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Efficacy of salvage therapy supported by autologous stem cell transplant, in relapsed/ refractory Hodgkin lymphoma treated in the first line with an escalated BEACOPP regimen

Skuteczność leczenia ratunkowego z autologicznym przeszczepieniem komórek macierzystych, w nawrotowym/opornym chłoniaku Hodgkina u chorych leczonych w pierwszej linii schematem BEACOPP eskalowany

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Additional key words:
autologous stem cell transplantation
BEACOPP
Hodgkin lymphoma
relapsed
salvage

Dodatkowe słowa kluczowe:
autologiczne przeszczepienie komórek macierzystych
BEACOPP
chłoniak Hodgkina
leczenie ratunkowe
nawrót

Introduction: Modern polychemotherapy protocols consolidated where indicated with involved field radiotherapy, significantly improved the outcome of Hodgkin lymphoma (HL) patients. In relapsed/ refractory (R/R) cases, high-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (ASCT) remains the treatment of choice.

Objectives: We evaluated the efficacy of salvage HDCT supported by ASCT in advanced-stage HL patients, treated with an up-front escalated BEACOPP protocol, allowing for therapy modification based on early PET-CT ([^{18}F] fluorodeoxyglucose positron emission tomography-computed tomography) assessment.

Material and Methods: We retrospectively collected the data of 52 patients, diagnosed between 2003-2013, qualified to ASCT in primary refractory disease (n=23), relapse (n=16) or first line therapy consolidation (n=13). Complete response (CR) rate and Progression free survival (PFS) were primary endpoints of our study.

Results: The ASCT procedure was not performed in 8 (15.4%) patients who failed stem cell mobilization and 6 (11.5%) cases refractory to salvage therapy. Response to salvage chemotherapy, was confirmed by PET-CT in all patients subjected to ASCT. In an intend to treat analysis, complete response rate in primary refractory, relapsed and high risk 1st CR consolidated patients was 56.5, 63.5 and 100% respectively. At the median follow up period of 10.4 years (range 0.3-18.4), the 10-year PFS in the whole cohort was 51.9%: 39.1, 37.5 and 92.3% in primary refractory, relapsed and 1st CR consolidated patients respectively.

Wstęp: Wprowadzenie nowoczesnej chemioterapii z ewentualną radioterapią znacznie poprawiło wyniki pacjentów z chłoniakiem Hodgkina (HL). Jednakże w przypadkach nawrotów/oporności choroby leczenie wysokodawkowaną chemioterapią (HDCT), a następnie autologiczne przeszczepienie komórek macierzystych (ASCT) jest postępowaniem z wyboru.

Cele: Oceniliśmy skuteczność ratunkowego HDCT i ASCT u pacjentów w zaawansowanym stadium R/R HL po leczeniu I linii wg schematu BEACOPP eskalowany.

Materiał i Metodyka: Oceniliśmy retrospektywnie dane 52 pacjentów, zdiagnozowanych w latach 2003-2013, zakwalifikowanych do ASCT w pierwotnie opornej chorobie (n=23), nawrotach (n=16) lub konsolidacji terapii pierwszego rzutu (n=13). Odpowiedź na leczenie i czas przeżycia bez progresji choroby (PFS) były pierwszorzędowymi punktami końcowymi naszego badania.

Wyniki: Nie przeprowadzono procedury ASCT u 8 (15,4%) pacjentów, u których nie udało się zmobilizować komórek macierzystych i 6 (11,5%) przypadków opornych na leczenie ratujące. U wszystkich chorych poddanych ASCT potwierdzono badaniem PET-CT chorobę chemiowrażliwą na leczenie ratunkowe. W analizie oceniającej skuteczności leczenia, całkowita odpowiedź na ASCT u pacjentów z chorobą pierwotnie oporną, nawrotową i konsolidacją pierwszej całkowitej remisji (CR) wynosiła odpowiednio 56,5; 63,5 i 100%. Przy średnim okresie obserwacji 10,4 lat (zakres 0,3-18,4), 10-letni PFS w całej kohorcie wynosił odpowiednio 51,9%: 39,1, 37,5 i 92,3% dla pacjentów z chorobą pierwotnie oporną, nawrotową i pierwszej CR.

Conflict of interest not declared

Received: 03.04.2019
Accepted: 06.05.2019

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Conclusions: HDCT with ASCT is a treatment of choice in R/R HL patients responding to salvage chemotherapy. In PET-CT era, there is no longer need for consolidating high-risk 1st CR cases. On intend to treat analysis, response to salvage protocols of relapsing patients treated by an up-front escalated BEACOPP regimen is satisfactory. The prognosis of R/R patients not responding to salvage regimen is poor – new targeted treatment approaches such as anti CD30 monoclonal antibodies or checkpoint inhibitors are now considered a bridge to allogeneic stem cell transplantation.

