Comparable safety profile of BeEAM (bendamustine, etoposide, cytarabine, melphalan) and BEAM (carmustine, etoposide, cytarabine, melphalan) as conditioning before autologous haematopoietic cell transplantation

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Introduction

The prognosis of patients with relapsed/refractory (RR) Hodgkin’s lymphoma (HL) and non-Hodgkin lymphomas (NHL) treated with conventional-dose salvage regimens is poor. High-dose chemotherapy (HDCT) followed by autologous haematopoietic cell transplantation (autoHCT) is a standard therapeutic option for the majority of chemosensitive RR lymphoma patients. This procedure, being relatively safe (transplant related mortality (TRM) between 1 and 5%), was demonstrated to improve both overall survival (OS) and progression-free survival (PFS) compared to conventional-dose salvage regimens [1–3].

BEAM (carmustine, etoposide, cytarabine, melphalan) is the most common regimen used as conditioning before autoHCT for patients with RR lymphomas [4]. In order to potentially increase the efficacy [5, 6] and to reduce pulmonary toxicity [7, 8], other agents, like thiotepa, lomustine, or bendamustine, have been proposed to replace carmustine (TEAM, CEAM, and BeEAM, respectively) [9–11].

The mechanisms of in vitro cytotoxicity of bendamustine are well described. The mustard group of the particle is responsible for its alkylating activity, while the purine analogue group reveals its antimetabolite activity. It also displays features unrelated to other alkylating agents. It activates DNA-damage stress response and apoptosis. In the case of dysfunction of apoptotic path (e.g. p53 mutation) it also inhibits mitotic checkpoints, which leads to mitotic catastrophe in tumour cells [12]. Bendamustine, unlike other alkylators, activates a base excision DNA repair pathway rather than an alkyltransferase DNA repair mechanism. Moreover, in vitro experiments on cell lines showed that both bendamustine and carmustine potentiate the activity of cytarabine and melphalan [5]. These differences explain the efficacy of bendamustine in patients with relapsed lymphoma refractory to other alkylating agents [12]. The drug has a proven clinical activity in RR lymphoproliferative disorders like chronic lymphocytic leukaemia, multiple myeloma, or indolent lymphomas [13–16].

Although many trials on safety and efficacy profiles of various conditioning regimens have been published [5, 17, 18], to the best of our knowledge the comparison of BeEAM and BEAM safety profiles has not been reported so far. The aim of this study was to compare both regimens with respect
to their tolerance and effect on engraftment. Preliminary data regarding their efficacy have also been reported.

**Material and methods**

**Study design**

This was a retrospective, single-centre study including consecutive patients with either HL or NHL treated with HDCT using either BEAM or BeEAM between January 2011 and August 2016. Patients with mantle cell lymphoma as well as those with peripheral T-cell lymphoma, except for anaplastic large cell lymphoma ALK−, had indications for autoHCT in first remission. For other lymphoma subtypes HDCT was considered in cases of primary resistance or relapse, followed by salvage conventional-dose chemotherapy.

All patients were treated in Maria Sklodowska-Curie Institute – Oncology Centre in Gliwice, Poland. All data used for the analysis were obtained based on patients’ hospital files. Patients referred for autoHCT signed written informed consent forms to use their files for scientific purposes.

**Conditioning regimens and supportive care**

BEAM consisted of carmustine 300 mg/m² given intravenously (IV) in a 2-h infusion with 500 mL 0.9% NaCl on day −6, etoposide 150–200 mg/m² IV BID in 30-min infusion with 500 mL NaCl on day −6, cytarabine 200 mg/m²/d IV BID in a 30-min infusion with 500 mL NaCl 0.9% on days −5 to −2, and melphalan 140 mg/m² IV in a single 1-h 500 mL infusion with 0.9% NaCl on day −1.

In the BeEAM group carmustine was replaced by bendamustine; the agent was administered on days −7 and −6 at the dose of 160–200 mg/m²/day IV in a 2-h infusion. Other cytostatics were given in the same way as in the BEAM protocol.

