed necessary by the individual investigator.

**Stem-Cell Collection**

Stem cells were collected by bone marrow aspiration according to standard procedure or by separation of peripheral stem cells after prior mobilization with granulocyte colony-stimulating factor in a dosage of 10 μg/kg after treatment cycles 2 or 3. There were no recommendations concerning the source of stem cells. At the time of initiation in 1990, most patients received autologous bone marrow. Since 1994, peripheral stem cells have been the source of choice. No purging procedures were required or recommended.

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**Schematic Diagram**

Fig 1. Treatment schema: arm A, five cycles of CHOEP followed by involved-field [IF] radiotherapy; arm B, three cycles of CHOEP followed by high-dose BEAM therapy and IF radiotherapy

<table>
<thead>
<tr>
<th>CHOEP</th>
<th>CHOEP</th>
<th>CHOEP</th>
<th>CHOEP</th>
<th>CHOEP</th>
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<td></td>
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<td></td>
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</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Stage (II/III/IV)</th>
<th>Serum LDH (U/L)</th>
<th>Disease (Hodgkin’s disease, non-Hodgkin’s disease, acute lymphoblastic leukemia)</th>
<th>Treatment (CHOEP, CHOEP + HDT)</th>
<th>Eligible patients (n)</th>
<th>Randomized patients (n)</th>
</tr>
</thead>
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<tr>
<td>18-60</td>
<td>II/III/IV</td>
<td></td>
<td></td>
<td></td>
<td>312</td>
<td>154 + 158</td>
</tr>
</tbody>
</table>
was 46 years (range, 19 to 60 years) in treatment arm A and 45 years (range, 19-60 years) in arm B. Median age of the whole study population was 46 years.

Patients were retrospectively classified according to the age-adjusted International Prognostic Index. In arm A, 26% of the population were grouped as low intermediate, 55% as high intermediate, and 20% as high risk; in arm B, 26% were grouped as low intermediate, 50% as high intermediate, and 24% as high risk (Table 2).

The Revised European-American Lymphoma classification was retrospectively applied to all cases. The distribution of the histologic subtypes was as follows (arm A versus arm B): 61% versus 58% diffuse large B-cell lymphoma (centroblastic + immunoblastic), 16% versus 19% primary mediastinal large B-cell lymphoma, 10% versus 9% anaplastic large-cell lymphoma, 5% versus 11% lymphoblastic or Burkitt’s lymphoma, and 4% versus 3% peripheral T-cell lymphoma.

Induction Treatment

After two cycles of CHOEP, a formal restaging was performed. In treatment arm A, the two cycles of CHOEP were given to 152 patients (98.7%); in arm B, they were given to 150 patients (94.9%). After two cycles of CHOEP, 298 patients (94.9%) achieved at least a minor response. Fourteen patients (94.9%) received CHOEP a third time.

During the induction phase, five patients died, four patients after the first cycle and one patient after the second cycle.

Consolidation Treatment

In treatment arm A, the three consolidation courses after two cycles of CHOEP were given in 137 patients (89%). In treatment arm B, HDT was administered to 103 (65%) of the 158 assessable patients. In 94 of these patients, HDT was administered according to protocol guidelines after a third cycle of CHOEP; in nine cases, there were deviations from the protocol (application of further CHOEP cycles in five patients, further cycles of dexamethasone, carmustine, etoposide, cytarabine, and melphalan in patients cases, and mobilization therapy with cyclophosphamide in one patient). In 54 patients (35%), HDT was not administered for the following reasons: lack of response or progressive disease before the planned HDT (n = 19 and therefore exclusion according to the protocol), patient denial (n = 14), concomitant diseases (n = 4), toxicity after previous chemotherapy (n = 5), failure to mobilize peripheral stem cells (n = 2), and other (n = 7). Three patients in arm B died during induction treatment. In 20 patients (19%), HDT was followed by reinfusion of autologous bone marrow; in 82 patients (81%), peripheral stem cells were used for transplantation. One additional patient received blood stem cells and bone marrow. The median number of CD34-positive cells was 5.7 × 10^6 per kilogram of body weight (range, 1.4 to 24.3 × 10^6 per kilogram of body weight).

