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ORIGINAL ARTICLE

Multiple Myeloma of the Young – a Single Center Experience Highlights Future Directions

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Abstract

Multiple myeloma is quite uncommon in the young population. We performed a retrospective review in our database from 2006 to 2015 to examine the clinical features, outcomes and survival of multiple myeloma patients ≤40 years old. Among 312 newly diagnosed patients we found sixteen (5.1%) who were 40 years old or younger. Their characteristics including M-protein type, genetical alterations, clinical symptoms and disease stage were as various as those in the older population. All but two young patients underwent autologous stem cell transplantation after the induction treatment. Their response to treatment did not differ markedly from the older patients. We also compared the survival data of patiens ≤40 years and > 40 years old. The 5-year progression-free survival were 48% and 35%, the 5-year overall survival were 83% and 53% respectively, the latter showing a significant advantage for the younger population. 70% of the young patients received maintenance or consolidation therapy after the initial treatment. Although several effective new therapies have been introduced recently, there is still an unmet need for curative treatment options for young and fit multiple myeloma patients.

Keywords Multiple myeloma · Young · 40 years · Progression-free survival · Overall survival

Introduction

Multiple myeloma (MM) is characterized by abnormal proliferation of plasma cells that infiltrate the bone marrow or form solitary tumor (plasmacytoma). It accounts for 10% of all hematological malignancies and represents 1% of all cancers. It mainly affects the elderly population, the mean age at diagnosis is 65 years. The incidence varies from 2 to 15 / 100.000, however, the disease is more common in people of African origin [1]. The main symptoms and complications can be summarized by the acronym „CRAB": C as hypercalcaemia, R as renal failure, A as anaemia, B as bone lesion [2]. Multiple myeloma is still considered as an incurable disease, its clinical course is characterized by remissions and relapses. However, thanks to the novel therapeutic approaches that incorporate the administration of proteasome inhibitors, immunomodulatory agents, monoclonal antibodies and stem cell transplantation, the survival results of MM patients have significantly improved recently [3]. Nowadays the 5-year overall survival (OS) rates can vary from 40 to 82%, while the progression-free survival rates vary from 24 to 55%, respectively [1]. The patients' prognosis is influenced by several risk factors which include both host- and tumor-dependent factors. The most important host-derived factor is age. Elderly patients are often frail and have significant comorbidities which may result in treatment-related toxicities and dose delays. On the other hand, younger patients are expected to tolerate any therapies better, although „real young" people represent only a very small proportion of all MM cases [4].

The objective of this study was to describe presenting features and outcomes of multiple myeloma patients ≤40 years and to compare their survival data to the older MM population.

Methods

Patients

Patients who were 40 years or less and diagnosed with multiple myeloma at our institute between 01 January 2006 and 31 December 2015 were included in this study. The diagnosis of

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multiple myeloma was established according to the relevant International Myeloma Working Group (IMWG) criteria. Those patients who had monoclonal gammopathy, smoldering myeloma or solitary plasmacytoma were excluded from the trial. Genetical alterations were examined with the fluorescence in situ hybridization (FISH) method. The treatment they received was administered according to the current recommendations of the national myeloma working group. Response to treatment and progression were assessed using the IMWG criteria.

Statistical Analysis

Examining the survival rates, overall survival (OS) was determined by consideration of death events due to any reasons, while progression-free survival (PFS) was determined by consideration of relapses or disease progression that indicated further treatment. Descriptive statistical analysis was used to charactarize the patient populations. Normality of the parameters were examined applying the Wilk-Saphiro test. Comparing two groups, F probe and t test were administered by normal distribution of the parameters, otherwise the non-parametrical Mann-Whitney test was applied. Differences were significant if probability level was less than 5% ($p < 0.05$). Survival rates were calculated using the Kaplan-Meier's method, while the survival data were compared using the log-rank test.

