TREATMENT WITH AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS – A 10-YEAR SINGLE CENTRE EXPERIENCE

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TERAPIJA BOLESNIKA SA MULTIPLIM MIJELOMOM AUTOLOGOM TRANSPLANTIRACIJOM MATIČNIH ĆELIJA-DESETOGODIŠNJE ISKUSTVO JEDNOG MEDICINSKOG CENTRA

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ABSTRACT:

Background - *Multiple myeloma is a malignant neoplasm of plasma cells. Autologous stem cell transplantation (ASCT) has become the first line of therapy because of the low transplant-related mortality and its ability to prolong event-free survival, which results in improved quality of life. High–dose therapy (HDT) with ASCT should be part of the primary treatment in newly diagnosed patients under the age of 65 with adequate performance status and organ function.*

Aim: *The aim of this study is to present our ten-year experience in treating multiple myeloma patients with ASCT.*

Materials and methods: *Over a 10 -year period, we have performed 35 courses of HDT and consecutive ASCT in 31 patients with multiple myeloma (4 tandem transplantations). In this study, we retrospectively analysed the epidemiological characteristics of this group of patients.*

Results: *There were 14 female and 17 male patients. The median patient age was 52 years (range 43-64). The conditioning regimen used was high-dose Melphalan in doses of 200 mg/m^2, and the dose used in the second (tandem) transplantation was 140 mg/m^2. The median count of infused CD34+ cells was 3.65x10^6/kg. As a source of added stem cells, we used phlebotomy in 3 patients. The median period from diagnosis to transplantations was 10 months. Of 31 patients, 21 (67%) are currently alive and 10 (33%) have died (3 renal failure, 3 multi-organ failure, 2 infections, and 2 fatal cerebral bleeding). The disease-free survival was 24 months.*

Conclusions: *ASCT offers better survival and quality of life compared to patients treated only with standard chemotherapy.*

Keywords: *multiple myeloma, stem cell transplantation*

SAŽETAK

Multipli mijelom je maligna bolest plazma ćelija. Autologna transplantacija matičnih ćelija (ASCT) postala je prva linija terapije, uglavnom zbog niske smrtnosti i produženog preživljavanja , tako da dovodi do poboljšanja kvaliteta života. Terapija visokim dozama citostatika (HDT) sa ASCT treba da budu deo primarnog lečenja kod novootkrivenih pacijenata do 65 godina starosti uz adekvatan opšti klinički status.

Cilj: *Cilj ovog rada je da predstavi deset godina našeg iskustva u lečenju obolelih od multiplog mijeloma putem ASCT.*

Materijal i metode: *Tokom desetogodišnjeg perioda, obavili smo 35 tretmana HDT i konsekutivnog ASCT kod 31 bolesnika sa multiplim mijelomom (4 Tandem transplantacije). U ovoj studiji smo analizirali retrospektivno epidemiološke karakteristike ove grupe pacijenata.*

Rezultati: *Odnos ženske i muške populacije iznosi 14:17, prosečne starosti: 52 godine (od 43-64). Visoke doze Melphalana u dozama 200mg/m2 korišćene su kao kondicioni režim, u drugoj (tandem) transplantaciji 140mg/m2. Srednji broj unetih CD34 + ćelija bio je 3,65 k106/kg. Kao izvor dodatih matičnih ćelija, koristili smo flebotomiju kod 3 bolesnika. Srednji period od dijagnoze do transplantacija bio je 10 meseci. Od 31 bolesnika, 21 (67%) su živi, 10 (33%) je umrlo (3 od bubrežne insuficijencije, 3 od multiorganske disfunkcije, 2 od infekcije, 2 od fatalnog cerebralnog krvavljenja. Preživljavanje bez ponovnih simptoa bolesti je 24 meseca.*

Zaključci: *ASCT obezbeđuje bolje rezultate za opstanak i kvalitet života u poređenju sa pacijentima lečenim standardnom hemoterapijom.*