Radiotherapy

Data on radiotherapy were available for 154 patients in arm A and 154 patients in arm B. Radiotherapy was completed in 107 patients (69%) randomized to arm A and in 82 patients (53%) randomized to arm B. In both arms, the main reason for not administering radiotherapy was treatment failure. In arm A, radiotherapy was not administered to 43 patients (28%). The main reason was insufficient response (23 patients) followed by patient’s wishes or patient’s refusal (four patients) and concomitant disease (four patients). In four patients (3%), radiotherapy was stopped because of disease progression or relapse (three patients) and side effects (one patient). In nine patients, radiotherapy was completed but interrupted because of toxicity. In the high-dose arm, radiotherapy was not administered to 55 patients (36%) and was stopped in 17 patients (11%). The major reasons for not administering radiotherapy were insufficient response (27 patients) followed by hematopoietic insufficiency (particularly thrombocytopenia, 15 patients) and patient denial (three patients). The main reason for abrogation of radiotherapy in treatment arm B was hematopoietic insufficiency (11 patients), particularly thrombocytopenia, followed by disease progression or relapse (five patients). In nine patients, radiotherapy was completed but it was interrupted because of toxicities. The median time interval between BEAM and radiotherapy had been planned to be 6 weeks after hematologic recovery, according to

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 154)</td>
<td>(n = 158)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
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<tr>
<td>Stage</td>
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<td>25</td>
</tr>
<tr>
<td>IV</td>
<td>38</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>63</td>
</tr>
<tr>
<td>51-60 years</td>
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</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>&lt; 400 U/L</td>
<td>50</td>
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<tr>
<td>&gt; 400 U/L</td>
<td>50</td>
</tr>
<tr>
<td>Performance status &gt; 2</td>
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</tr>
<tr>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Bulky disease</td>
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</tr>
<tr>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Histologic diagnosis</td>
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<tr>
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<td>Immunoblastic lymphoma</td>
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</tr>
<tr>
<td>Anaplastic large-cell lymphoma</td>
<td>10</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
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</tr>
<tr>
<td>T-cell lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
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</table>

### Table 2. Classification of Patients According to the International Prognostic Index

<table>
<thead>
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<th>Risk</th>
<th>Arm A</th>
<th>%</th>
<th>Arm B</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intermediate</td>
<td>39</td>
<td>26</td>
<td>41</td>
<td>27</td>
<td>80</td>
<td>26</td>
</tr>
<tr>
<td>High intermediate</td>
<td>83</td>
<td>55</td>
<td>69</td>
<td>45</td>
<td>152</td>
<td>50</td>
</tr>
<tr>
<td>High</td>
<td>30</td>
<td>20</td>
<td>43</td>
<td>28</td>
<td>73</td>
<td>24</td>
</tr>
</tbody>
</table>
the protocol. In fact, it was 59 days (range, 14 to 154 days). Overall, 102 patients (66%) in arm A and 73 patients (47%) in arm B received radiotherapy without interruption.

**Treatment Results**

The median observation time was 45.6 months.

**Response.** For the entire patient population (n = 312), the CR rate at the end of treatment was 66.3% (n = 207) and the PR rate was 16.6% (n = 42). In arm A, the CR rate was 62.9% (n = 97) and the PR rate 22.7% (n = 35); in arm B, the CR rate was 69.9% (n = 110) and the PR rate was 10.7% (n = 17).

**Survival.** The 3-year survival rate was 63% in arm A versus 62% in arm B. The difference was not statistically significant (P = .68, one-tailed log-rank test, Fig 2). The 3-year event-free survival rate was 49% in arm A versus 59% in arm B (Fig 3). The difference was not statistically significant (P = .22, one-tailed log-rank test). Event-free survival and overall survival for patients with high intermediate and high risk factors according to the International Prognostic Index did not reveal statistically significant differences (Figs 4 and 5). After patients with Burkitt’s lymphoma and lymphoblastic lymphoma were excluded, there was still no advantage for the HDT with regard to survival (P = .95) and event-free survival (P = .12). Survival curves for this subgroup of 290 patients is shown in Figs 6 and 7.

Among patients who received HDT, the median time to neutrophil recovery greater than 500/µL was 10 days (range, 5 to 56 days); the median time to platelet recovery 20,000/µL was 11 days (range, 0 to 150 days). Median stay in hospital after HDT was 16.5 days (range, 10 to 78 days).

**Relapse pattern.** Among the 132 patients in arm A who received the whole chemotherapy protocol and reached PR or CR, relapse or disease progression was documented in 61 patients (46%). In 16 (28%) of these patients, relapse or progression occurred exclusively in sites of previous tumor involvement; in 16 (28%) of the patients, it occurred exclusively in previously noninvolved sites; and in 26 (45%) of the patients, it occurred in new and previously involved sites. In three patients, the relapse pattern could not be determined conclusively.