Results

Among 312 multiple myeloma patients there were sixteen (5,1%), ten males and six females who were 40 years old or younger at the time of diagnosis. Eight patients had IgG, three patients has IgA-type disease, three had light-chain myeloma and two of the had non-secretory disease. FISH test was performed in eleven patients, hyperdiploidity was detected in six, t(4;14) in three and del(17p) in two cases, respectively. The most common 'CRAB' symptom was bone disease (fourteen cases), followed by hypercalcaemia (three cases), anaemia (two cases) and kidney failure (two cases). Five patients had two or more CRAB symptoms. The distribution of the ISS disease stages was the following: seven patients had stage 1, five patients had stage 2 and four patients had stage 3 disease at the time of diagnosis. Regarding the induction treatment, twelve patients received bortezomib-containing regimens including VTD (bortezomib, thalidomide, dexamethasone), PAD (bortezomib, doxorubicine, dexamethasone), CyBorDex (cyclophosphamide, bortezomib, dexamethasone) or VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatina, doxorubicine, etoposid, cyclophosphamide), two patients recieved thalidomide-dexamethasone and two patients recieved VAD (vincristine, doxorubicine, dexamethasone) protocol. Two patients died because of progressive disease during the period of induction treatment, one of them had primary plasma cell leukaemia. Fourteen patients underwent autologous peripheral stem cell transplantation (APSCT), the conditioning regimen was high-dose melphalan (200 mg/m^2) in all cases. Ten patients were administerred consolidation or maintenance therapy after the APSCT, that included either bortezomib-based combinations or monotherapies (thalidomide or interferon) (Table 1).

Altogether 294 patients underwent APSCT in our institute within the 10 years' period, 132 of them (45%) were diagnosed and treated in other hospitals beforehand. We compared our young patients' treatment results to those patients' data who received APSCT but were older than 40 years at the time of diagnosis. The results are shown in Table 2. There were no significant differences found between treatment results, however, young patients were more likely to receive maintenance or consolidation therapies.

We also compared the survival data of patiens ≤40 years and > 40 years old. The 5-year overall survival were 83% and 53%, the 5-year progression-free survival were 48% and 35%, respectively. The Kaplan-Maier survival curves are shown on Figs. 1 and 2.

Discussion

Multiple myeloma is a disease of the elderly population with a peak incidence in the seventh decade of age. Patients younger than 40 years old are estimated to represent only 2% of all patients [5]. Cheema et al. reported thirty-eight cases (5.8%) who were ≤ 40 years of age at the time of diagnosis among 646 multiple myeloma patients who underwent autologous stem cell transplantation at the Mayo Clinic [6]. We found sixteen young patients in the whole population diagnosed with multiple myeloma at our institute within a 10 years' period and this ratio (5.1%) is higher than in other centers. Young MM patients used to be thought to have more indolent courses of the disease presenting with multiple solitary or extramedullary plasmacytomas, more osteolytic lesions, but fewer infiltrating plasma cells within the bone marrow [7, 8]. However, Blade et al. reported a cohort of 72 patients younger than 40 years old who had the very same clinical features as the older population [9]. Jurczyszyn et al. published a multi-institutional case-control study in which they compared the characteritics and outcomes of MM patients aged 21–40 versus 41–60 years. In their large cohort, they could analyze the data of 173 young patients and found a higher incidence of lytic bone lesions among them than in the older group [10]. The same working group found 52

Table 1 Clinical characteristics of young multiple myeloma patients

Patient	Sex	Age at diagnosis	Time of diagnosis	M-protein	FISH	ISS	CRAB	Induction therapy	APSCT
1	female	40	Jan 2006	kappa light chain	not done	1	bone	VAD	yes
2	male	40	Mar 2006	IgG kappa	not done	2	bone	VAD	yes
3	female	34	Mar 2008	IgG kappa	not done	1	bone	Thal/dex	no
4	female	39	Mar 2009	IgA lambda	not done	1	bone	PAD	yes
5	male	31	Sept 2009	IgG lambda	not done	2	bone	Thal/Dex	yes
6	female	37	Mar 2010	IgA lambda	hyperdiploid	2	bone anaemia	VTD	yes
7	female	40	Jul 2012	IgA kappa	del17p	2	bone	VTD	yes
8	male	38	Jul 2013	lambda light chain	hyperdiploid	3	kidney	VTD	yes
9	male	38	Aug 2013	kappa light chain	hyperdiploid	3	bone, kidney hypercalcaemia	VTD	yes
10	male	40	Dec 2013	IgG kappa	del17p	1	bone	VTD	yes
11	male	34	Dec 2014	IgG lambda	t(4;14)	2	bone	VTD	yes
12	male	40	Feb 2015	IgG lambda	t(4;14)	3	bone hypercalcaemia	VTD	yes
13	female	37	Aug 2015	non secretory	hyperdiploid	1	bone	VTD	yes
14	male	39	Nov 2015	non secretory	hyperdiploid	1	bone	VTD	yes
15	male	40	Dec 2015	IgG kappa	t(4;14)	3	kidney plasma cell leukaemia	VTD-PACE	no
16	male	40	Dec 2015	IgG kappa	hyperdiploid	1	bone anaemia hypercalcaemia	VTD	yes

