Introduction

High-dose chemotherapy (HDT) combined with autologous stem cell transplantation (ASCT) has been considered a promising treatment option aiming to improve the outcome of lymphoma patients who fail to achieve complete remission after first-line chemotherapy [1–2]. In relapse-refractory disease, salvage regimens are needed to overcome therapeutic resistance with implementation of new drugs. The achievement of remission after salvage regimens, usually platinum-based is of great importance for success of further transplant. Induction treatment of lymphoma is disease-dependent and for Hodgkin lymphoma (HL) it is ABVD or BEACOPPes/4 according to risk group, while in non-Hodgkin lymphoma (NHL), induction consists of immunochemotherapy (R-CHOP or R-CHOP like regimens). Standard conditioning regimens are BEAM or CBV. However, relapses after ASCT are extremely unfavorable and need innovative therapies with targeted drugs.

The role of ASCT in Hodgkin lymphoma

Concerning HL, patients are usually cured by first-line therapy alone or with combined modality with additional radiation. Unfortunately, about 15% to 30% of patients with HL experience either primary refractoriness or relapse despite modern treatment options.
The role of ASCT in non-Hodgkin lymphomas

With regard to chemosensitive relapse of NHL, HDT with ASCT is still standard of care. Among NHLs, aggressive diffuse large B-cell lymphoma (DLBCL) is the most common disease. The probability of being cured by the initial treatment is well predicted by the International Prognostic Index (IPI) [8].

Prior to the introduction of rituximab, the probability of long-term survival varied from 26-73%, [8]. With adding rituximab to standard induction regimens, outcomes got better across all IPI groups [9,10]. For patients with relapsed, chemosensitive DLBCL, the Parma trial established HDT with ASCT as superior compared to conventional salvage chemotherapy alone [11]. However, this study was conducted in the pre-rituximab era, making its relevance in DLBCL patients treated in rituximab era with frontline or salvage regimens uncertain.

Although HDT with ASCT is treatment of relapsed NHL patient, in mantle cell lymphoma, it is therapy for consolidation of first remission. Namely, MCL classically responds to upfront chemotherapy, but it remains incurable with standard approaches. For patients in need of frontline therapy, the initial decision is whether to proceed with an intensive treatment strategy or a non-intensive treatment strategy. In general, younger and fit patients can be considered for intensive strategies. With current high-dose cytarabine-containing immunochemotherapy regimens followed by ASCT, the median PFS has exceeded 7 years [12].

Similarly as mentioned, our results in the treatment of high-risk relapse/refractory lymphomas have also demonstrated the advantage of HDT with ASCT.

Material and Methods

In this study, the results of treating 120 patients with lymphoma were analyzed; HL (90 patients), NHL (30 patients) in whom HDT with ASCT was conducted over a ten-year period (2006-2016). All patients were treated at the Clinic for Hematology KCS. In patients with HL, initial therapy was protocol ABVD, and salvage protocols were DHAP or ICE, which were used for stem cell mobilization. In 3 patients who were poor mobilizers, plerixafor was used. Second ASCT performed in 6 patients. As consolidation of first remission, ASCT performed in MCL patients treated initially with R-CHOP/R-DHAP or R-Hyper CVAD/HDMTX-AraC. In FL and DBKL, patients initially received R-CHOP, and afterward a salvage protocol ESHAP, which was also used for stem cell mobilization. The conditional protocol was BEAM or CBV.
Median survival of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) was 8 years for HL patients and 12 years for NHL patients. However, 46% of patients after transplant have failed treatment either due to a disease-progression or consecutive relapse. Median survival of patients with HL was 12 years, and for NHL patients it was 8 years.

**Results**

The average age of patients with HL was 29 (18-51), while in patients with NHL, it was 40 (23-62). The average length of the mobilization was 6 days (5-12), the average number of CD34+ cells in the apheresis product was 8.6x10⁶/kg tm (2-25), the average volume of the apheresis product was 325 (150-900) ml, the average leukocyte engraftment was on day 13 (7-21), platelet engraftment on day 14 (9-30), and transplant related mortality was 0.8%. In HL, the initial Hasenclever index: International Prognostic Score (IPS) ≥ 3 was associated with shorter overall survival and survival after transplant (log rank = 7.128, p <0.008) (Graph 1).

