Long-term clinical and molecular remissions in patients with follicular lymphoma following high-dose therapy and autologous stem cell transplantation


Background: Long-term clinical and molecular remissions in patients with follicular lymphoma (FL) following high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) have been evaluated in only a few studies. Results are especially limited for second-line HDT with BEAM (BCNU, etoposide, cytarabine and melphalan).

Patients and methods: Sixty patients with FL received ASCT in our institution (18 first-line with total body irradiation and cyclophosphamide, 34 second-line with BEAM and 8 ≥ third-line with BEAM). In the case of long-term remission (>6 years; N = 17), peripheral blood was tested for minimal residual disease by t(14;18)- and IGH-PCR.

Results: Ten-year overall survival, progression-free survival and freedom from progression (FFP) after first-line ASCT were 79%, 57% and 64% after second-line ASCT 41%, 35% and 42%, respectively. Prognostic factors for FFP were treatment line and FLIPI (Follicular Lymphoma International Prognostic Index). Ten-year FFP for second-line ASCT and low-risk FLIPI was 57%, intermediate risk 37% and high risk 33%. No relapses occurred after 6 years following ASCT. Sixteen patients developed sustained long-term clinical and molecular remissions of up to 17.5 years.

Conclusion: Sustained long-term clinical and molecular remissions can be achieved following ASCT, including HDT with BEAM in second line.

Key words: autologous stem-cell transplantation, follicular lymphoma, long-term remission, MRO, relapse, secondary malignancies

Introduction

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is known as an effective therapy which can achieve long-term remissions in a significant proportion of patients with disseminated follicular lymphoma (FL). However, a considerable number of patients relapse after ASCT. So its role in the management of patients remains controversial [1–14]. Up to now, only a few long-term molecular remissions (over 10 years) were described, mostly after total body irradiation (TBI) and high-dose cyclophosphamide [15–18]. This high-dose protocol is under debate because of an increased rate of secondary acute myeloid leukaemia and myelodysplastic syndrome (MDS) [8, 9]. No sufficient data regarding long-term molecular remissions after high-dose chemotherapy with BEAM (BCNU, etoposide, cytarabine and melphalan) are available, a protocol causing less secondary malignancies [9]. Long-term follow-up is frequently difficult.
patients and methods

Eligible for this study were all patients who had undergone HDT with ASCT for disseminated FL from 1995 to April 2012 on consecutive protocols active at Klinikum Oldenburg. Patients with high-grade transformation before ASCT were excluded. Consecutive patients with advanced-stage disease were included in a first-line ASCT protocol if they had a diagnosis of stage III/IV FL according to the WHO or REAL classification or centroblastic-centrocytic lymphoma according to the Kiel classification, respectively, symptoms or special reasons requiring therapy, age of 18–60 years and adequate performance status and organ function. All these patients (N = 18) were included in a trial of the German Low Grade Lymphoma Study Group (GLSG, principal investigator W. Hiddemann) [6]. For the salvage ASCT protocol, patients with an age of up to 66 years were accepted following relapse or progression after one or more of previous treatment lines.