Wnioski: HDCT z ASCT jest opcją leczenia u pacjentów z R/R HL, jednak dla chorych, którzy nie odpowiadają na leczenie ratunkowe, z nieskuteczną mobilizacją komórek macierzystych lub nawrotem po ASCT, rokowanie jest nadal bardzo złe, wymagające zastosowania nowych metod leczenia, takich jak brentuksymab vedotin lub programowane inhibitory śmierci komórek (nivolumab), uważane za pomost do allogenicznego przeszczepienia komórek macierzystych.

Introduction

The introduction of modern multi-agent chemotherapy consolidated where indicated with involved field radiotherapy, significantly improved the outcome of Hodgkin lymphoma (HL) patients [1,2]. However, in 15-30% of relapsing/refractory (R/R) patients, salvage chemotherapy regimens [3], consolidated with high dose chemotherapy (HDCT) chemotherapy followed by autologous stem-cell transplantation (ASCT) is the treatment of choice. It allows for long-term remissions in 40-50% of relapsed patients and 25-30 % of those with primary refractory disease [4,5]. Two randomized phase III trials comparing HDCT/ASCT with standard dose regimens demonstrated improved progression free survival (PFS), however no significant differences in overall survival (OS) [6,7]. Prognosis and the probability of long-lasting remissions depends on the risk factors such as: presence of B symptoms, duration of the initial response, disease stage, presence of bulky disease at the time of transplantation, number of prior chemotherapy lines and applied regimens [8,9]. Transplant results are best in patients achieving complete remission (CR) in response to salvage therapy -- there are no randomized clinical trial data supporting ASCT in non responders [10,11]. Approximately 10-15% of HL patients, who will not be cured with first-line regimens or subsequent salvage regimens consolidated with ASCT are candidates for alternative therapies, including monoclonal antibodies against CD30 (Brentuximab Vedotin) or checkpoint inhibitors (Nivolumab, Pembrolizumab) considered as an adequate bridging to allogeneic stem cell transplantation.

Material and Methods

In this retrospective analysis we assessed the efficacy of HDCT/ASCT to rescue patients with R/R advanced HL treated in the first line with escBEACOPP (escalated BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). We collected the data of 52 patients qualified to ASCT, selected from 188 consecutive, advanced-stage HL patients, who completed the first-line treatment at Department of Haematology, Jagiellonian University in Krakow between April 2003 and August 2012. The initial diagnosis of classical HL was based on histopathological assessments, according to the World Health Organization 2001 and 2008 classification [12,13]. At diagnosis and before ASCT patients were staged according to Ann Arbor classification with Cotswolds modification [14]. International Prognostic Index (IPI) was calculated in all cases [15]. Patient's characteristics and demographics before the salvage are summarized in table I.

Initially patients were treated with escBEACOPP followed after 2 cycles by early PET-CT assessment. Patients with PET-CT CR received 4 cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine). The remaining 25% of the cases were continued on escBEACOPP. Chemotherapy regimens were administered in accordance to their original description [16,17]. A PET-CT CR was initially defined as an involved sites activity inferior to mediastinal blood pool structures (MBPS). In 2010 we switched to Deauville criteria where CR is defined as score of 1-3 [18]. Final response to first-line treatment was assessed in concordance with the original Cheson's criteria [19,20] and PET-CT scan results performed within a month after first-line treatment completion [18].

Patients with partial remission (PR), stable disease (SD), progressive disease (PD) after completing the first-line treatment or relapsing within three months after first-line treatment completion, were regarded as primary refractory and qualified to further salvage therapy consolidated with ASCT (n=16). HDCT/ASCT was also proposed as consolidation of first remission to 13 high-risk patients (IPI of 3 or greater, bulky disease at the diagnosis and presence of B-symptoms) and relapsing cases (n=23). An ESHAP regimen (etoposide, methylprednisolone, cisplatin and cytarabine) used as salvage chemotherapy [21], served for peripheral blood stem cell (PBSC) mobilization and collection. Autologous stem cell transplants were conditioned in 36 patients with BEAM chemotherapy (high--dose carmustine, etoposide, cytarabine and melphalan) and in 2 cases with CY/TBI (combination of high-dose cyclophosphamide and total body irradiation – 10-12 Gy). All patients received supportive treatment per local standard, including prevention of tumour lysis syndrome, antibacterial/ antiviral /antifungal therapy and transfusions of red blood cells/platelets as required.