Patient	Response to 1st line th.	PFS after APSCT (months)	Consolidation therapy	Maintenance therapy	Number of relapses	Further treatment	OS (months)	Alive
1	VGPR	57	no	thalidomide	3	Vel/Dex carfilzomib lenalidomide	143	yes
2	VGPR	23	no	thalidomide	2	Vel/Dex carfilzomib	135	no
3	progression death	0	NA	NA	0	NA	17	no
4	PR	24	Vel/Dex	no	2	Vel/Dex lenalidomide	105	yes
5	CR	72	VTD	interferon	0	no	99	yes
6	PR	8	no	bortezomib	1	carfilzomib lenalidomide	46	no
7	VGPR	27	VTD	thalidomide	0	no	65	yes
8	progression death	0	NA	NA	0	NA	6	no
9	VGPR	32	Vel/Dex	no	0	no	52	yes
10	VGPR	17	Vel/Dex	no	2	carfilzomib lenalidomid daratumumab	48	yes
11	VGPR	24	no	thalidomide	0	no	36	yes
12	VGPR	16	no	interferon	0	no	34	yes
13	CR	13	no	no	0	no	28	yes

Table 1 (continued)

Patient	Response to 1st line th.	PFS after APSCT (months)	Consolidation therapy	Maintenance therapy	Number of relapses	Further treatment	OS (months)	Alive
14	VGPR	13	no	no	0	no	25	yes
15	progression death	0	NA	NA	0	NA	1	no
16	PR	4	no	no	1	lenalidomide	12	yes

Abbreviations: VAD: vincristine, doxorubicine, dexamethasone; Thal / Dex: thalidomide, dexamethasone; VTD: bortezomib, thalidomide, dexamethasone; VTD-PACE: bortezomib, thalidomide, dexamethasone, cisplatina, doxorubicine, cyclophosphamide, etoposide; VGPR: very good partial remission, PR: partial remission, CR: complete remission

patients who were ≤ 30 years of age, 22% of them presenting with light chain-only disease [11]. In the Mayo Clinic cohort, higher rates of plasma cell leukaemia and renal failure were found under 40 years of age [6]. In our patients, the ratio of ISS stages was more or less of equipartition and the most common CRAB finding was bone lesion, however, no statistical analysis could be performed due to the low number of cases. Only one patient presented with primary plasma cell leukaemia. Ludwig et al. were the first who analyzed citogenetical alterations in multiple myeloma patients younger than 50 years old and found no difference from older population in the frequency of any cytogenetic abnormality [8]. However, the Polish group detected higher incidence of adverse genetical alterations in patients aged 21–40 years [10]. We performed FISH tests in only ten patients and as a result both standard and high-risk alterations were available.

All of our young patients were considered as potential candidates of autologous stem cell transplantation, however two of them passed away shortly after the establishment of diagnosis because of primary refractory disease / plasma cell leukaemia. The induction treatment they received was concordant with the current recommendations of the IMWG: VAD protocol was administered until 2007 then thalidomide and bortezomib-based regimens were prefered. Former publications reported on only conventional chemotherapies administered in young MM patients before APSCT [8, 9]. The response to primary treatment (induction + APSCT) was not significantly diferrent between the younger and older population. However, both progression-free and overall survival results were more favorable in the cohort of patients ≤40 years. Authors from the Mayo Clinic reported same survival results after APSCT among young and older myeloma patients [6], on the other hand, Ludwig et al. found older age as an adverse risk factor in terms of the life expectancy of newly diagnosed MM patients [8]. Thus, we have to underline that both of the latter studies were published before the era of novel therapies. The more recent publicaton by Jurczyszyn et al. reported on similar overall response rates in younger and older patients (79 vs 83%) after novel agent-based therapies, however patients aged 21–40 years were found to have significantly more favorable five- and ten-year overal survival results (83% vs 67% and 56% vs 39%, respectively) than the group aged 41–60 years. [10]