If carried out as part of first-line treatment, therapy comprised induction with a CHOP-like standard regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) until maximum response (four to six courses)—since 2001, usually combined with rituximab, followed by stem-cell mobilization with Dexam-DEAM (dexamethasone 3 × 8 mg on days 1–10, carbamustine 60 mg/m² on day 2, etoposide 75 mg/m² on days 4–7, cytarabine 100 mg/m² every 12 h on days 4–7 and melphalan 20 mg/m² on day 3). For salvage treatment, most patients received three to four courses of the ESHAP protocol (etoposide, prednisolone, cytarabine and cisplatin) or ICE protocol (ifosfamide, carboplatin and etoposide)—since 2001, also usually combined with rituximab. Stem cell apheresis was usually carried out following these protocols or cyclophosphamide (3 g/m²). The collection and cryopreservation of the peripheral stem cells as well as the measurement of CD34-positive cells and stem cell assays in the apheresis products were carried out in the blood bank of the German Red Cross adjacent to our hospital. HDT consisted in TBI (12 Gy) and high-dose cyclophosphamide (120 mg/kg body weight) for first-line treatment and BEAM (BCNU 300 mg/m², etoposide 800 mg/m², cytarabine 1600 mg/m² and melphalan 140 mg/m²) for salvage treatment (according to the Lym1 trial of the EBMT [22]), except one patient with BEAM in the first cohort and another patient with TBI/cyclophosphamide in the second cohort. Ten patients were treated within the Lym1 trial, other patients after relapse according to the standard arm of this protocol. The median transplanted CD34-positive cell number was 3.0 million per kilogram body weight (range 2.0–7.3). Five patients received rituximab as maintenance therapy after ASCT within the Lym1 trial (375 mg/m² four times within 8 months). Patients with partial remission after ASCT were irradiated with 30–36 Gy in the field of persisting lymphoma, if possible, except participants of the Lym1 trial. The study was carried out in accordance with the Declaration of Helsinki. Protocols had been approved by the responsible institutional review boards. Patients gave written informed consent.

MRD analysis

DNA from PB was extracted with the Qiagen Blood Mini Kit (Qiagen, Hilden, Germany). In diagnostic and follow-up peripheral blood samples of patients in long-term clinical remission, lymphoma cells were assessed by t(14;18) or IGH multiplex PCR as published [26]. PCR products were visualized on a 0.8% agarose gel and in the case of a clonal PCR, product size determination for quality reasons was carried out by genescanning.

Samples with a t(14;18) rearrangement were further quantified by real-time quantitative PCR (RQ-PCR) of t(14;18) rearrangements as published by Ladetto et al. [27]. All RQ-PCR reactions were carried out on an ABI PRISM 7700 thermal cycler (Applied Biosystems). The sensitivity of the assay was 1 × 10^-5 when 500 ng of DNA was used. Albumin was used as a control gene to correct for DNA amount or PCR inhibitors according to Pongers-Willemse et al. [28]. Positivity of a sample was defined if any of the triplicates gave a positive result by RQ-PCR analysis. Evaluation of quantitative PCR results was done according to the Biomed criteria [29].

MRD response was defined as the absence of PCR-detectable neoplastic cells in PB or BM at any time point investigated by RQ-PCR with a sensitivity of at least 10^-4.

statistical analysis

Survival times were estimated using the Kaplan–Meier method, and comparisons between survival curves in different strata were carried out using the log-rank test. Significance levels were set at 0.05. Overall survival (OS) is defined as time from ASCT to death from any cause. Progression-free survival (PFS) is defined as time from ASCT to relapse, progression or death from any cause. Freedom from progression (FFP) is defined as time from ASCT to documented progression or relapse. Relapse/progression was defined as appearance of new lesions and/or an increase of known lesions of >25%. Calculations were done using IBM SPSS Statistics Version 21. Data were analysed as of 19 July 2012.

results

With a median follow-up for the 41 surviving patients of 5.7 years (range 0.3–17.5), 29 relapses occurred in 60 patients after 2–74 months following ASCT (median 12). Nineteen patients died after 3–120 months (median 37). Median overall survival (OS) and PFS were not yet reached and 68 months, respectively. The 10-year OS and PFS were 53% and 40%, respectively. The 10-year OS after ASCT and from first
diagnosis for the first-line cohort were 79% and 86%, respectively; 41% and 70%, respectively, for the second-line cohort; 47% and 38%, respectively, for the ≥ third-line cohort (Figure 1). The median OS from the first diagnosis for the first-line cohort was not yet reached; 134 months for the second-line cohort and 119 months for the ≥ third-line cohort.