PET-CT assessment was performed after the salvage regimens to confirm chemo-sensitivity. Response to HDCT/ASCT was also assessed in PET-CT three months after the procedure, followed by CT scans thereafter (at 3-month intervals within the first year, every 6 months in the second year, and every 12 months until the end of the 5th year). Later imaging studies were performed on individual basis, when appropriate.

Descriptive statistics and Kaplan-Meier survival analysis (PFS and OS) was performed using STATISTICA software.

Results

A total of 52 patients were initially qualified for salvage therapy with ASCT consolidation. In the analysed group, the median age was 29 years (range 18-52) a with a male/female ratio of 1.24. A total of 46 patients (88.5 %) presented at diagnosis B symptoms, 39 (75%) had stage III or IV disease and 13 (25%) stage IIBX; 44 (84.6 %) had a high risk according to IPI (3-7). ASCT was considered in 23 patients (44.2%) with primary refractory disease, 16 (30.8%) patients due to HL relapse and 13 (25%) patients with high-risk disease as consolidation of 1st line CR.

The ESHAP salvage therapy was administered to 52 patients. Four patients with primary refractory disease and 2 patients in relapse did not respond to salvage. In further 4 with primary refractory disease and 4 patients treated in relapse (all after 6 escBEACOPP cycles in the first line therapy) PBSC collection was not possible. We were able to collect the mean of 4.9 x 10^8 mononuclear cells/kg (range 1.9 – 21), in 1 to 4 apheresis (median 2) in 38 (73.1%) patients.

ASCT was performed in 38 patients (15/23 primary refractory patients, 10/16 patients with disease relapse and 13/13 patients as consolidation of first-line treatment). BEAM chemotherapy was used as a conditioning regimen before ASCT in 36 (94.7%) patients and CY-TBI in 2 (5.3%) patients. All 38 patients became cytopenic after conditioning therapy. The median time to recover a neutrophil count greater than 0.5 x 10^9/L was 12 days (range 5 to 66 days) and to achieve a self-sustained platelet count greater than 20 x10^9/L was 14 days (range 5 to 89 days). The incidence of grade 3 or 4 anaemia, thrombocytopenia, neutropenia, diarrhoea, stomatitis and neutropenic fever was similar in patients treated upfront with 6 cycles of escBEACOPP and 2 x escBEACOPP – 4 x ABVD combination. In our analysis we observed relatively few adverse events with no secondary malignancies, myelo-

Table I

Baseline characteristics and demographics at diagnosis in patients qualified and subjected to transplant (N=52).

Charakterystyka i dane demograficzne chorych w momencie diagnozy, którzy zostali zakwalifikowani i poddani transplantacji (N=52).

	Patients qualified to ASCT (N=52)	Patients subjected to ASCT (N=38)
Age median (range)	29 years (18–52)	30 years (19-50)
Male, n (%)	31 (59.6)	22 (57.8)
Median ECOG performance status	1 (0-1)	1 (0-1)
Histological subtype of lymphoma		
Nodular Sclerosis (NS), n (%)	30 (57.7)	23 (60.5)
Mixed Cellularity (MC), n (%)	2 (3.8)	1 (2.6)
Lymphocyte Rich (LR), n (%)	1 (1.9)	1 (2.6)
Lymphocyte Depleted (LD), n (%)	1 (1.9)	1 (2.6)
Unclassified, n (%)	18 (34.6)	12 (31.5)
Ann Arbor		
IIBX, n (%)	13 (25)	9 (23.7)
III, n (%)	10 (19.2)	6 (15.8)
IV, n (%)	29 (55.8)	23 (60.5)
Bulky disease, n (%)	40 (76.9)	30 (78.9)
B symptoms, n (%)	46 (88.5)	34 (89.5)
International Prognostic Index		
0–2, n (%)	9 (15.4)	4 (10.5)
3–7, n (%)	44 (84.6)	34 (89.5)
1st line therapy regimen		
6 escBEACOPP, n (%)	29 (55.8)	17 (44.7)
2 escBEACOPP+ 4 ABVD, n (%)	23 (44.2)	21 (55.3)
Radiotherapy	18 (34.8)	15 (39.4)
Indication to ASCT		
First CR consolidation, n (%)	13 (25)	13 (34.2)
Primary refractory disease, n (%)	16 (30.8)	10 (36.3)
Disease relapse, n (%)	23 (44.2)	15 (39.4)

Abbreviations: CR – complete remission, ECOG – Eastern Cooperative Oncology Group

Table II

Response to salvage regimen and ASCT (N=52). An intent-to-treat analysis.

