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Feasibility of up-front autologous stem cell transplantation for high risk diffuse large B-cell lymphoma – non-randomized analysis of 58 consecutive patients

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Anna Armatys,
Agata Wieczorkiewicz-Kabut,
Dariusz Kata,
Krzysztof Woźniczka,
Anna Kopińska,
Anna Koclęga,
Adrianna Spałek,
Grzegorz Helbig*

Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, School of Medicine in Katowice, Katowice, Poland

Abstract

Introduction: High-dose chemotherapy supported by autologous stem cell transplantation (ASCT) continues to be a standard of care for relapsed diffuse large B-cell lymphoma (DLBCL) and may be considered as a frontline consolidation for a proportion of patients with high-risk features. Aim: We evaluated the feasibility and safety of ASCT for high-risk DLBCL who are in first complete remission after standard treatment with chemotherapy ± rituximab. Material and methods: A retrospective analysis of 58 patients (36 males and 22 females) receiving up-front ASCT between 1996 and 2018 for remission consolidation. Results: Of the diagnosed, fifty patients were in clinical stage ≥ III. Forty-two (72%) of transplanted patients had age-adjusted IPI ≥ 2. The "B" symptoms were present in 34 patients. The conditioning consisted of cyclophosphamide, carmustine, etoposide (CBV) in 32 patients, carmustine, cytarabine, etoposide, melphalan (BEAM) in 18, and 8 patients received bendamustine, cytarabine, etoposide, melphalan (BeEAM). The transplant-related mortality was 0% at day +30 and +100 after ASCT. Median overall survival (OS) was 4.2 years whereas progression-free survival (PFS) reached 3.0 years. The estimated 5-year OS and PFS were found to be 66% and 64%, respectively. The presence of "B" symptoms remained significance in multivariate analysis (HR 4.17 [95% CI: 1.19–14.5]; $p = 0.02$). No grade 3 or 4 non-hematological adverse events were observed. Conclusions: Up-front ASCT was found to be a safe and feasible procedure with long-term remission in approximately 70% of patients.

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Keywords:
autologous stem cell transplantation, diffuse large B-cell lymphoma, remission, outcome

Introduction

Diffuse large B-cell lymphoma non-otherwise specified (DLBCL-NOS) is an aggressive type of B-cell non-Hodgkin lymphoma (NHL) that accounts for ~30% of all NHL in Western countries. DLBCL-NOS is more common in males than females and usually occurs in elderly (6^{th}–7^{th} decade); however, it may be observed in children and young adults [1, 2].

The etiology of DLBCL-NOS remains unexplained, although its development may be associated with exposure to prior chemotherapy especially in combination with radio- and/or immunotherapy. Moreover, risk factors include exposure to chemicals, viral infections, and radiation [2, 3]. Most patients present with rapidly progressing lymphadenopathy with strongly expressed constitutional symptoms. DLBCL-NOS can be demonstrated less frequently as extra-nodal manifestation [2, 4].

DLBCL often responds well to treatment and immune-chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) regimen allows to achieve complete remission (CR) rate in approximately 50–70% of patients [5]. High-dose chemotherapy supported by autologous stem cell transplantation (ASCT) continues to be a standard of care for relapsed setting and may be considered as frontline consolidation for patients having specific high-risk features. Though this latter indication remains controversial, some beneficial effects have been demonstrated [6, 7]. All patients with advanced clinical stage and/or intermediate/high-risk and high-risk DLBCL on international prognostic index (IPI) who achieved CR1 after standard R-CHOP induction proceed to ASCT according to the transplant policy of our center. Herein, we present our data on safety and feasibility of ASCT in 58 consecutive patients transplanted during the last 22 years.

Patients and methods

A total of 58 patients (36 males and 22 females) at median age of 49 years at diagnosis (range 18–60) received up-front ASCT between 1996 and 2018 for remission consolidation. Fifty patients were diagnosed with clinical stage ≥ III. Forty-two (72%) of the transplanted patients had age-adjusted IPI ≥ 2. The "B" symptoms were present in 34 patients. A histological diagnosis of DLBCL was done by a local pathologist on the excised lymph node using immunochemistry. The disease stage was evaluated according to the Ann Arbor staging system and age-adjusted IPI score was calculated as published elsewhere [8]. The diagnostic work-up included physical examination, complete blood count with differential and biochemistry tests. Imaging studies including computed tomography (CT) of the neck, chest, abdomen, and pelvis and/or positron emission tomography (PET) were performed at diagnosis and for response assessment.