Ključne reči: *multipli mijelom, transplantacija matičnih ćelija*

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INTRODUCTION

Multiple myeloma is a malignant haematological neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure (1). The disease develops in 1–4 per 100,000 people per year. The disease is more common in men and is twice as common in blacks as it is in whites (2). With conventional treatment (MP regimen), the prognosis is 3–4 years, and it may be extended to 5–7 years or longer with advanced treatments. Multiple myeloma is the second most common haematological malignancy (13%) and constitutes 1% of all cancers. It was estimated that multiple myeloma would account for 19,920 new cancer cases in the United States in 2008. This figure includes 11,190 cases in men, 8,730 cases in women, and 10,690 deaths. The median age of myeloma patients at diagnosis is 69 years for men and 72 years for women (3). High-dose chemotherapy with autologous stem cells transplantation should be part of the primary treatment in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (Grade A; level Ib) according to the British Council of Haematology and UK Myeloma. The diagnostic criteria according to Durie and Salmon are used to confirm diagnosis (4). A bad prognosis is associated with partial or complete deletion of chromosome 13. Melphalan and prednisone (MP) have remained the standard therapy for decades, and the median survival with this therapy was approximately 3 years. High-dose therapy (HDT) and Autologous Stem Cell Transplantation (ASCT) havse been used in the management of myeloma since the efficacy of high dose melphalan in the treatment of high-risk myeloma and plasma cell leukaemia was first reported more than 20 years ago (5). ASCT has become the first line standard of care in patients deemed suitable for transplant. ASCT is the standard of care because of the low transplant-related mortality and the prolonged event-free survival (EFS), which results in improved quality of life (6). Treatment with high-dose therapy and single autologous stem cell transplantation is a category I recommendation of the National Comprehensive Cancer Network. In young patients, the impact of dose intensity has been demonstrated, and single HDT supported with ASCT using a conditioning regimen with Melphalan alone should be considered as a standard of care (7). Double transplantation can be proposed to patients failing to achieve a very good partial response after the first stem cell transplantation (BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma Sept 2010). Stem cells are now almost exclusively derived from peripheral blood following stimulation with growth factors with or without chemotherapy. The optimal regimen for mobilising peripheral blood stem cells (PBSC) is unclear, but cyclophosphamide (1.5 to 4 g/m^2) with G-CSF is widely used. Purging harvested stem cells with monoclonal antibodies and/or CD34+ stem cell selection does reduce contamination with tumour cells but does not influence the relapse risk (8). High-dose melphalan (200 mg/m^2) remains the standard conditioning prior to ASCT in first transplants, while a reduced dose of 140 mg/m^2 is used in second transplantation. Recent studies have shown that the dose of melphalan can be increased to 220 mg/m^2 (9), with improved PFS compared with historical controls, or to 240–300 mg/m^2 in combination with amifostine. However, this approach is associated with increased toxicity (10). The addition of total body irradiation (TBI) results in increased toxicity with no improvement in response rate or PFS, whereas combination chemotherapy increases the toxicity (11,12,13). Bortezomib has shown synergistic effects with melphalan without prolonged hematologic toxicity. The recently reported IFM phase 2 study enrolled 54 untreated patients to receive bortezomib (1 mg/m2x 4) and melphalan (200 mg/m^2) as a conditioning regimen. They reported a response ≥VGPR in 70% of patients and a 32% CR. There were no toxic deaths observed, and there was minimal peripheral neuropathy. Different studies have reported that the combination of chemotherapy plus new drugs can induce 70-90% partial response and 30-40% complete response (14,15,16). The introduction of lenalidomide (analogue of thalidomide), bortezomib, and other novel agents have been extensively investigated to improve the duration of response (17,18,19). According to guidelines from the British Haematology Council and International Myeloma Forum published in September 2010, the following recommendations are supported: HDT with ASCT should be part of the primary treatment in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (Grade A; level Ib); HDT with ASCT should be considered in patients aged >65 years with good performance status (Grade B; level IIa); and conditioning with melphalan alone, without TBI, is recommended (Grade B; level IIa). The usual dose is 200 mg/m^2, but the dose should be reduced in older patients (over 65-70 years) and those with renal failure.

MATERIALS AND METHODS

Over the 10-year period from September 2000 to September 2010haematology, 195 stem cell transplantations were performed at our institution (University Clinic of Haematology, Medical Faculty, Skopje) on various haematological malignant and non-malignant diseases (AML: 109, ALL: 7, CML: 9, CLL: 1, NHL: 15, HD: 15, Myelofibrosis: 1, Ewing sarcoma: 1, Aplastic anaemia: 2, Multiple myeloma: 35). Allogeneic transplantation from HLA identical siblings were used to treat 56 patients, and autologous transplantation was used to treat 139 patients. Peripheral blood stem cells were used in 165 transplantations, and bone marrow was used in 30 transplantations. In 31 patients with multiple myeloma, we performed 35 high-dose chemotherapy and autologous stem cells transplantations (4 tandem transplantations) from peripheral blood stem cells. The high-dose conditioning regimen consisted of 200 mg/m^2 Melphalan in first transplantation, while the second (tandem) transplantation used a dose