So far, 17 patients developed sustained long-term remissions of at least 6 years (up to 17, median 9 years; patient characteristics are summarized in Table 2). The median duration of follow-up of these patients treated with first-line ASCT (N = 9) and second-line ASCT (N = 7) was 9.1 years (range 5.6–15.5) and 9.6 years (range 6.0–17.3), respectively. One patient treated with ASCT in the fourth therapy line had a follow-up of 11.0 years. Regarding rituximab treatment in this long-term remission cohort, three of nine patients following first-line ASCT had never received rituximab (follow-up after ASCT 15.5, 11.6 and 9.7 years, respectively), just as one of seven patients following second-line ASCT (follow-up 17.3 years). The mentioned patient following ASCT in the fourth line had been refractory to rituximab before ASCT.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ASCT (first line)</th>
<th>ASCT (second line)</th>
<th>ASCT (≥ third line)</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>18</td>
<td>34</td>
<td>8</td>
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<td>Age (years, median/range)</td>
<td>48/25–60</td>
<td>52/31–66</td>
<td>56/53–65</td>
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<td>Sex (female/male), n</td>
<td>10/8</td>
<td>12/22</td>
<td>3/5</td>
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<tr>
<td>BM histological positive, n (%)</td>
<td>14 (78)</td>
<td>10 (30)</td>
<td>2 (25)</td>
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<td>FLIPI score at induction chemotherapy</td>
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<tr>
<td>Low/intermediate/high risk, n</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FLIPI score at salvage chemotherapy</td>
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<tr>
<td>Low/intermediate/high risk, n</td>
<td></td>
<td>13/12/9</td>
<td>5/0/3</td>
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<td>No CR at ASCT, n (%)</td>
<td>9 (50)</td>
<td>18 (53)</td>
<td>6 (75)</td>
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<td>2/2–2</td>
<td>3/1–5</td>
<td>3/2–5</td>
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<td>Prior chemotherapy cycles, median/range</td>
<td>7/5–7</td>
<td>11/2–14</td>
<td>11.5/8–40</td>
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<td>Prior treatment with anthracyclines, n (%)</td>
<td>18 (100)</td>
<td>33 (97)</td>
<td>7 (88)</td>
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<td>Prior rituximab, n (%)</td>
<td>12 (67)</td>
<td>25 (74)</td>
<td>7 (88)</td>
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<td>Prior interferon, n (%)</td>
<td>0</td>
<td>14 (41)</td>
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<tr>
<td>Prior ESHAP, n (%)</td>
<td>0</td>
<td>19 (56)</td>
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<td>Cyclophosphamide before apheresis, n (%)</td>
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<td>Rituximab-maintenance after ASCT, n (%)</td>
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<td>5 (15)</td>
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<td>Prior RT, n (%)</td>
<td>1 (6)</td>
<td>8 (24)</td>
<td>5 (63)</td>
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<td>RT after ASCT, n (%)</td>
<td>2 (11)</td>
<td>5 (15)</td>
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<td>8/6–118</td>
<td>31/13–108</td>
<td>49/23–115</td>
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<td>Therapy-free interval before relapse (months)</td>
<td>–</td>
<td>13/1–66</td>
<td>8/0–15</td>
</tr>
</tbody>
</table>

BM, bone marrow; FLIPI, Follicular Lymphoma International Prognostic Index [19–21]; CR, complete remission; ESHAP, etoposide, prednisolone, cytarabine, cisplatin; RT, radiotherapy.

**Figure 1.** Overall survival, progression-free survival and freedom from progression of 60 patients after autologous stem cell transplantation (ASCT), by treatment line.

**prognostic factors for relapse**

Log-rank comparisons considering treatment line of ASCT showed a favourable effect of first-line ASCT on PFS and FFP: P = 0.041 and 0.027, respectively. The 10-year PFS and FFP for the first-line cohort were 57% and 64%, respectively; 35% and 42%, respectively, for the second-line cohort and 17% and 17%, respectively, for the ≥ third-line cohort (Figure 1).