Odpowiedź na schemat ratunkowy i ASCT (N=52). Analiza wyników w grupach wyodrębnionych zgodnie z zaplanowanym leczeniem.

Indication to ASCT	All	PBSCC Failure n (%)	Lack of response to salvage n (%)	Subjected to ASCT n (%)	CR after to ASCT n (%)	Relapse after ASCT n (%)	Patients with PFS at 10 years n (%)
1st line consolidation	13	0	0	13 (100.0)	13 (100.0)	1 (7.6)	12 (92.3)
Primary refractory HL	23	4 (17.3)	4 (17.3)	15 (65.2)	13 (56.5)	6 (26.0)	9 (39.1)
HL relapse	16	4 (25.0)	2 (12.5)	10 (62.5)	10 (62.5)	4 (25.0)	6 (37.5)
Overall	52 (100)	8 (15.4)	6 (11.5)	38 (73.1)	36 (69.2)	11 (21.2)	27 (51.9)

Abbreviations: ASCT – autologous stem cell transplantation, HL – Hodgkin lymphoma, PBSCC – peripheral blood stem cell collection, CR – complete response, PFS – Progression Free Survival

dysplastic syndrome (MDS) or acute myeloid leukaemia (AML). There were no episodes of deaths related to treatment or ASCT procedure.

In intend to treat analysis in a primary refractory disease we confirmed 13 (56.5%) CR, 6 PR (26.0 %) and 4 (17.3%) PD. The response was higher in relapsing patients: 10 (63.5%) CR, 4 (25%) PR and 2 (12.5%) PD. In high-risk patients, consolidated in CR achieved after the first line therapy, we confirmed 100% of CR after the transplant (Tab. II). Eleven patients relapsed after ASCT (10 patients within four years after ASCT). Four patients who progressed after ASCT were allografted and have been living until the time of the last analysis. There were 21 deaths in the analysed group including 7 patients who relapsed after ASCT and 14 patients not subjected to ASCT.

After the median post-transplant follow up period of 10.4 years (range 0.3-18.4), the 10-year PFS in the whole cohort was 51.9%: 39.1, 37.5 and 92.3% in primary refractory, relapsed and 1st CR consolidated patients respectively. In patients subjected to ASCT, PFS at 10 years in the whole group was 74%. PFS analysis of transplanted patients with respect to indication to ASCT is presented in figure 1. The prognosis for patients not subjected to ASCT was poor. All patients progressed and were treated with the low-dose palliative chemotherapy with a median PFS 0.9 years (range 0.3 – 2.1).

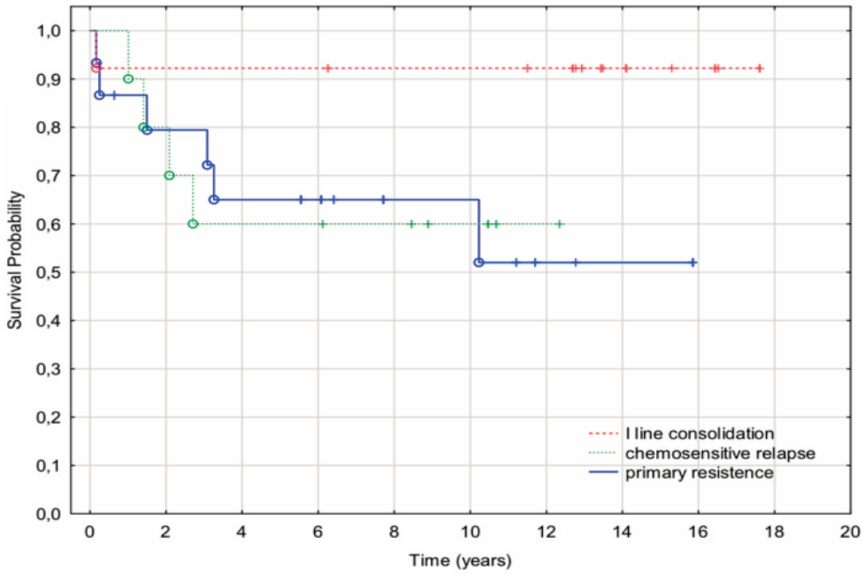

Figure 1
Progression free survival analysis in patients subjected to ASCT, according to transplant indications (N=38).
Analiza czasu wolnego od progresji u pacjentów poddanych ASCT, zgodnie ze wskazaniami do transplantacji (N=38).