In arm B, 28 patients (27%) relapsed among the 103 patients who received the whole treatment plan including HDT. Among
these 28 patients, the relapse pattern was as follows: five patients (18%) had a relapse in a previously involved site, 11 patients (39%) had relapses in both new and previously involved sites. Relapse after HDT occurred early, with a median interval of 3 months. Median survival after relapse was 7.5 months for patients who relapsed after HDT (n = 28) and 38 months for patients who relapsed after conventional treatment (n = 58). The duration of survival after relapse is shown in Fig 8. The differences between these groups are statistically significant (P = .0022, log-rank test). Salvage HDT after relapse was administered to 26 patients (24 patients who relapsed in arm A and two patients in arm B who relapsed after initial denial of primary HDT). Median survival of patients receiving salvage HDT was 15 months.

**Treatment-Related Mortality, Side Effects, and Secondary Neoplasia**

Thirty-nine patients died during the course of treatment. Thirty-one patients died due to progressive disease. In eight patients (2.6%) who died during treatment, death was judged as possibly treatment related. Patient characteristics are listed in Table 3. Among these eight patients, five died during the first or second cycle of CHOEP, two died within the third cycle of CHOEP, and one patient died after having received five cycles of CHOEP. Six of the eight patients had serum LDH levels that were two times the normal value at diagnosis, which indicates a high tumor load. This led us to implement a cytoreductive treatment with prednisone and vincristine in high-risk patients. No patient died due to HDT, but the 100-day mortality rate after HDT was 5%. All patients died due to disease progression.

Following HDT in treatment arm B, 39% of patients experienced grade 3/4 stomatitis, 27% experienced grade 3/4 infection, and 17% had grade 3/4 diarrhea. In treatment arm A during the corresponding fourth and fifth cycles of CHOEP, no patient experienced grade 3/4 stomatitis or diarrhea, 1% of patients experienced grade 3/4 infection, 73% experienced grade 3/4 leukopenia, and 9% experienced grade 3/4 thrombocytopenia.

With a median observation time of 45.6 months, six secondary neoplasias (1.9%) were reported. A case of acute myeloid leukemia (AML) of French-American-British type M2 occurred 8 years after HDT, another patient developed AML of French-American-British type M1 4 years after HDT, a case of AML occurred 3 years after five cycles of CHOEP, and a case of myelodysplasia (refractory anemia with excess blasts in transformation) occurred 1 year after five cycles of CHOEP. One patient developed breast cancer and

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>LDH (U/mL)</th>
<th>No. of Cycles</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>462</td>
<td>2</td>
<td>Leukopenic sepsis</td>
</tr>
<tr>
<td>59</td>
<td>308</td>
<td>1</td>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>55</td>
<td>523</td>
<td>1</td>
<td>Leukopenic sepsis</td>
</tr>
<tr>
<td>58</td>
<td>271</td>
<td>3</td>
<td>Hemorrhagic shock due to peptic ulcer</td>
</tr>
<tr>
<td>37</td>
<td>634</td>
<td>1</td>
<td>Acute abdomen, sepsis</td>
</tr>
<tr>
<td>58</td>
<td>4,500</td>
<td>1</td>
<td>Neutropenic colitis</td>
</tr>
<tr>
<td>53</td>
<td>1,311</td>
<td>5</td>
<td>Heart failure</td>
</tr>
<tr>
<td>53</td>
<td>1,440</td>
<td>3</td>
<td>Pneumonia during leukopenia</td>
</tr>
</tbody>
</table>

**Fig 6.** Overall survival after 3 years for all patients except patients with Burkitt's and lymphoblastic lymphoma.

**Fig 7.** Event-free survival after 3 years for all patients except patients with Burkitt's and lymphoblastic lymphoma.

**Fig 8.** Survival after relapse: relapse after prior HDT (n = 28) versus relapse after conventional treatment (n = 59).
another patient developed an adenocarcinoma of the bile duct, 2 years after five cycles of CHOEP in both cases.

**DISCUSSION**

The aim of this study was to compare HDT as part of the primary treatment to conventional chemotherapy in patients with newly diagnosed, disseminated, aggressive lymphoma and the risk factor of elevated LDH. Thus far, the study has failed to show any benefit of intensive treatment until now in an intent-to-treat evaluation.

In previous studies, CHOEP followed by involved-field radiotherapy was proved to be an effective regimen in the treatment of patients with aggressive lymphoma, and this treatment resulted in stable remission in the majority of patients in this study. It can be administered without major toxicities and with tolerable long-term side effects. The German High-Grade Lymphoma Study Group has conducted a randomized study comparing CHOEP with standard CHOP in 890 patients ≤ 60 years of age with low risks; the study is currently under evaluation.