The 10-year FFP for all patients with low-risk FLIPI was 53%; intermediate risk 65% and high risk 17%, showing a
significant difference ($P = 0.001$), similar to OS and PFS (Figure 2). Patients with low risk or intermediate risk FLIPI at first-line treatment had a lower relapse probability than high-risk patients (10-year FFP 75%, 100% and 0%, respectively). Regarding patients with second-line treatment, 10-year FFP was 57%, 37% and 33%, respectively, related to low-, intermediate- and high-risk FLIPI at salvage therapy. For ≥third-line ASCT, 10-year FFP was 30% for low risk and 0% for high risk. Statistically significant differences cannot be shown because of the small subgroups.

Other variables (sex, bone marrow involvement before treatment, age at ASCT, rituximab pretreatment before salvage therapy and remission status at ASCT) showed no significant differences.

radiotherapy following ASCT

It is noteworthy that, in the long-term remission cohort ($N = 17$), four patients were included who received BEAM and ASCT in the second (in one case fourth) partial remission and were afterwards irradiated (with 30–36 Gy) in the field of persisting lymphoma. The median remission duration of these four patients amounts to 10.3 years (range 9.1–17.5). The patient with the longest remission duration had a high-risk FLIPI score at relapse.

minimal residual disease

Sixteen of the 17 long-term remission patients were MRD-negative at the last follow-up. One patient was MRD-positive (low-level MRD) at the last control (67 months after ASCT in first line). However, pre-treatment samples of only 11 of these patients had been available for initial marker identification. Seven of 11 patients were MRD-positive before treatment and MRD-negative at the last follow-up. Four patients had no detectable pre-therapeutic marker. In five patients, no diagnostic sample was available for marker identification.

time to relapse

The median time to relapse (in relapsed patients) is shorter after ASCT in the second remission compared with ASCT in the first remission in our two cohorts at 13 months (range 2–63) and 35 months (range 4–74), respectively. For patients with time to relapse of <12 months, the median OS is only 25 months after ASCT (95% confidence interval 9–41); for the other patients, it is 101 months (95% confidence interval 74–128, $P < 0.001$).

The median FFP after second-line ASCT and ≥third-line ASCT was 36 months (range 2–208) and 25 months (range 2–132), respectively, clearly longer than after the last therapy before ASCT [13 months (range 1–66) in the second-line cohort and 8 months (range 0–15) in the ≥third-line cohort].

treatment of relapse

Sixteen of 29 relapsed patients received another chemotherapy regimen, mostly combined with rituximab. Four patients were irradiated. Three patients received, up to now, no treatment. Six patients received an allogeneic transplantation, four of whom died due to transplant-related problems. One patient is in sustained long-term remission (13 years) and good

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**Table 2. Characteristics of patients with long-term remissions**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median/range</td>
<td>48/25–60</td>
</tr>
<tr>
<td>Sex (female/male), n</td>
<td>9/8</td>
</tr>
<tr>
<td>BM histologically positive, n (%)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>FLIPI score at induction chemotherapy</td>
<td>3/6/0</td>
</tr>
<tr>
<td>FLIPI score at salvage chemotherapy</td>
<td>4/2/2</td>
</tr>
<tr>
<td>No CR at ASCT, n (%)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Prior treatment regimens, median/range</td>
<td>2/2–6</td>
</tr>
<tr>
<td>Prior chemotherapy cycles, median/range</td>
<td>7/3–20</td>
</tr>
<tr>
<td>Prior treatment with anthracyclines, n (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Prior rituximab, n (%)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Prior rituximab before last relapse, n (%)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Prior interferon, n (%)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Prior ESHAP, n (%)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Cyclophosphamide before apheresis, n (%)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Rituximab maintenance after ASCT, n (%)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Prior RT/RT after ASCT, n</td>
<td>3/4</td>
</tr>
<tr>
<td>TBI and first-line ASCT, n</td>
<td>9</td>
</tr>
<tr>
<td>BEAM and second-line ASCT, n</td>
<td>7</td>
</tr>
<tr>
<td>BEAM and fourth-line ASCT, n</td>
<td>1</td>
</tr>
<tr>
<td>Time from diagnosis to ASCT, median/range</td>
<td>13/7–78 months</td>
</tr>
<tr>
<td>Therapy-free interval before relapse (n = 8)</td>
<td>10.5/1–29 months</td>
</tr>
</tbody>
</table>

BM, bone marrow before induction or salvage chemotherapy; FLIPI, Follicular Lymphoma International Prognostic Index; RT, radiotherapy.