*Corresponding author: Grzegorz Helbig, Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Dabrowski 25, 40-032 Katowice, Poland, phone: +48 322591310, fax: +48 322554985, e-mail: ghelbig@o2.pl

Bone marrow biopsy was performed at diagnosis and as needed. Patients were eligible for ASCT if they met the following criteria: (1) first complete remission after conventional immuno-chemotherapy, (2) advanced clinical stage [III/IV] or age-adjusted IPI ≥ 2, (3) Eastern Cooperative Oncology Group performance staus(ECOG) 0–2, (4) age < 60 years, and (5) adequate hepatic, renal, and cardiac function. All patients signed an informed consent. The clinical characteristics of patients are presented in table I.

Treatment

Induction treatment includes R-CHOP regimen (n = 50) or CHOP only (n = 8) and all patients studied achieved the first CR before ASCT. Fifty patients were transplanted during or after the year 2000. Peripheral blood was the source of stem cells in 50 patients (86%), whereas 8 subjects received bone marrow. The ifosfamide, etoposide, epirubicin (IVE) regimen was used for stem cell mobilization. The granulocyte colony stimulating factor (G-CSF) at 10 mg/kg/day was started from day +5 until the last day of apheresis. At least 2×10^6 CD34-positive cells/kg were required for transplant; however, it was not the case in 4 patients. The apheresis product frozen to −180°C, stored, and re-infused after completion of conditioning was processed. The conditioning consisted of cyclophosphamide, carmustine, etoposide (CBV) in 32 patients, carmustine, cytarabine, etoposide, melphalan (BEAM) in 18, and 8 patients received bendamustine 200 mg/m^2, cytarabine, etoposide, melphalan (BeEAM).

Response criteria

The response to therapy was evaluated at 3 and 6 months after ASCT and 6 months thereafter using CT ± PET. CR was defined as a disappearance of all disease-related symptoms and measurable lesions. Relapse was defined as enlargement of initial tumor manifestations or occurrence of new lesions during post-ASCT follow-up.

Statistical methods

All calculations were made from the date of transplantation. Comparisons between the variables were carried out by log-rank test. Statistical significance was defined at a *p*-value <0.05. The probability of overall (OS) and progression-free survival (PFS) was calculated according to Kaplan–Meier method. Transplant-related mortality (TRM) was defined as death within 30 days of high-dose therapy and not related to the disease, relapse, and progression. Proportional hazards models (Cox regression) were fitted to investigate the effects of prognostic factors for OS. The following factors were entered in the model (1) patient-related: age, clinical

Table I. Patients' characteristics

Parameter	DLBCL (n = 58)
Male/female; no	36/22
Age at diagnosis (years; median, range)	49 (18–60)
Hemoglobin level (g/dL; median, range)	12.7 (7.3–16.0)
Platelet count (×10^9/L; median, range)	222 (46–621)
Leukocyte count (×10^9/L; median, range)	6.9 (1.9–189.0)
Lymphocyte count (×10^9/L; median, range)	1.6 (0.1–140.0)
Monocyte count (×10^9/L; median, range)	0.59 (0.0–2.0)
LDH activity (IU/mL; median, range)	223 (116–939)
B2M concentration (mg/L; median, range)	2.75 (0.88–5.31)
Bone marrow involvement at diagnosis; no, %	16 (28)
Central nervous system involvement at diagnosis; no, %	1 (2)
Splenomegaly; no, %	14 (24)
Hepatomegaly; no, %	18 (31)
Number of involved nodal areas (median, range)	3 (0–7)
Number of involved extra-nodal areas (median, range)	1 (0–5)
Clinical stage; no, % I II III IV	 4 (7) 8 (14) 12 (21) 38 (66)
Age-adjusted IPI risk; no, % Low Low-intermediate High-intermediate High	 4 (7) 12 (21) 40 (69) 2 (3)
B symptoms; no, %	34 (59)
Rituximab containing regimen pre-ASCT; no, %	50 (86)
Radiotherapy prior ASCT; no, %	21 (36)