All patients received granulocyte – colony stimulating factor (G-CSF) at 5 µg/kg b.w. starting from day +4 after AH SCT until absolute neutrophil count reached 0.5 × 10⁹/l for three consecutive days. All patients received antiviral (oral acyclovir), antifungal (oral fluconazole), and antibacterial (oral ciprofloxacin) prophylaxis. Since the start of conditioning until day 0, hyperuricaemia prophylaxis was given (oral allopurinol 100 mg TID). Substitution of platelets or red blood cells was given when platelet count was lower than 20 × 10⁹/l or haemoglobin level was lower than 80 g/l, respectively.

**Measurements and definitions**

CD34⁺ cell count was assessed using flow cytometry, as previously described [19]. Toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE 4.0). Engraftment was defined as the presence of neutrophils > 0.5 × 10⁹/l for three consecutive days and platelets > 50 × 10⁹/l with no need of substitution.

OS was defined as the time from autoHCT to death from any cause or last follow-up. PFS was defined as the time from autoHCT until first relapse/progression, death, or last follow-up. Remission status before autoHCT and at day 100 after the procedure was assessed using TK or 18FDG PET-TK imaging.

**Statistical analysis**

The probabilities of OS and PFS as well as engraftment were estimated using the Kaplan-Meier method. Log-rank test was used for comparison of both study groups. The frequencies of adverse events were compared using χ² test. P-values < 0.05 were considered statistically significant. Analyses were performed using Statistica Version 12 (Statsoft, Tulsa, OK).

**Results**

**Patients characteristics**

We analysed 237 patients, including 110 (46.4%) with HL and 127 (53.6%) with NHL. Among NHL subtypes the diagnosis of DLBCL predominated (89 patients). Clinical characteristics of both groups were comparable; they are summarised in Table 1. The median age at autoHCT was 46.5 years for BEAM and 45 years for BeEAM, respectively.

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The number of patients with stable or progressive disease was 15 (8.3%) and 10 (15.9%) in BEAM and BeEAM groups, respectively. The remaining patients entered the procedure in a phase of chemosensitive relapse. Peripheral blood was the source of stem cells in all cases, and the median of infused CD34+ cells was significantly higher in the BEAM compared to the BeEAM cohort (Table 1).

Engraftment

The kinetics of neutrophil and platelet recovery are illustrated in Figure 1 and Figure 2, respectively. Median time to neutrophil recovery was 10 days in both groups (p = 0.12). Median time to platelet count regeneration > 50 × 10⁹/l was 13 and 14 days after BEAM and BeEAM, respectively (p = 0.29).

Four (1.7%) patients died in the early phase of the AHSCT, before haematological engraftment; three in the BEAM group (1.7%) and one in the BeEAM group (1.6%) (p = 0.94). In all cases the mortality was caused by infections; in three cases by severe pneumonia and in one case by septic shock.

Adverse events

Nausea grade 2–4 was the most common side effect, which occurred in 32.1% of patients treated with BEAM and 41.3% of patients treated with BeEAM, respectively (p = 0.19) (Table 2). The rates of grade 3–4 nausea as well as grade 3–4 vomiting were comparable. Arterial hypertension and severe hypokalaemia occurred in two and three patients, respectively, all of them in the BeEAM group (p = 0.02 and p = 0.004, respectively, for the comparisons with the BEAM group). Other non-haematological complications were incidental and did not differ significantly according to the type of conditioning regimen. Two cases of transient acute kidney injury (AKI) grade 2 were observed, one in each group; there was no need for dialysis in any case. Moderate cardiac arrhythmias (grade 2); supraventricular extrasystoles and atrial fibrillations were observed in three patients in the BEAM group. Mild and moderate metrorrhagia (grade 1 and 2) as well as allergic reaction