Patient	Age	Gender	Ig	Bence-Jones	Renal failure	Fracture	Ro.Th	Months Dg./Tx	Months A/D
V.A	64	M	IgG	Negative	No	Th12/L1	Yes	6	A=92
T.S.	45	F	IgG	Negative	No	No	No	4	A=96
N.V.1	43	M	IgG	Negative	No	Th12/L1	Yes	5	A=61
V.Z.1	53	F	IgG	Negative	No	Hip	Yes	11	A=58
V.Z.2	53	F	IgG	Negative	No	No	Yes	17	A=64
G.Z.1	51	F	IgG	Negative	No	No	No	7	A=63
G.Z.2	51	F	IgG	Negative	No	No	No	10	A=66
S.J.	46	F	IgG	Negative	No	No	No	5	A=102
A.Dz.	50	M	IgG	Negative	No	L2	No	22	A=75
N.V.2	43	M	IgG	Negative	No	Th12/L1	Yes	8	A=69
S.S.	43	F	IgA	Positive	Yes	Negative	No	12	A=6
Z.G.	50	M	IgA	Positive	Yes	L2L3	Yes	5	A=6
A.L.	43	M	IgG	Positive	Yes	No	No	10	A=8
M.T.	50	M	IgG	Negative	No	Yes	Yes	6	A=16
M.Sh.	52	M	IgG	Negative	No	Yes	Yes	8	A=12
G.D.	48	F	IgG	Negative	No	No	No	5	A=15
Kr.Kos.	57	M	IgG	Positive	No	No	No	9	A=25
Lj.M.	56	M	IgG	Positive	Yes	No	No	6	A=24
M.D.	48	M	IgG	Negative	No	No	No	12	A=24
Ka.K.	52	F	IgG	Positive	Yes	No	No	6	A=27
S.B.	48	F	IgG	Positive	Yes	Th9	Yes	20	A=32
E.L.	60	M	IgG	Negative	No	No	Yes	11	A=34
A.T.	60	F	IgG	Negative	No	No	No	6	A=6
N.O.1	50	M	IgG	Negative	No	No	No	4	A=36
N.O.2	50	M	IgG	Negative	No	No	No	4	A=40
M.M.	47	M	Kappa	Positive	Yes	No	No	4	D=50
P.N.	60	F	IgA	Negative	No	No	No	12	D=62
A.C.	57	F	IgG	Negative	No	No	No	44	D=127
B.J.	60	M	IgA	Negative	No	L1	Yes	6	D=66
Z.S.	59	M	IgG	Negative	No	No	No	12	D=42
Da.K	63	M	IgG	Negative	No	No	No	20	D=45
Di.Ko	46	M	IgG	Negative	No	No	No	8	D=36
T.K.	42	F	IgG	Negative	No	Th12	Yes	15	D=44
D.L.	52	F	IgG	Positive	Yes	L2	Yes	22	D=36
A.L.	56	F	IgG	Positive	Yes	Yes	No	8	D=54

Table 1. Patient epidemiological and clinical data

of 140 mg/m^2 Melphalan. All patients were treated in a sterile room conditioned with HEPA filtration. In our study, we analysed 31 patients with multiple myeloma diagnosed according to Salmon and Durie diagnostic criteria. All patients were diagnosed and treated with induction therapy to reach remission at our hospital using various chemotherapeutic regimens. The standard chemotherapy regimen in our hospital is the VAD protocol in patients eligible for autologous transplantation. VAD (Vincristine, Adriamycin, Dexamethasone) is administered in 4 cycles every 28 days. Patients who achieved complete remission received priming therapy with Endoxan 2.0-4.0 g/m^2 plus G-CSF for peripheral stem cell mobilisation and harvesting. Non-responders received Thalidomide+Dexamethasone as a second line therapy for a 5-month period. As a third-line therapy, we used Bortezomib (Velcade). The median period from diagnosis to transplan-

tation in our group of patients was 10 months (from 4-44 months). Usually, we performed 2 apheresis procedures (1-3) to harvest adequate numbers of CD 34+ cells. A Baxter CS 3000 cell separator was used in 40 procedures, and a Cobe Spectra was used in 35 procedures. DMSO, Earhle's medium, and autologous plasma were used as a cryoprotectant. The cryopreservation was performed using a controlled Air Space Freezing system. The cryopreserved stem cells were stored at -172°C. The high-dose Melphalan was administered on day -2 and day -1 in 30-minute infusions through the central venous line. Approximately 24 hours after chemotherapy was completed, the autologous stem cells were thawed in a sterile bath and re-infused into the patient. As an anti-infective prophylaxis, every patient received Ciprofloxacin 1,0 gr/day, Difluconazol, or Itraconazole 200 mg/day, i.v. Acyclovir 1500 mg/day., and i.v. immunoglobulins 0,1/kg once a week. G-CSF was introduced from day +1 until neutrophil recovery. This research study was performed in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee. All patients signed a consent form.