ASCT – autologous stem cell transplantation; B2M – beta2microglobulin; DLBCL – diffuse large B-cell lymphoma; IPI – international prognostic index; LDH – lactate dehydrogenase

stage, age-adjusted IPI, the presence of B symptoms, hepatomegaly, splenomegaly, bone marrow involvement, blood parameters, use of rituximab, and radiotherapy; and (2) transplant-related: type of conditioning and date of transplant. All computations were performed with StatSoft Poland analysis software (version 12.0).

Results

Cell dose and engraftment

The median number of transplanted CD34-positive cells was 4.2 × 10^6/kg (range 1.3–39.2). All patients engrafted. The median time to neutrophil recovery was 12 days (range 8–18) and platelet count > 20 × 10^9/l occurred after median of 13 days (range 5–107).

Adverse events

The most common complaints included mucositis, diarrhea, and infections of the upper respiratory tract. None of the patients had bacteremia within the first 100 days after ASCT. Grade 3 or 4 non-hematological adverse events were not observed. All patients required G-CSF support during early post-transplant period.

Outcome and prognostic factors

The TRM was 0% at day +30 and +100 after ASCT. Median OS was 4.2 years (range 0.04–21.7), whereas PFS reached 3.0 years (range 0.04–17.8). The estimated 5-year OS and PFS were found to be 66% and 64%, respectively (Fig. 1 and 2). A 5-year OS did not differ

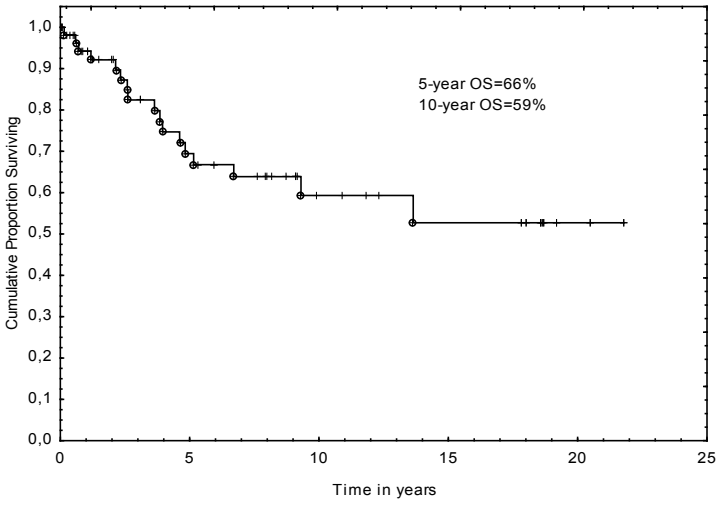

Fig. 1. OS for DLBCL after ASCT

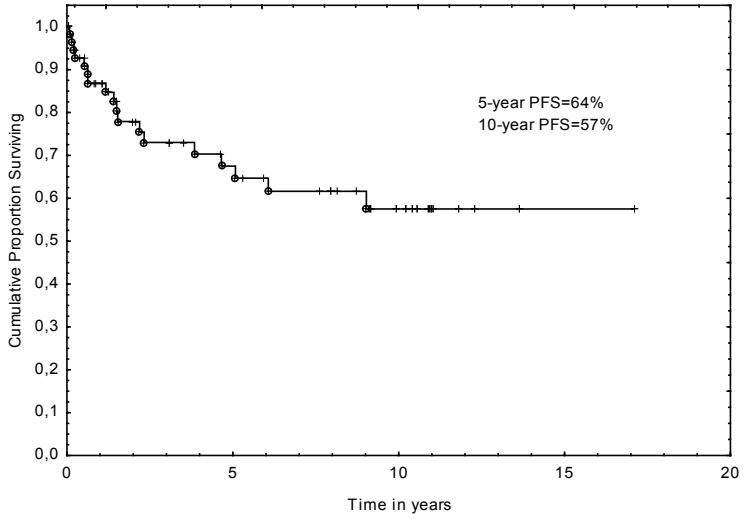

Fig. 2. PFS for DLBCL after ASCT

depending on the type of conditioning and was as follows: 45% vs. 73% vs 100% for CBV, BEAM, and BeEAM, respectively (p = 0.26). In univariate analysis bone marrow involvement, advanced clinical stage and the presence of "B" symptoms were found to influence OS; however, only "B" symptoms remained significant in multivariate analysis (HR 4.17 [95% CI: 1.19–14.5]; p = 0.02) (Fig. 3). At the last contact, 41 (71%) patients are alive due to CR, 16 patients died of disease progression with subsequent chemotherapy resistance. One patient is alive being on salvage chemotherapy.