Treatment results and survival data of multiple myeloma patients have significantly improved since the introduction of new drugs including proteasome inhibitors, immunomodulatory agents and monoclonal antibodies [12]. However, despite the encouraging results, myeloma is still considerred as an uncurable disease characterized by remissions and relapses. While the prolongation of lives of elderly people seems to be a good compromise, clinicians may not accept anything but complete cure for young patients. Still, there is no specific, widely-accepted treatment protocol available for young MM patients, studies rather focus on high-risk cases [13, 14]. There

Table 2 Comparison of results of patients ≤40 years and > 40 years who underwent autologous stem cell transplantation

	age ≤ 40 years ($n = 14$)	age > 40 years ($n = 278$)	p
male	9	147	0.453
female	5	131	
response to treatment			
CR + VGPR	10	182	0.270
PR	3	67	
progression	1	29	
Post-APSCT treatment (maintenance, consolidation)	10	56	**0.006**
Progression within 2 years after APSCT			
yes	4	126	0.386
no	10	133	
death	3	97	0.260
alive	11	163	
5-year PFS	48%	35%	0.795
5-year OS	83%	53%	**0.047**

are several approaches targeting this population that include tandem autologous transplant, several generations of total therapies and administration of new drugs. Consolidation and maintenance therapies also seem to be reasonable approaches to prolong remission periods. Unfortunately, unlike from chronic myeloid leukaemia, there is no perfect maintenance treatment in multiple myeloma as tolerability and side effects are strong limiting factors. Recently, the most accepted maintenance therapy is the administration of lenalidomide [15] Seven of our long-term survival patients received some kind of maintance therapy after APSCT that included thalidomide, bortezomib or interferon as lenalidomide was not available in our institute.

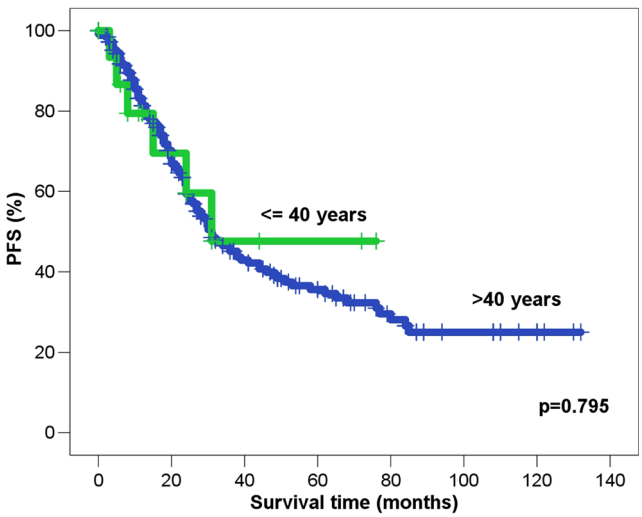

Fig. 1 Progression free survival of patients aged < and > 40 years

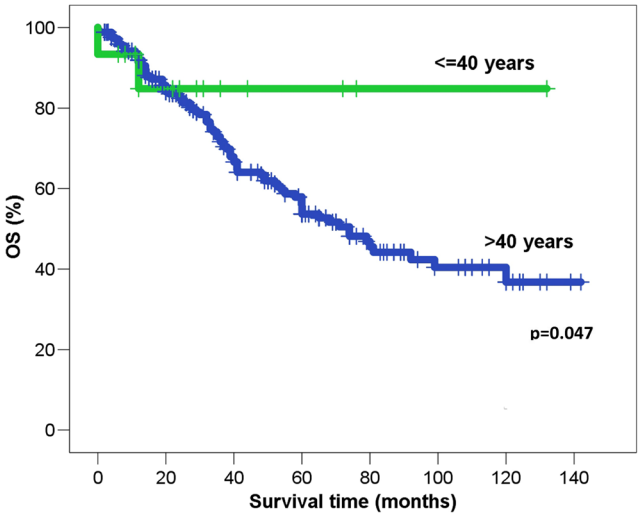

Fig. 2 Overall survival of patients aged < and > 40 years

Allogeneic stem cell transplantation is considered as the only curative treatment method in multiple myeloma, however, its role is still controversial. Due to the high mortality rates, it is still offered as a kind of 'end-of-the-road' option for refractory-relapsing patients. As reduced intensity conditioning strategy is not eligible for myeloablation, a preceeding autologous stem cell transplantation is neccessary to perform and high-dose therapy is required before allografting. Mir et al. found only 24 months' median overall survival among those patient who underwent allogeneic stem cell transplantation at the Mayo Clinic and the 10 year OS was only 8%. [16] However, long-term survival results after allogeneic stem cell transplantation have been recently found to be superior compared to the tandem autologous setting [17]. None of our young MM patients have undergone allogeneic transplantation so far, the main reasons were either the lack of consent or non-eligibility. However, we are planning to consider this treatment modality for high-risk patient who relapse shortly after the autologous stem cell support.