Table 2. Side effects of conditioning regimen

<table>
<thead>
<tr>
<th></th>
<th>BEAM n = 174</th>
<th>BeEAM n = 63</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>56 (32.1)</td>
<td>26 (41.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>24 (13.8)</td>
<td>7 (11.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>22 (12.6)</td>
<td>9 (14.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>8 (4.6)</td>
<td>2 (3.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Mucositis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>29 (16.7)</td>
<td>11 (17.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>11 (6.3)</td>
<td>5 (7.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Diarrhoea, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>26 (14.9)</td>
<td>13 (20.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>8 (4.6)</td>
<td>4 (6.35)</td>
<td>0.59</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>6 (3.5)</td>
<td>2 (3.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>3 (1.7)</td>
<td>1 (1.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Febrile neutropaenia, n (%)</td>
<td>36 (20.7)</td>
<td>36 (20.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>grade 2–4</td>
<td>36 (20.7)</td>
<td>13 (20.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>36 (20.7)</td>
<td>13 (20.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypokalaemia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 2–4</td>
<td>0 (0)</td>
<td>3 (4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>0 (0)</td>
<td>3 (4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>0 (0)</td>
<td>2 (3.2)</td>
<td>0.02</td>
</tr>
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<td>grade 2–4</td>
<td>3 (1.7)</td>
<td>1 (1.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>2 (1.2)</td>
<td>1 (1.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cardiac arrhythmias, n (%)</td>
<td>3 (1.7)</td>
<td>0 (0)</td>
<td>0.3</td>
</tr>
<tr>
<td>grade 2–4</td>
<td>8 (4.6)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Metrorrhagia, n (%)</td>
<td>5 (2.9)</td>
<td>0 (0)</td>
<td>0.17</td>
</tr>
<tr>
<td>grade 2–4</td>
<td>2 (1.2)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>1 (0.6)</td>
<td>1 (1.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Allergic reaction, n (%)</td>
<td>5 (2.9)</td>
<td>0 (0)</td>
<td>0.17</td>
</tr>
<tr>
<td>grade 2–4</td>
<td>2 (1.2)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
<tr>
<td>grade 3–4</td>
<td>1 (0.6)</td>
<td>1 (1.6)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Fig. 1. Neutrophil recovery > 0.5 × 10⁹/l

Fig. 2. Platelet recovery > 50 × 10⁹/l
grade 2–4 occurred in eight and five patients, respectively, only in the BEAM group.

The rates of febrile neutropenia were almost the same for both study groups: 20.7% after BEAM and 20.6% after BeEAM. Four patients suffered from severe pneumonia (three cases in the BEAM group and one case in the BeEAM group); the complication was fatal in three cases.

Long-term outcome

The median follow-up for survivors was 29 months in the BEAM group and seven months in the BeEAM group. Probabilities of the OS at 24 months were 91% (95% confidence interval, 89–93%) and 89% (83–95%), respectively (p = 0.73). PFS rates at 24 months were 81% (78–84%) and 76% (69–83%), respectively (p = 0.55).

Discussion

Although HDCT followed by autoHCT is considered the treatment of choice in chemosensitive RR lymphomas, the optimal conditioning regimen has not yet been defined. Regimens most frequently used in RR NHL are BEAM, CBV (cyclophosphamide, carmustine, etoposide), or total body irradiation–containing schedules, while in a setting of HL, BEAM is considered standard [13].

Carmustine as a part of BEAM is associated with the risk of pulmonary toxicity manifested by interstitial pneumonia. In order to avoid this complication and potentially to increase the efficacy of the regimen, it has been proposed that bendamustine be used instead of carmustine. The efficacy and tolerance of BeEAM was initially evaluated by Visani et al., in a prospective study including 43 patients with HL and NHL. TRM was 0%, while the cumulative incidence of infectious complications was 60%, without non-haematological serious adverse events. The study revealed that the new protocol was safe and effective, especially for heavily pretreated patients [5]. The updated follow-up at 41 months after transplant revealed 72% probability of PFS at three years [6].

Gilly et al. reported a retrospective cohort of 39 patients treated with BeEAM as conditioning prior to autoHCT. The most common grade 3–4 non-haematological toxicities comprised mucosal side effects (69%). Pulmonary toxicity was observed in one patient (2.5%), and one patient died of septic complications.

In the current study, for the first time the safety profile of BeEAM was compared with BEAM. The group of patients treated with BeEAM was the largest reported in the literature so far. The analysis revealed no differences in terms of neutrophil and platelet engraftment. Furthermore, the rate of infectious and non-infectious complications did not differ between groups, except of slightly more frequent incidence of hypokalaemia and hypertension in the BeEAM group compared to the BEAM group. Finally, the rate of early TRM was small and comparable for patients treated with BEAM and BeEAM, not exceeding 2% regardless of the type of the regimen.

According to a previous phase I study on patients with solid tumours, cardiac complications (such as supraventricular tachycardia, premature supraventricular complex-
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Submitted: 9.06.2017
Accepted: 26.03.2018