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Allogeneic hematopoietic cell transplantation in refractory Hodgkin's lymphoma cases, the chance for long-term remission

Alloprzeszczepienie komórek krwiotwórczych w opornych przypadkach chłoniaka Hodgkina szansą na długotrwałą remisję

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S u m m a r y

The role of allogeneic hematopoietic cell transplantation (alloHSCT) in the treatment of Hodgkin's lymphoma is still debated.

In Department of Hematology and BMT Medical University of Silesia, among the 390 hematopoietic cell transplantations in Hodgkin's lymphoma patients (pts), 7 pts with refractory or relapsed HD (median age 22), who had the full matched sibling donor, were undergone alloHSCT, two of them twice time. Each patient received at least three lines of chemotherapy. Two pts were undergone autologous hematopoietic cell transplantation before alloHSCT. At the time of alloHSCT 1 pts was in complete remission, 4 were in partial remission and 4 during active phase of the disease. Non-myeloablative conditioning regimens preceding alloHSCT were used.

Due to alloHSCT one patient died (TRM 22%). Hematopoietic recovery after alloHSCT was: ANC > 0.5 x 10 ^ 9/L after median of 22 days and platelet > 50 x 10 ^ 9/L after 21 days. Two pts had to undergo second alloHSCT, because of relapse for the first, and the second one because of lack of engraftment.

4 pts died due to progression or early relapse. Two pts are still alive (both with chronic graft versus host disease); one survived longer than 10 years in CR and the other one survived 21 months in PR. The median time of survival is 21 months (4-120).

Conclusions. AlloHSCT with non-myeloablative conditioning regimen in patient with relapsed or refractory Hodgkin's lymphoma could be considered as a treatment option for a patient with full matched sibling donor and can be an opportunity to extend the life of these patients.

Key words: Hodgkin lymphoma, treatment, bone marrow transplantation

S t r e s z c z e n i e

Skuteczność alloprzeszczepienia komórek hematopoetycznych (alloHSCT) w leczeniu chłoniaka Hodgkina (HLy) jest nadal dyskutowana.

W Klinice Hematologii i Transplantacji Szpiku Śląskiego Uniwersytetu Medycznego spośród 390 przeszczepień w przypadkach HLy w 7 opornych/nawrotowych przypadkach (mediana wieku 22 lata) posiadających zgodnego rodzinnego dawcę szpiku przeprowadzono alloHSCT, u dwóch pacjentów (pts) zabieg wykonano dwukrotnie (analizie poddano 9 zabiegów alloHSCT). Każdy z chorych otrzymał co najmniej trzy linie leczenia, a dwóch pts przebyło wysokodawkowaną chemioterapię z przeszczepieniem autologicznych komórek krwiotwórczych.

Procedury alloHSCT przeprowadzono u 1 pts w całkowitej remisji, u 4 w remisji częściowej, a u 4 w aktywnej fazie choroby. Przed alloHSCT stosowano kondycjonowanie niemieloablacyjne.

Rekonstytucja układu krwiotwórczego przebiegała następująco: granulocyty > 0,5 x 10 ^ 9/L – mediana – 22 doba, płytki krwi > 50 x 10 ^ 9/L – 21 doba. U dwóch chorych przeprowadzono dwukrotnie alloHSCT: u jednego z powodu progresji HLy, u drugiego z powodu braku wszczepu. W trakcie alloHSCT zmarł 1 pacjent (TRM 22%). Z powodu progresji lub wczesnej wznowy zmarło 4 pacjentów. Dwóch chorych żyje nadal (obaj z przewlekłą chorobą przeszczep przeciw gospodarzowi): jeden w całkowitej remisji trwającej ponad 10 lat, drugi w remisji częściowej trwającej 21 miesięcy. Mediana przeżycia całkowitego wynosi 21 miesięcy (4-120).

Wnioski. AlloHSCT z niemieloablacyjnym kondycjonowaniem może być rozważane jako leczenie dające szansę na długotrwałe przeżycie w opornych/nawrotowych przypadkach chłoniaka Hodgkina posiadających zgodnego rodzinnego dawcę szpiku.

