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CLINICAL STUDY

Impact of autologous stem cell transplantation (ASCT) on progression free survival (PFS) in newly diagnosed multiple myeloma patients (NDMM) with high risk cytogenetic abnormalities

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ABSTRACT

OBJECTIVES: ASCT has been considered the standard of care for younger patients with NDMM, however, not all the studies published so far have uniformly demonstrated the complete superiority of ASCT over chemotherapy at standard doses. A systematic review and meta-analysis of randomized studies has shown a significant benefit with single ASCT in terms of prolonged progression-free survival (PFS), but not of overall survival (OS). In our retrospective analysis we investigated the impact of high dose (HD) chemotherapy followed by ASCT in special population of patients with high risk cytogenetic profile on the PFS and treatment outcome.

METHODS: Retrospective analysis of NDMM patients eligible for HD chemotherapy followed by upfront ASCT in the era of novel agents, who underwent the ASCT in the Department of hematology and oncohematology LF UPJŠ and UNLP Košice in the timeframe of 54 months (from 01/JAN/2019 to 30/JUN/2023). Patients were stratified according to their cytogenetic profile. PFS was defined by the time from ASCT to the disease progression. The OS was defined as the time from the the start of treatment to the death from disease progression. The high risk cytogenetic abnormalities (HRCA) were defined as t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperploidy, gain (1q).

RESULTS: Inclusion criteria were met by 65 patients with NDMM who received HD chemotherpy followed by ASCT. We identified 22 (33.8 %) patients with HRCA and 43 (66.2 %) patients with standard cytogenetic risk. During the monitored period we recorded 4 deaths due to disease progression, all of them in the HCRA subgroup. The response was enhanced by the ASCT in both subgroups. The very good partial response (VGPR) increased from 42 % to 46 % and complete remission (CR) increased from 23 % to 45 % after the ASCT. The number of patients achieving only partial response (PR) decreased from 35 % to 9 % after ASCT. In the subgroup of patients with HRCA the median PFS after ASCT was lower compared to the patients with standard cytogenetic risk (17 vs 38 months). The average PFS in both subgroups was 22.9 months. The median OS in both subgroups was not reached, however the only deaths due to disease progression were recorded in the HRCA subgroup. At the time of analysis, 100 % (43) of patients are alive in the standard cytogenetic subgroup versus 72 % (18) of patients in HRCA subgroup.

CONCLUSION: HD chemotherapy followed by ASCT remains the standard of care for NDMM eligible for high dose chemotherapy. Our results confirm the benefit of ASCT even in the presence of HRCA. Lower PFS in the HRCA subgroup might indicate the need for more intensive treatment, which may be achieved by tandem ASCT defined as two ASCT performed within a period of no more than six months. Additionally, as three- and four-drug induction therapies are becoming increasingly available and effective, resulting in high minimal residual disease (MRD) negative rates, it is important to continue discussing and further personalizing upfront ASCT to avoid overtreatment and possible toxicities especially in the non-high-risk patient population *(Tab. 5, Fig. 2, Ref. 9)*. Text in PDF *www.elis.sk*

KEY WORDS: multiple myeloma, autologous stem cell transplantation, progression free survival, overall survival, high-risk cytogenetics

Introduction

Multiple myeloma (MM) is a disease of the elderly. Overall, only 35 % of the patients are younger than 65 years at the time of diagnosis, whereas the remaining two-thirds are older. Age is an independent prognostic factor in MM and, importantly, provides a major criterion by which patients can be considered eligible to tolerate high-dose therapy (HDT) with autologous hematopoietic

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Tab. 1. Patient clinical characteristics.