Discussion

HDCT followed by ASCT is the treatment of choice for fit patients with R/R HL, chemo-sensitive to salvage therapy. Our analysis, although limited by its retrospective nature and by a relatively small number of patients, is the first in Poland to address HDCT/ASCT in the advanced-stage HL treatment failures after the first line treatment with escBEACOPP.

Disease status at ASCT is the most important prognostic factor: in CR patients we observe longer PFS and OS [22-24]. Both time to treatment failure (TTF) and OS also decreases with the number of therapy lines before ASCT [22]. Therefore, autologous stem cell transplants are recommended relatively early in the disease course, before development of disease resistance or therapy related organ impairment. The Spanish GEL/TAMO data (n=494) clearly demonstrated significantly higher TRM (transplant related mortality) in patients receiving more than one line of treatment before ASCT (10.8% vs 2.3%, *p*=0.042) [22]. Shortened disease-free survival (DFS) and increased risk of relapse and TRM were also reported by British and Dutch clinical studies [8,25]. Also, the retrospective analysis, and European Bone Marrow Transplantation (EBMT) Group reports, consistently emphasize the negative influence of number of chemotherapy lines before ASCT on the final outcome [26,27]. Selection of patients qualified for transplant, described in our paper is optimal, fully in line with all above recommendations. All of them were qualified to salvage therapy after failing the first line therapy; only chemo-sensitive patients were subjected to ASCT. In our retrospective intend to treat analysis of patients failing intensive 1-st line therapy, PFS at 10 years was 51.9%. Only 11.5% of the patients did not respond to salvage chemotherapy, in further 15.4% (all after 6 escBEACOPP cycles) PBSC collections was ineffective. These are the first data, in Polish population, confirming the good efficacy of salvage therapy followed by ASCT consolidation in patients failing first line escBEACOPP, where we expected an inferior outcome. In fact, our results were comparable to GEL/TAMO analysis, in patients failing ABVD regimen, where the 5-year OS was 54.5% and a 5-year TTF was 45% [22]. In transplanted patients, PFS at 10 years were 74%, which confirms fully the efficacy of the ASCT consolidation in patients with disease chemo-sensitive to the salvage therapy. Furthermore, we did not observe in our group any differences in outcome of patients transplanted with primary refractory disease and in the first relapse, which again underlines the importance of chemo-sensitivity to salvage regimens. In the era of PET-CT assessment, we should regard consolidation of first-line CR in high risk patients inadequate; PFS curves in patients undergoing ASCT in the first remission is literally identical to those not subjected to ASCT.

Second malignancies (SPM) emerged as a serious problem in HL patients subjected to ASCT. In the already mentioned GEL/TAMO analysis, their 5-year cumulative incidence was 4.3%, including 12 patients developing MDS or AML, similar to the data available in literature [22,28-30]. Alkylating agents, radiation therapy (especially TBI), combined-modality therapy and splenectomy are all responsible for the development of SPM [31-33]. In one analysis, comparing the risk of SPM, ASCT did not increase the incidence of secondary MDS/AML, although the risk of developing solid tumours was higher [28]. We were not able to confirm any secondary MDS / AML nor solid tumours in our data, despite relatively long median follow-up, exceeding 10 years.

ASCT is the best treatment option for HL patients with a chemo-sensitive disease and effective PBSC collection. At this point, it is particularly important to underline the poor prognosis of those, not- responding to salvage and those with an ineffective stem cell mobilization. Problems with acquiring adequate numbers of the stem cells in our patients were observed only after 6 cycles of escBEACOPP. Additionally, our analysis was performed in patients treated between 2003-2012, when plerixafor, was not available. In our study we described the patients treated before the era of anti CD30 monoclonal antibodies and checkpoint inhibitors, which are now the backbone of therapy in resistant cases and ASCT failures, as a bridge to Allo-SCT. Although introducing those new drugs prolonged significantly OS, our analysis was based on response rates and PFS, which makes our observation still important for undertaking clinical decisions.

In summary, this retrospective analysis confirmed the possibility of long-lasting PFS and OS in HL patients failing initial escBEACOPP regimen, subjected to ASCT.

Authorship Statement

MDD, MP, KW, PMG and WJ performed the study and analysed the data

WJ designed the study

MDD and WJ had substantial contributions to conception and design of the study

MDD, MP, KW and WJ drafted the manuscript

MDD and WJ critically revised the manuscript for important intellectual content

MDD, MP, KW, PMG and WJ contributed substantially to the acquisition, analysis, and interpretation of the data for the study.

The authors had full access to the data and take full responsibility for data integrity. All authors have read and agreed with the content of the manuscript. All authors declare no conflict of interest. This study hasn't been published in any other paper.

The work described has been performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for experimentation with human individuals.

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