**Figure 2.** Overall survival, progression-free survival and freedom from progression of 60 patients after autologous stem cell transplantation (ASCT), by FLIPI.
condition after early relapse (10 months) following TBI with ASCT in first line.

non-relapse mortality
One male patient (of the TBI cohort) died 71 months after ASCT due to pneumonia (6 months after suspicion of MDS). One female patient (of the second-line cohort) died as result of a heart attack (suspicion of myocardial infarction) in remission 113 months after ASCT. No patient died due to apparent toxicity of HDT with ASCT.

secondary malignancies
Four of 60 patients developed secondary invasive malignancies in remission after ASCT: in the TBI cohort, 2 of 18 patients (1 with suspicion of MDS after 65 months following ASCT, 1 with metastasized colon cancer after 141 months); in the BEAM cohort, 2 of 41 patients (1 breast cancer after 75 months following ASCT in second line, 1 male patient with oesophagus cancer following earlier alcohol and tobacco abuse after 72 months following ASCT in third line). Another female patient of this cohort suffered from MDS 94 months after ASCT, 55 months after relapse and additional chemotherapy following ASCT. The patients suffering from secondary MDS died; the others are still alive. In addition, three patients developed basal cell carcinoma in the BEAM cohort (excision without complications).

discussion
These data show that sustained long-term clinical and molecular remissions (up to 17 years) can be achieved following ASCT, including high-dose chemotherapy with BEAM and ASCT in second line therapy or beyond. There are only a few publications with a similar approach. Kornacker et al. [15] describe encouraging long-term results in 241 retrospectively analysed patients, of whom 64% received a first-line ASCT and 36% a salvage ASCT, 56% of 241 patients with TBI, 44% with BEAM (altogether 10-year PFS 49% and 10-year OS 75%, median follow-up for surviving patients 8 years, maximum 16.5). Relapses followed a biphasic pattern with continuing relapse during the first 6 years after ASCT and only few events thereafter (only three, the last one after 10.7 years). Twenty-four patients who were in ongoing complete remission >8 years after ASCT had a bcl-2/IgH PCR marker available for molecular MRD assessment (in the peripheral blood). After a follow-up from 85 to 155 months (median 132 months), three of these patients were MRD-positive (at a low level), while the remainder showed no evidence of disease persistence at the molecular level. However, it was not differentiated how many long-term molecular remissions were seen in patients with salvage ASCT after the BEAM protocol. Hicks et al. [16] describe 23 patients with second-line ASCT after high-dose chemotherapy (cyclophosphamide, BCNU and etoposide) with in vivo purging and maintenance with rituximab, resulting in a 5-year PFS of 59%, and two sustained molecular complete remissions lasting 7.0 and 7.25 years, respectively. Corradini et al. [17] report on 70 patients with indolent lymphoma (40 of these with FL) following high-dose chemotherapy with mitoxantrone and melphalan (9 of these with salvage ASCT), resulting in two MRD-negative patients in clinical remission lasting more than 10 years (maximum 12 years), although not differentiating between histological subtypes.