Clinical characteristic (n=65)	Median	Range	% (n)
Male			80 (52)
Female			20 (13)
Age	59	42–67	
Age (male)	63.1	42–67	
Age (female)	55.6	43–66	
Age (male) ≤ 65 yo	60	42–65	
Age (male) ≥ 65 yo	66.4	66–67	
Age (female) ≤ 65 yo	53.7	44–63	
Age (female) ≥ 65 yo	66	66	
MM subtype			
IgG kappa			35.4 (23)
IgG lambda			20 (13)
IgA kappa			10.8 (7)
IgA lambda			7.7 (5)
IgM kappa			1.54 (1)
Light chain kappa MM			7.7 (5)
Light chain labda MM			15.4 (10)
Biclonal MM			1.54 (1)
Non-secretory MM			6.21 (4)
Induction regimen			
CAD			6.21 (4)
BDD			9.21 (6)
BCD			63.1 (41)
LCD			3.11 (2)
VTD			1.54 (1)
BD			7.7 (5)
VRD-PACE			3.1 (2)
RD			4.6 (3)
DCEP			1.54 (1)
Cytogenetic risk			
High risk			33.8 (22)
Standard risk			66.2 (43)
DS staging			
I			3.11 (2)
II			4.61 (3)
IIIA			83.11 (54)
IIIB			9.2 (6)
R-ISS staging			
I			9.2 (6)
II			41.5 (27)
III			49.2 (32)

CAD – cyclophosphamide, doxorubicin, dexamethasone, BDD – bortezomib, doxorubicin, dexamethazone, BCD – bortezomid, cyclophosphamide, dexamethasone LCD – lenalidomide, cyclophosphamide, dexamethasone, VTD – bortezomib, thalidomide, dexamethasone, BD – bortezomib, dexamethasone, VRD-PACE – bortezomib, lenalidomide, dexamethasone, cisplatin, cyclophosphamide, etoposide, doxorubicin, RD – lenalidomide, dexamethasone, DCEP – cisplatin, etoposide, cyclophosphamide, dexamethasone, High risk cytogenetics definition as per IMWG 2016: t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperploidy, gain(1q), DS – Durie Salmon staging system, R-ISS – revised international staging system

Tab. 2. Treatment characteristics.

Treatment characteristics	% (n)
Mobilization regimen	
Cyclophosphamide 4.5g/m^2	95.41 (62)
Cyclophosphamide 3g/m^2	4.6 (3)
ID-Ara C	1.54 (1)
Conditioning regimen	
Melphalan 200 mg/m^2	97 (63)
Melphalan 140 mg/m^2	3 (2)

Tab. 3. Complications > 2 Grade.

Toxicity, Grade > 2 (n= 34)	% (n)
Mucositis	12.3 (8)
Enterocolitis	23.1 (15)
Febrile neutropenia	12.3 (8)
Sepsis	3.1 (2)
Invasive aspergilosis	1.54 (1)

Tab. 4. Blood count recovery after ASCT.

Blood count recovery after ASCT	Median (days)	Range (days)
Neutrophils >1 x 10^9/l	12.6	8–14
Trombocytes > 20 x 10^9/l	12.8	8–15

Tab. 5. Treatment results.

Treatment results	Median (months)	Range (months)	% (n)
PFS	22.9	2–55	
PFS high cytogenetic group	17	2–35	
PFS standard cytogenetic group	38	12–55	
OS high risk cytogenetic	Not reached		
OS standard cytogenetic group	Not reached		
OS after 4 years high risk cytogenetic			72 (18)
OS after 4 years standard risk cytogenetic			100 (43)

stem cell transplantation (ASCT). Over the last decade, the survival of patients with newly diagnosed MM, particularly those younger than 60 years, has significantly improved. The widespread use of ASCT and the introduction into clinical practice of the novel agents have significantly contributed to major advances in MM therapy and prognosis. ASCT has been considered the standard of care for younger patients with NDMM, however, not all the studies published so far have uniformly demonstrated the complete superiority of ASCT over chemotherapy at standard doses. A systematic review and meta-analysis of randomized studies has shown a significant benefit with single ASCT in terms of prolonged progression-free survival (PFS) (1, 2), but not of overall survival (OS) (3). In our retrospective analysis we investigated the impact of high dose (HD) chemotherapy followed by ASCT in special population of patients with high risk cytogenetic profile on the PFS and treatment outcome (4, 5).