Patients with HL in whom the initial complete remission (CR,) > 12 months had two times longer overall survival (OS) compared to patients with CR,. <12 months (161 vs. 83 months). In lymphomas (HL and NHL) treated with VDT-ASCT, post-transplant CR at D+100 was the most powerful predictor of long-term OS (p <0.0001). The use of this type of treatment in HL increased the rate of favorable therapeutic response to D+100 (CR + PR) compared to the initial by more than 30%. However, 46% of patients after transplant have failed treatment either due to a disease-progression, or consecutive relapse. Median survival of patients with HL was 12 years, and for NHL patients it was 8 years.

**Graph 2. Median survival of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)**

**Discussion**

Our results showed the importance of HDT with ASCT in terms of increasing the response rate, as well as the satisfactory survival of high-risk patients with lymphoma, overcoming the significant degree of their therapeutic resistance.

For HL, HDT and ASCT represent the standard of care for patients with chemotherapy-sensitive relapsed or primary refractory HL. Certainly, the patients with negative pre-transplant PET/CT have much better post-transplant outcomes. The question whether patients with chemosensitive disease, but persistent positive PET/CT, benefit from additional salvage therapy before ASCT still remains to be determined. There is no consensus concerning the optimal conditioning regimen for ASCT or the role of tandem ASCT. But, patients with primary refractory HL are unquestionably candidates for tandem ASCT, following Morchauser criteria for high risk diseases [13]. The treatment of HL patients with completely refractory disease or those who experienced relapse after ASCT remains a great challenge. The use of RIC allogeneic-SCT (allo-SCT) can be of help for some unfavorable patients, and should be considered, especially if the disease can be controlled to a minimal state pre-transplant. In the allo-SCT setting many questions remain unresolved, regarding the optimal conditioning protocol, the use of DLI, T-cell depletion, and the optimal donor source of stem cells. With each of these treatments, the integration of targeted therapies into conditioning regimens, or as maintenance post-transplant therapy may additionally improve therapeutic outcomes.

In DLBCL patients, HDT followed by ASCT is a potentially curative option for patients with chemosensitive relapse or refractory disease, but more than 50% of patients will ultimately relapse. Many prognostic factors are associated with post-ASCT outcome in patients with relapsed/refractory DLBCL, including pre-ASCT remission status, as assessed by PET/CT, time to relapse, and prognostic indices (e.g. IPI, or revised IPI) [14]. Although these clinical prognostic factors are useful, new tumor-specific biomarkers may allow for improving prognosis prediction. For instance, double-hit lymphomas (DHLs) are a subset of DLBCL with concurrent chromosomal rearrangements involving the MYC and BCL-2 and/or BCL-6 genes, which comprise approximately 2-10% of newly diagnosed DLBCL. Patients with DHLs have dismal therapeutic outcomes with standard induction immunochemootherapy (R-CHOP) [15]. Double-expressor lymphomas are DLBCL with co-expression of the MYC and BCL-2 proteins by immunohistochemistry and encompass 21-34% of newly diagnosed patients with DLBCL.

**Conclusion**

Although some patients with relapsed/refractory diffuse large B-cell lymphoma had long-term remission after autologous stem cell transplant, the low survival rate in this group point to the fact that alternative transplant strategies, including allogeneic stem cell transplantaion or peri-autologous stem cell transplant relapse prevention strategies, should be considered. Therefore, the precise definition of the disease risk degree is necessary before deciding to proceed to autologous stem cell transplantation as a further treatment strategy for these high-risk lymphomas.
The post-transplant complete remission (day+100) is the most important factor in favorable prognosis for long-term survival of patients with lymphomas treated with high dose chemotherapy with autologous stem cell transplantation. Also, the absence of chemo-sensitivity to the application of salvage therapy is an indicative area solely for the application of the so-called “target” therapy modalities.

References