Discussion

High-dose chemotherapy followed by ASCT remains a standard therapeutic approach for relapsed/refractory chemo-sensitive DLBCL. An advantage of ASCT over non-rituximab conventional chemotherapy was demonstrated decades ago by PARMA study showing a significant 5-year OS benefit for transplanted patients when compared to those on chemotherapy only (53% vs. 32%, p = 0.038) [9]. The addition of rituximab to standard CHOP regimen was associated with substantial improvement of patients' outcomes. Several randomized trials showed improved progression-free and overall survivals in DLBCL patients treated with R-CHOP [10, 11, 12]. It was speculated that DLBCL may benefit from more intensive induction regimens, e.g. dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) when compared to R-CHOP; however, such difference in PFS/OS was not demonstrated. Moreover, DA-EPOCH-R was found to be more toxic [13]. Nevertheless, even in the rituximab era, the survival rates of patients being classified in high or intermediate IPI risk groups remained unsatisfactory [14]. In this context, ASCT as remission consolidation should be taken under consideration but its long-term benefit is to be elucidated. The potential advantage of ASCT as a front-line treatment for high-intermediate and high-risk patients on the IPI with aggressive NHL was studied in 397 patients who received R ± CHOP regimen as induction. After achieving a response, patients were randomized between ASCT (n = 125) and 3 additional cycles of chemotherapy (n = 128). A 2-year PFS was significantly better for transplant cohort when compared to non-transplant group, 69% and 56%, respectively (p = 0.005), whereas OS was comparable (74% vs.71%). The results were even more encouraging for those at high-risk category [7]. The Italian Study Group enrolled 412 DLBCL patients with high-risk age-adjusted IPI. Two induction regimens were used before ASCT: 4 × R-CHOP14 and 4 × R-MegaCHOP14. This treatment was followed by high-dose chemotherapy with rituximab, cytarabine, mitoxantrone, and dexamethasone. BEAM conditioning was given prior to transplant. The patients in non-transplant arm received 8 × R-CHOP14 and 6 × R-MegaCHOP14. It was demonstrated that patients randomized to transplant arm had better 3-year PFS compared to the non-transplant group: 70% vs. 59%; p = 0.01. No difference in 3-year PFS was observed between induction arms (R-CHOP14 vs. R-Mega-CHOP14). OS was comparable between transplant and non-transplant group. The risk of relapse was significantly reduced in ASCT group [15]. It appears that ASCT as up-front treatment in low-risk DLBCL improves PFS and reduces relapse risk but does not have an impact on OS, and these findings were also confirmed by other study groups [16, 17]. In contrast, a Chinese study showed that patients who received up-front ASCT fared much better than the non-transplant group in terms of not only PFS but also OS [18]. Apart from the fact that our study was non-randomized with limited number of included patients, the post-transplant outcomes were comparable with data published elsewhere [7, 15–18]. The role of up-front ASCT for DLBCL has been recently discussed in metaanalysis. The authors analyzed 4 studies with 1,173 patients and compared conventional chemotherapy with rituximab vs chemotherapy with rituximab and ASCT demonstrating no difference between two arms [19]. Some studies have evaluated the consolidative role of ASCT in DLBCL of particular high-risk groups defined by the presence of dual translocations (double hit lymphomas-DHL) or dual protein-overexpression of *MYC* and *BCL6* (or *BCL2*) (double