Material and methods

We conducted the retrospective analysis of NDMM patients eligible for HD chemotherapy followed by upfront ASCT in the era of novel agents, who underwent the ASCT on the Department of hematology and oncohematology LF UPJŠ and UNLP Košice in the timeframe of 54 months (from 01/JAN/2019 to 30/JUN/2023). The demographic and clinical characteristics of the patients are defined in the Table 1.

Patients were stratified according to their cytogenetic profile and after achieving at least PR following the induction regimen, their eligibility for the HD chemotherapy and ASCT was assessed. The PFS was defined by the time from ASCT to the disease progression. The OS was defined as the time from the the start of treatment to the death from disease progression. The high risk cytoge-

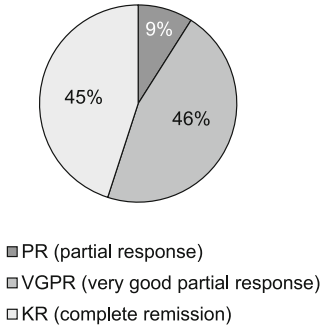

Fig. 1. Response achieved after ASCT.

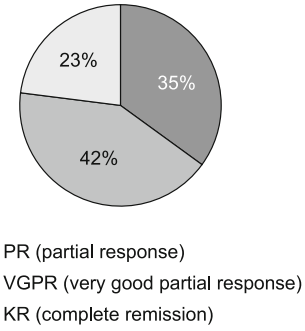

Fig. 2. Response achieved before ASCT.

netic abnormalities (HRCA) were defined as t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperploidy, gain (1q).

Results

In the analysed period we identified 65 patients eligible for the ASCT. After the succesful mobilization of sufficient number of peripheral blood cells using the mobilization regiments shown in Table 2, the patients were admitted to the intensive care unit for the administration of the conditioning regimen and stem cells. Melphalan in the dose of 200 mg/m^2 was used in 97 % (63) of patients, 3 % of patients needed the reduction of melphalan dose due to the mild renal function impairment.

Toxicity grade of > 2 was reported in the 54 % (34) of patients, most common was postcytostatic enterocolitis and mucositis, as shown in Table 3. In the analyzed period we recorded 0 treatment related deaths.

Median time to neutrophils recovery (>1 x 10^9/l) was 12.6 days and the time to trombocytes recovery (Trombocytes > 20 x 10^9/l) was 12.8 days as demonstrated in Table 4. We identified 22 (33.8 %) patients with HRCA and 43 (66.2 %) patients with standard cytogenetic risk. During the monitored period we recorded 4 deaths due to disease progression, all of them in the HCRA subgroup. The response was enhanced by the ASCT in both subgroups as presented in Figure 1 and Figure 2. The very good partial response (VGPR) increased from 4 2% to 46 % and complete remission (CR) increased from 23 % to 45 % after the ASCT. The number of patients achieving only partial response (PR) decreased from 35 % to 9 % after ASCT. In the subgroup of patients with HRCA the median PFS after ASCT was lower compared to the patients with standard cytogenetic risk (17 vs 38 months). The average PFS in both subgroups was 22.9 months. The median OS in both subgroups was not reached, however the only deaths due to disease progression were recorded in the HRCA subgroup. At the time of analysis, 100 % (43) of patients are alive in the standard cytogenetic subgroup versus 72 % (18) of patients in HRCA subgroup as shown in Table 5.

Discussion

HD chemotherapy followed by ASCT remains the standard of care for NDMM eligible for high dose chemotherapy (6, 7). Our results confirm the benefit of ASCT even in the presence of HRCA. Lower PFS in the HRCA subgroup which might indicate the need for more intensive treatment, which may be achieved by tandem ASCT defined as two ASCT performed within a period of no more than six months (8). Additionally, as three and four-drug induction therapies are becoming increasingly available and effective, resulting in high minimal residual disease (MRD) negative rates, it is important to continue discussing and further personalizing upfront ASCT to avoid overtreatment and possible toxicities especially in the non-high-risk patient population (9).

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