Słowa kluczowe: chłoniak Hodgkina, leczenie, przeszczepienie szpiku

In patients with advanced clinical stages of Hodgkin's lymphoma who demonstrated the presence of risk factors at the time of diagnosis, after the standard treatment using chemo-therapy and/or radiotherapy complete remission (CR) in more than 80% of patients is obtained (1, 2). In some patients the disease is, however, refractory and recurrent despite the regular treatment. In these cases, the following methods can be applied: chemotherapies with increased strength (so-called second- or third-line therapies such as ESHAP, DHAP (3, 4)), introducing a new medication (e.g. gemcitabine (5, 6, 7)), supplemental radiation therapy (8) and an intensive multidrug chemotherapy with autologous hematopoietic cells transplantation (autoHSCT) are used as well (9, 10). For the treatment of Hodgkin's lymphoma monoclonal antibodies: anti-CD20 (rituximab) (11) and a new generation of monoclonal anti-CD30 antibody (brentuximab vedotin) have been introduced also. The last one is applied mainly in order to eradicate residual tumor remaining despite aggressive treatment and for the treatment of refractory and recurrent form of lymphoma showing the expression of CD 30 (12). The role of allogeneic bone marrow hematopoietic cell transplantation (alloHSCT) for the treatment of Hodgkin's lymphoma cases, where the immunological effect of allogeneic transplanted cells play the main role (GVL – *graft versus lymphoma*), is still under consideration. Some patients benefited from treatment using alloHSCT, as evidenced, however, only few papers are published (6). In the Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia in Katowice, 390 hematopoietic cells transplantations in Hodgkin's lymphoma cases were performed (the total number of transplantations performed in this Department amounts over 2600 procedures), including only 9 procedures of allogeneic transplantation.

This paper presents a retrospective long term analysis of the procedures of allogeneic hematopoietic cells transplantations from sibling donors in heavily pretreated patients with refractory Hodgkin's lymphoma., who, before alloHSCT, were treated using chemotherapy programs including autoHSCT.

MATERIAL AND METHODS

During the period from December 2004 until July 2011 seven patients with refractory or relapsed Hodgkin's lymphoma underwent alloHSCT procedure, including two double alloHSCT which means 9 alloHSCT procedures in the Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia in Katowice.

The median age of patients at diagnosis was 22 years (from 15 to 29 years), most of them male (n = 5, 71%). The clinical stages of the disease at diagnosis, according to the Anbor Ann classification, were as follows: II-16%, III-12%, IV-72%. 70% of patients presented B symptoms. All the patients received at least three types of chemotherapy (tab. 1) as well as involved field radiotherapy (IF).

The time from diagnosis of Hodgkin's lymphoma to alloHSCT procedures ranged from 23 to 119 months.

Before alloHSCT 2 patients were treated using high dose chemotherapy with autoHSCT. For autoHSCT, stem cells were collected from peripheral blood after IVE chemotherapy (IVE – ifosfamide 3 g/m^2 iv in days 1-3, etoposide 200 mg/m^2 in 1-3 d., epirubicine 50 mg/m^2 iv in 1 d.) and subsequent administration of granulocyte-colony stimulating factor (G-CSF) at a dose of 10 ug/kg/day, starting from +5 day after chemotherapy until the last day of collection. The patients collected the sufficient number of CD34+ cells for AHSCT procedure. Conditioning regimens before autoHSCT consisted of BEAM (carmustine 300 mg/m^2, etoposide 200 mg/m^2, cytosine arabinoside 300 mg/m^2, melphalan 140 mg/m^2). Despite the use of high dose chemotherapy with autologous haematopoietic cells transplantation a sustained remission was not achieved.

Before the start of alloHSCT the disease's phases were as follows: complete remission (CR) in 1 patient, a partial remission (PR) in 4, the active phase of the disease without remission (NR) was also seen in 4 patients.

All patients had a fully compatible family donor for HLA tissue antigens evaluated using low-resolution methods (LR).