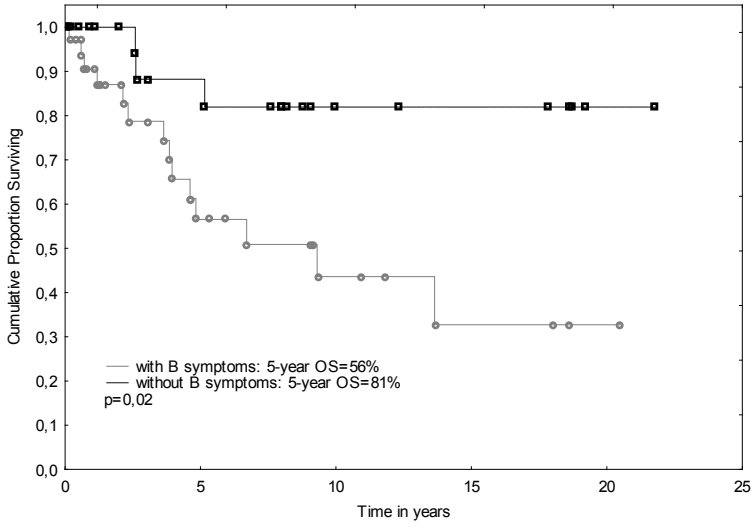

Fig. 3. Survival curves depending on the presence of B symptoms

protein-expressing lymphoma – DPL). With a median follow-up of 127 months, there was a tendency toward better outcomes after ASCT for patients with DPL, but not with DHL [20]. No significant benefit of ASCT in the first CR for DHL was demonstrated by others too [21, 22].

Conditioning regimen and its impact on post-transplant outcome is of interest. The role of preparative regimen was analyzed in a large study of Spanish Cooperative Group. Briefly, two pre-transplant regimens were compared: chemotherapy only (BEAM, BEAC, CBV) vs. radio-chemotherapy (cyclophosphamide with total body irradiation; [Cy/TBI]). A significant advantage of chemotherapy-based conditioning over Cy/TBI in terms of OS/RFS was demonstrated. After a median follow-up of 28 months, OS at 8 years was significantly more favorable for patients treated with BEAM/BEAC vs. CBV [23]. Compared to BEAM, CBV regimen was associated with higher mortality in DLBCL patients [24]. In our study, the type of preparative regimen had no impact on post-transplant outcome; however, all patients on BeEAM are alive during the last follow-up. The latter finding requires further studies with larger patient population. Some prior studies have demonstrated the feasibility and efficacy of this conditioning for patients with aggressive lymphomas [25].

Several other factors may have an impact on post-transplant OS in DLBCL patients in remission. Bone marrow (BM) involvement, advanced clinical stage, and the presence of "B" symptoms influenced survival in univariate analysis of patients from our study; however, only "B" symptoms remained significant in multivariate analysis. It was found that bone marrow involvement is a strong adverse factor influencing OS/PFS in patients with DLBCL regardless of the type of therapy (induction immunochemotherapy with or without subsequent ASCT). A 3-year PFS and OS were significantly ineffective in BM-positive vs BM-negative patients (46% vs. 73% and 65% vs. 83%, respectively) [26]. There was a tendency toward better outcome in BM-negative vs BM-positive patients in our study (79% vs. 50% at 5 years; $p = 0.06$). A multivariate analysis performed by the Chinese Study Group revealed that the none-germinal center B cell (non-GCB) and IPI 3-5 negatively influenced OS [18]. Unfortunately, data on the cell of origin subtype were not available for our patients.

It should be noted that ASCT as a frontline treatment in patients with DLBCL in CR1 remained an extremely safe procedure. All side effects were mild and easily manageable. No death was observed in the first 100 days after procedure; however, all patients were <60 years. The present study had many limitations. First, it was a non-randomized study and the number of treated patients was relatively small. Second, the data on the cell of origin subtype were not available and longer follow-up would be advisable.

Conclusions

In approximately 70% of transplanted patients, up-front ASCT was found to be a safe and feasible procedure having long-term efficacy.

Authors' contributions

AA, GH – equally contributed in this paper, performed statistics, wrote a manuscript, collected data, critically reviewed. AWK, DK, KW, AK, AK, AS – collected data, post-transplant care, critically reviewed the manuscript.

Conflict of interest

GH has received a speaker honorarium from Novartis. All other authors declare no conflict of interest.

Financial support

Not applicable.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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