RESULTS

Over a 10-year period at our hospital, we treated 31 patients with multiple myeloma. In 4 patients, we performed tandem transplantation (at a period from 4-6 months after the first transplantation). The dose of Melphalan was 200 mg/m^2 in the first and 140 mg/m^2 in the second transplantation. The median count of re-infused CD34+ cells was 3,65 x 10^6/kg b.w. (from 2,0 – 12,5). Engraftment was established on day +11 (from day +7 to day +16). The median number of days for G-CSF use was 10 days (from 7-14 days). During the first 30 days after transplantation, which is the period of aplasia, there were only a few infective complications in our group of patients. The early transplant related mortality (until day +100) was 0. The most common complication after transplantation was mucositis. There was Grade IV mucositis present in 8 patients. There were central venous catheter infections with coagulase negative staphylococcus in 5 patients. The fatal outcomes were due to renal failure in 3 patients (50, 62, and 127 months after transplantation), multi-organ failure in 3 patients (66, 42, and 45 months after transplantation), infections in 2 patients (one with aggressive hepatitis B virus infection 36 months after transplantation, and one with pneumonia 44 months after transplantation), and 2 fatal cerebral bleeding (36, 54 months after transplantation). All of the patients died with active relapse of myeloma disease.

DISCUSSION

Multiple myeloma was the most frequent indication for which autologous stem cell transplantation is performed (20). However, autologous stem cell transplantation is not curative, and most patients relapse within a median of 3 years. The median survival after transplantation in our

Number of patients	31
Number of transplantations	35 (4 tandem transplantations)
Age	52 years (43-64)
Gender	Male: 17 (55%) Female: 14 (45%)
Myeloma types	IgG =30(85%); IgA=4(11%) Light chain=1(4%)
Bence-Jones proteinuria	10 (28%)
Lytic bone lesion with fracture	13 (37%)
Previous radiotherapy	13 (37%)
Period from Diagnosis to transplantation	10 (4-44 months)
Living 21 patients (67%)	6-102 months after transplantation
Deceased 10 patients (33%)	36-127 months after transplantation

Table 2. Summary of patient characteristics treated with autologous transplantation

	Median	Range
number of apheresis	2	1 - 3
counts of infused CD34+ cells	3,65	2,0 – 12,5
days of G-CSF	10	7 – 14
day of engraftment	+11	+7 - +16
blood transfusions	2	0 – 6
platelet transfusions	6	0 – 18

Table 3. Graft characteristics

Febrile episodes	10
Central venous catheter infections	5
Mucositis	8
Pneumonia	2
Neutropenic enterocolitis	2

Table 4. Early post-transplant complications

group was 38 months (from 36 months to 127 months after transplantation). The superiority of autologous stem cell transplantation over conventional chemotherapy was first demonstrated by The Intergroupe Francophone du Myelome (IFM) (21). In multiple myeloma, the standard high-dose therapy is single agent Melphalan at a dosage of 200 mg/m^2. Attempts to improve this regimen with conventional drugs or total body irradiation have failed to improve the response rate but have increased both haematologic and non-haematologic toxicities. A synergistic effect between bortezomib and melphalan has been demonstrated. Allogeneic stem cell transplantation was introduced in the treatment of multiple myeloma 25 years ago, but the toxicity was very high, with a transplant related mortality in excess of 50% in studies including heavily pre-treated patients (22,23,24,25). Allogeneic SCT using conventional conditioning and HLA-matched sibling donors can result in long-term survival and may have a role in younger patients, but it is an option for only a very few selected patients. One of the main problems with allografting using conventional conditioning was the high transplant-related mortality (TRM). However, there is now evidence from both the EBMT and individual centre studies that this has improved in the last 10 years. The 2-year TRM has fallen from 46% before 1994 to 30% since 2000 (Russell et al, 2000; Gahrton et al, 2001). This may reflect transplantation earlier in the course of the disease, improved supportive care and/or careful patient selection. Several well-designed, non-randomised studies show little benefit from allografts in the progressive disease/relapse situation (Einsele et al, 2003; Kröger et al, 2004). Patients transplanted in first remission have a 60% chance of entering CR, and one-third of these patients are in a persistent molecular remission with a very low risk of relapse (Corradini et al, 2003). Therefore, allografts should be performed in first chemo-sensitive phase. The potential benefit of this outcome may justify the risks of allogeneic SCT in patients up to 50 years of age, particularly for patients early in their disease. Therefore, allogeneic stem cell transplantation should not be proposed to patients older than 50 years of age. The combination of high-dose chemotherapy and autologous stem cell transplantation is an effective strategy to treat multiple myeloma patients and appears superior to standard chemotherapy. Novel agents, such as lenalidomide, bortezomib, and other treatments, have improved the survival of these patients. Introducing these agents earlier in the course of the disease together with autologous stem cell transplantation will improve the duration of remission.

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