The conditioning regimens, which applied used before alloHSCT, were nonmieloablative one; 5 patients received treatment which included: melphalan, fludarabine, alemtuzumab, and the remaining: fludarabine, busulfan (1 patient), carmustine, melphalan, gemcitabine (1 patient), carmustine, meplhalan, etoposide (2 patients).

The median number of transplanted cells was as follows: WBC 4.2 x 10 ^ 8/kg b.w. (0,97-9,56), CD34 + cells 2.36 × 10 ^ 6/b.w. (1,37-6,3), CD3 +cells 30.99 x 10 ^ 7/kg b.w. (5,07-54,54). The detailed data are enclosed in table 2.

Table 1. The type and numer of cycles of chemotherapy before the alloHSC procedures.

Patient*	First line of treatment**	Second line therapy	Third line of treatment
1	ESHAP (6)	BEACOPP (3)	CN3OP (6)
2	ABVD (6)	ESHAP (6)	BEACOPP (2)
3	MVPP (4)	B-DOPA (4)	ABVD (1)
4	ABVD (8)	BEACOPP (3)	ESHAP (2)
5	CMOPP (6)	ABVD (6)	ICE (6)
6	ABVD (3)	ESHAP (6)	BEACOPP (1)
7	MOPP (6)	ABVD (5)	BEACOPP (4)

*ordinal numer of patient
**total numer of cycles

Table 2. Characteristics of patients undergoing the alloHSCT.

Patient/ /alloHSC*	Phase of the disease before alloHSCT	Donor/ /recipient	AutoHSCT before alloHSCT Yes/No	Age of recipient during alloHSCT	Conditio-ning treat-ment before alloHSCT	Numer of CD34+ x 10^6/kg b.w.	Number of CD3+ x 10^7/kg b.w.	Acute GVHD (involved organ)	Chronic GVHD	Survival time after alloHSCT (months)
1/1	NR	m/f	No	32	Camph+ Flud.+ Melph.	2.79	31.8	No	No	5
2/1	CR	m/f	Yes	26	Camph+ Flud.+ Melph	2.36	54.54	No	No	6
3/1	PR	m/m	No	17	Camph+ Flud.+ Melph.	2.21	49.4	No	No	6
3/2	PR	m/m	No	17	Camph+ Flud.+ Melph.	5.45	24.2	No	No	4
4/1	NR	f/m	Yes	27	Flud.+ Busul.	5.02	30.99	Yes (skin)	Yes	12
5/1	NR	m/m	No	32	Camph+ Flud.+ Melph.	2.12	24.4	No	No	13
5/2	NR	m/m	No	33	Gemc.+ BCNU+ Melph.	6.3	27.6	No	No	4
6/1	PR	f/m	No	24	Etop.+ Melph.+ BCNU	1.66	47.38	Yes (skin)	Yes	120
7/1	PR	m/m	No	24	Etop.+ Melph.+ BCNU	1.37	5.07	No	No	Early death during alloHSCT

Abbreviations used in the table: NR – non responder, PR – partial remission, CR – complete remission, f – female, m – male, Camph. – Alemtuzumab, Flud. – Fludarabine, Melph. – Melphalan, Busul. – Busulfan, Gemc. – Gemcitabine, BCNU – carmustine, Etop. – Etoposide
*ordinal numer of patient/numer of performed alloHSCT procedures

RESULTS

During the alloHSCT procedure one patient died in day +9 due to infectious complications before the engraftment (Transplant Related Mortality up to + 100 days amounted to 22%).

The regeneration time after 8 alloHSCT procedures was as follows: granulocytes count > 0.5 G/l was reached after the median of 22 days (range 13-24 days), and platelets > 50 G/l, after the median of 21 days (range 14-25). Symptoms of acute graft versus host disease (aGVHD) in stage I occurred in 2 patients. The symptoms of aGVHD grade II and III did not occur. Symptoms of chronic graft versus host disease (cGVHD) occurred in two patients.

2 patients underwent re-alloHSCT: because of recurrence of lymphoma in the first one, and in the other one due to the graft failure (chimerism at the day +30 after transplantation was 20%).