Why did three cycles of CHOEP follow by BEAM not prove to be superior to five cycles of CHOEP in this patient group? Patients were randomized up front. One third of the patients randomized to treatment arm B did not receive HDT, mainly because of induction failure and patient’s choice. According to the study protocol, the interval between CHOEP cycles was to be 21 days. In fact, the fourth cycle in the conventional treatment arm was given after a median period of 63 days after the first cycle. However, in the high-dose arm, BEAM could only be administered after a median period of 78 days. Patients in the conventional arm therefore received more chemotherapy during that period than patients in the HDT arm. Involved-field radiotherapy was administered in both treatment arms. However, radiotherapy could only be completely administered in 53% of the patients in the high-dose arm compared with 69% in the conventional treatment arm. Major reasons for deletion of radiotherapy were induction failure and hematologic toxicities, predominantly persistent thrombocytopenia. The median interval between the last chemotherapy cycle and radiotherapy was 40 days in arm A; the median interval between HDT and radiotherapy was 59 days in arm B. Therefore, radiotherapy may have been more effective in treatment arm A. These data further illustrate the limited value of administering radiotherapy immediately after HDT.

An additional reason why there was no difference in survival between the two treatment groups may be that salvage therapy for patients who relapsed after primary treatment was more effective in patients treated in arm A than in arm B, with increased 2-year survival rates for relapsed patients in arm A (26%) compared with arm B (11%). Twenty-six of the 61 relapsed patients in arm A received salvage high-dose treatment leading to a median survival time of 15 months, whereas relapse after front-line HDT was associated with a median survival time of only 3.8 months. These data suggest that salvage therapy is more effective after conventional therapy than after HDT.

Seventy-five percent of the patients were classified as high intermediate or high risk according to the International Prognostic Index. In a subgroup analysis of these patients, there was no difference in event-free survival or overall survival.

A number of trials have evaluated HDT as part of front-line therapy. In the LNH87-2 trial of the Groupe d’Etude des Lymphomes de l’Adulte (GELA), patients who had achieved CR after four courses of induction therapy were randomized to receive HDT or conventional consolidation treatment. Survival and event-free survival did not reveal any difference, but subgroup analysis demonstrated a benefit in terms of event-free survival and overall survival for high-risk patients. The follow-up trial, which evaluated early intensification with BEAM after a shortened induction therapy compared with the conventional GELA arm, demonstrated a benefit for conventionally treated patients. The Genova group randomized patients to receive complete conventional therapy versus complete conventional therapy followed by autologous bone marrow transplantation; they did not see any benefit for the high-dose arm. The Milan group used a different approach, in which HDT was part of a sequentially escalated treatment regimen. With small patient numbers, sequential HDT was superior to conventional treatment with methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in terms of event-free survival after 7 years. The European Organization for the Research and Treatment of Cancer performed a trial in which patients were randomized after three cycles of a CHOEP-like regimen to receive either five more cycles of the same regimen or three more cycles followed by HDT. In contrast to the German trial, 70% of the 311 registered patients belonged to the low or low intermediate risk groups of the International Prognostic Index. Estimated 5-year survival rates did not differ between the two treatment groups. Two randomized trials addressed HDT in patients with delayed response after induction therapy. Both studies included only small patient numbers and failed to show an advantage of HDT for this patient population.

When physicians consider the value of up-front high-dose chemotherapy as front-line treatment, the option of salvage HDT has to be taken into account. The PARMA study demonstrated that patients who relapse after conventional treatment can benefit from salvage HDT. Our results suggest that patients who relapse after HDT have a worse prognosis than patients who relapse after conventional treatment. In any HDT protocol that is part of primary treatment, this effect has to be considered. This study, as well as previous ones, underscores that outside of clinical trials, there is no indication for up-front HDT. Until now, no prospective randomized trial has proven a survival benefit of high-dose chemotherapy applied after a shortened induction therapy, like the trial outlined above. Trials that have evaluated HDT after a complete course of standard chemotherapy have shown a benefit for a subgroup of patients in retrospective analysis. Is there any role for front-line HDT? A number of clinical trials are presently addressing this issue, including the European MISTRAL trial (Multicenter International Studies on the Treatment of Aggressive Lymphomas) conducted by the Swiss Group for Clinical Cancer Research, which is incorporating the sequential Milan schema, and the German High-Grade Lymphoma Study Group trial, which is evaluating the role of sequential up-front HDT.

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