Additionally, the publications on salvage autologous bone marrow transplantation (ABMT) after TBI/cyclophosphamide and purging of stem cells with monoclonal antibodies are of interest. Apostolidis et al. [18] reported on 99 patients, transplanted in the second remission or beyond, resulting in 63% freedom from recurrence at 5 years. Two of these patients developed a sustained MRD-negative long-term remission from 10 to 11 years. Similar results were described by Freedman et al. [23]: two MRD-negative long-term remissions (11 and 13 years) of 153 patients, with disease-free survival of 42% at 8 years. Rohatiner et al. [8] report on 121 patients, 48% of whom were disease-free at 10 years (no MRD assessment). A plateau was observed on the remission duration curve at 48% at 12 years (longest follow-up 19 years). In addition, Kasamon et al. [25] published recently long-term results following ABMT with 4-hydroperoxycyclophosphamide purging for 50 FL patients, resulting in 10-year event-free survival of 31% for patients with ABMT after relapse [the median follow-up for event-free patients was 16.6 years, up to 20 years, of all 80 patients with indolent or transformed (15%) lymphoma, 36% of 80 transplanted in the first remission]. Most relapses occurred within 3 years with a median time to relapse of 1.8 years (range 0.1–15.6). Fifteen patients (19%) were event-free for >15 years after ASCT, five of whom transplanted in the second remission, five in the third or higher remission, not differentiating the histologies of these patients. Three patients, all with FL, relapsed after 12 years, up to 15 years, without further details.

Obviously, the median time to relapse seems to be shorter after ASCT in the second remission compared with ASCT in the first remission, in our two cohorts 13 months and 35 months, respectively, as the proliferation of lymphoma cells apparently increases in the course of the disease. So the risk of very late relapses (after >10 years) might be low in this patient group, considering that our patients had usually received a more aggressive first-line treatment (anthracycline containing) than at times of ABMT.

MRD assessment is a highly sensitive tool to detect asymptomatic occult disease in B-cell lymphomas that has not only a prognostic impact but is also known to precede clinical relapse [12, 31–33]. Therefore, we analysed residual lymphoma cells by quantitative RQ-PCR in the peripheral blood of long-term remission patients at the last follow-up. All seven patients with MRD positivity before treatment demonstrated clinical and MRD response at long-term follow-up, indicating profound lymphoma control after ASCT. Only one patient without a pretreatment sample was MRD-positive at follow-up (67 months after ASCT in first line); however, RQ-PCR revealed only low level of circulating lymphoma cells, indicating a potential immunological control of the disease. Comparable results were obtained by Kornacker et al. [15] as mentioned above. Assessment of peripheral blood in the long-term remission appears to be sufficient for MRD assessment at the long-term follow-up as shown by Hirt et al. [33] even after rituximab-containing immunochemotherapy.
Altogether, the reported long-term clinical and MRD response after ASCT (in our patient cohort up to 17 years) point at the potential curability of FL. In the first remission, ASCT is not used any longer, as improvement of OS could not be demonstrated up to now [4]. For patients with relapsed FL, however, ASCT should be considered at the first relapse, best before development of high-risk disease, as our data show. It is noteworthy that pretreatment with rituximab before relapse and subsequent ASCT does not seem to be an unfavourable prognostic factor [24], in accordance with our preliminary observations. The treatment-related mortality of ASCT is fortunately low (in our cohort 0%), and the rate of secondary malignancies is obviously lower in BEAM-treated patients than previously reported with TBI/cyclophosphamide [8, 9].

However, continuing long-term observation of these patients including careful and regular cancer screening is required in order to further improve treatment options. Of special interest is the follow-up of the Lym1 trial of the EBMT, incorporating the BEAM protocol [22]. It could be demonstrated that both stem cell in vivo purging with rituximab before apheresis and rituximab maintenance following ASCT improve PFS in the second remission (63% PFS at 5 years), hopefully improving long-term survival in the future. For patients relapsing following ASCT, the prognosis is still relatively good, which does not appear to be different from that of disease recurrence after standard treatment. The situation seems less favourable for patients who relapse early (<12 months) after ASCT [15]. For these patients, an allogeneic transplant should be considered [30].

acknowledgements

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disclosure

The authors have declared no conflicts of interest.

references

Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC)


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Background: The OPTIMAL study found that erlotinib improved progression-free survival (PFS) versus standard chemotherapy in Chinese patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). This report describes the quality of life (QoL) and updated PFS analyses from this study.

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