The median time of survival is 21 months (range 4-120 months) for 7 reported cases. 4 patients died

because of the disease progression despite the alloHSCT.

Two patients of the seven are still alive, which accounts for 28%. These are patients who presented symptoms of the limited chronic graft versus host disease. One patient is still alive for more than 10 years in complete remission without recurrence of lymphoma. In the second patient surviving 21 months after alloHSCT, in the control study, positron emission tomography (FDG PET CT) showed an early recurrence of the disease within the skeletal system. He was treated with local radiotherapy (IF) with a good result. The patient is designated for the procedure of donor lymphocyte infusion (DLI).

DISCUSSION

Algorithm for treatment of Hodgkin's lymphoma patients is based on the degree of risk assessed at diagnosis and the effectiveness assessment of the first line chemotherapy (13-16). In cases of refractory and recurrent disease high dose chemotherapy with autologous hematopoietic cells (autoHSCT) (17-22) is used routinely. In some cases, patients are benefiting from a double (tandem) autoHSCT procedures (23-25). Recently in order to assess the effectiveness of treatment including the autoHSCT new diagnostic imaging methods have been in use. They allow not only for determining the presence of morphological changes, but also to assess the metabolic activity, which is detected in FDG-PET CT methods (26-29).

The report of the European Society of Bone Marrow Transplantation (EBMT) stated that in 2009 the European centres of bone marrow transplantation in 1901 cases of Hodgkin's lymphoma autoHSCT procedures were performed. The report also specified that with this diagnosis there were only 330 allogeneic bone marrow transplantation/hematopoietic cells, including the 92 cases which were performed after autoHSCT (EBMT Activity Survey on Transplant 2009, Basel 11.25.2010). The Department of Hematology and Bone Marrow Transplantation Medical University of Silesia is an accredited centre of the EBMT (Team No. 677) and the European reports also include procedures performed over here.

In our department treatment structure autoHSCT and allogeneic hematopoietic cell transplantations is similar to that published in the EBMT report. Allogeneic hematopoietic cell transplantation in Hodgkin's lymphoma patients is rarely performed in comparison to the number of autoHSCT.

In the reported group of 7 patients, only 2 cases were autoHSCT treated before alloHSCT procedures. In one of them alloHSCT was performed despite the lack of remission at the time of alloHSCT. The patient is still alive for 21 months and a phase of the disease is assessed as the PR. This good result was confirmed by the Italian group which published the observation that in the absence of remission after conducting autoHSCT patients benefit from alloHSCT compared with the use of salvage chemotherapy (30).

The standard conditioning treatment prior to alloHSCT that we used was a non-myeloablative (RIC), considering its lower toxicity for the patient. Such preparation for alloHSCT according to the recent publications (31, 32) is the preferred treatment of choice.

The transplant related mortality during the procedure alloHCT did not differ from the expected and was 1/7.

In one case due to the lack of an engraftment, alloHSCT procedure was performed again with good results.

For the success of alloHSCT good clinical condition of a patient is important as well as a phase of the disease, in which this treatment procedure is performed (33). In the analysed group of the patients only one person was in complete remission and the time from diagnosis to the date of alloHSCT amounted to 119 months. In cases of recurrence after alloHSCT The Report of the Committee on Treatment of Recurrence after Transplantation of Allogeneic Bone Marrow (34) recommends strengthening donor lymphocyte immune activity against lymphoma and the use of donor lymphocyte infusion (DLI). DLI can induce GVHD. In cases of mixed chimerism DLI reduces the risk of the disease recurrence through the induction of antitumor activity (35). Such a procedure is planned to be used in one of our reported patients.

In the reported cases, we observed long-term survival in patients only with the presence of chronic graft versus host disease. It can be assumed that it was due to the immunological effects of transplanted allogeneic cells leading to an active immunological control of the disease in one patient for over 10 years.

CONCLUSIONS

Allogeneic hematopoietic cell transplantation should be considered as a therapeutic option with the potential for long-term survival in patients with refractory Hodgkin's lymphoma who have a fully compatible family donor.

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