Our study's main limitation is that we processed the data of a relatively small number of patients within a single institution. However, our results may highlight that though the ratio of young cases is small, there is an unmet need for new therapies that provide complete cure or at least long-term remission for fit multiple myeloma patients. The introduction of novel drugs to the early treatment line may result in increasing number of minimal residual disease (MRD) negative cases and markedly polonged survival.

Compliance with Ethical Standards

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Kazandijan D (2016) Multiple myeloma epidemiology and survival: a unique malignancy. Semin Oncol 43(6):676–681
2. Rajkumar SV, Dimopoulos MA, Palumbo A et al (2014) International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:538–548
3. Kumar S (2017) Emerging options in multiple myeloma: targeted, immune and epigenetic therapies. Hematology Am Soc Hematol Educ Program 2017(1):518–524
4. Chng WJ, Dispenzieri A, Chim CS et al (2014) IMWG consensus on risk stratification in multiple myeloma. Leukemia 28:269–277
5. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1072 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78:21–33
6. Cheema PK, Zadeh S, Kukreti V, Reece D, Chen C, Trudel S, Mikhael J (2009) Age 40 years and under does not confer superior prognosis in patients with multiple myeloma undergoing upfront autologous stem cell transplant. Biol Blood Marrow Transplant. 15: 686–693
7. Geetha N, Jayaparkash M, Rekhenair A et al (1999) Plasma cell neoplasms in young. Br J Radiol 72:1012–1015
8. Ludwig H, Durie BGM, Bolejack et al (2008) Myeloma in patients younger than age 50 yearsa presents with more favorable features and shows better survival: an analysis of 10.549 patients from the Internationaly Myeloma Working Group. Blood. 111: 4039–4047
9. Blade J, Kyle RA, Griepp PR (1996) Presenting features and prognosis in 72 patients with multiple myeloam who were younger than 40 years. Br J Haematol 93:345–351
10. Jurczyszyn A, Nahi H, Avivi I, Gozzetti A, Niesvizky R, Yadlapati S, Jayabalan DS, Robak P, Pika T, Andersen KT, Rasche L, Mądry K, Woszczyk D, Raźny M, Usnarska-Zubkiewicz L, Knopińska-Posłuszny W, Wojciechowska M, Guzicka-Kazimierczak R, Joks M, Grosicki S, Ciepłuch H, Rymko M, Vesole DH, Castillo JJ (2016) Characteristics and outcomes of patients with multiple myeloma aged 21-40 years versus 41-60 years: a multi-institutional case-control study. Br J Haematol 175:884–891
11. Jurczyszyn A, Davila J, Kortüm KM et al (2018) Multiple myeloma in patients up to 30 years of age: a multicenter retrospective study of 52 cases. Leuk Lymphoma 22:1–6
12. Mateos MV, San Miguel JV (2017) Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program. 2017(1):498–507
13. Sonneveld P (2017) Management of multiple myeloma in the relapsed / refarcory patient. Hematology Am Soc Hematol Educ Program. 2017(1):508–517
14. Chan HSH, Chen CI, Reece DE (2017) Current review on high-risk myeloma. Curr Hematol Mal Rep 12:96–108
15. Ludwig H, Zojer H (2017) Fixed duration vs coninuous therapy in multiple myeloma. Hematology Am Soc Hematol Educ Program. 2017(1):212–222
16. Mir MA, Kapoor P, Kumar S, Pandey S, Dispenzieri A, Lacy MQ, Dingli D, Hogan W, Buadi F, Hayman S, Gandhi M, Gertz MA (2015) Trends and outcomes in allogeneic hematopoietic stem cell transplant for multiple myeloma at Mayo Clinic. Clin Ly Myeloma & Leuk 15:349–357
17. Htut M, D1Souza A, Krishnan A et al (2017) Autologous / Allogeneic hematopoietic Cell Transplant versus tandem autologous transplantation for multiple myeloma: comparison of long-term post-relapse survival. Biol Blood Marrow Transplant pii: S1083–8791(17)30793–0. doi: https://doi.org/10.1016/j.bbmt.2017.10.024. [Epub ahead of print]