First Line Therapy in Multiple Myeloma: VAD *vs* Bortezomib -Dexamethasone

EMA-CRISTINA BORSI[1], ADINA BUCUR[2]*, CRISTINA POTRE ONCU[1], OVIDIU POTRE ONCU[1], BIANCA CERBU[3], DAN COSTACHESCU[1], IOANA IONITA[1], CONSTANTIN TUDOR LUCA[4]*, HORTENSIA IONITA[1]

[1]University of Medicine and Pharmacy Victor Babes Timisoara, Department of Haematology, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[2]University of Medicine and Pharmacy Victor Babes Timisoara, Department of Public Health and Health Management, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[3]University of Medicine and Pharmacy Victor Babes Timisoara, Department of Infectious Diseases, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[4]University of Medicine and Pharmacy Victor Babes Timisoara, Department of Cardiology, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

Multiple myeloma (MM) is typically sensitive to a range of cytotoxic agents, both as initial therapy and as relapsed disease treatment. Unfortunately, the responses are transient, and MM is not considered curable with the current approaches. This paper aims to assess the response to first line treatment of patients included in the study and their correlation with the negative prognostic factors in multiple myeloma: age over 60 years, male gender, anemia, hypercalcemia, elevated levels of creatinine, Beta 2 microglobulin, hypoalbuminemia and Bence-Jones proteins type. The study was conducted on a group of 105 patients admitted to the Hematology Department of the Municipal Emergency Clinical Hospital of Timisoara from 01 January 2013 until 31 December 2017. Twenty-seven patients received VAD regimen, while 78 underwent Bortezomib + Dexamethasone regimen as fist line therapy. When analyzing anthropometrical data, different gender distribution in the two groups of patients is seen, while a higher percentage of patients over 60 years is observed in both groups, with 77.7% in the VAD group (21 out of 27 patients) and 56.4% in the group treated with Bortezomib + Dexamethasone (44 out of 78 patients). Only some of the factors analyzed in our study statistically significantly influenced the response to treatment and the duration of survival, i.e.: age over 60 years, hemoglobin <10g/dL, platelets under 150000/mm^3, creatinine >2mg/dL, serum calcium >10mg / dL, increased C-reactive protein, low serum albumin levels, high levels of Beta 2 microglobulin, total serum protein, as well as presence of cells in the peripheral smear. Defining a panel of negative prognostic factors that influence the evolution and response to multiple myeloma treatment would allow for tailoring of personalized therapies for each patient.

Keywords: treatment, multiple myeloma, survival

Multiple myeloma (MM) is typically sensitive to a range of cytotoxic agents, both as initial therapy and as relapsed disease treatment. Unfortunately, the responses are transient, and MM is not considered curable with the current approaches. Nevertheless, the MM treatment has rapidly evolved thanks to the introduction of new agents, such as Thalidomide, Lenalidomide, Bortezomib and Carfilzomib [1-3]. Studies of associated cytogenetic anomalies show that MM is a heterogeneous disease, suggesting that risk-adapted approaches and personalized treatments will contribute even more to improve patient management. [4,5]

Patients with symptomatic active multiple myeloma are receiving first line therapy, while in selected patients this is followed by a high-dose chemotherapy supported with autologous stem cells. Therapeutic agents, such as alkylating agents, may compromise stem cells reserves, so that regiments with such agents (particularly Melphalan) should be avoided in patients who are potential candidates for stem cell transplant (SCT). This is why the assessment of patients for transplant is a first step. It must be noted that advanced age and kidney dysfunction are not absolute contraindications for transplant. It is also important to consider supportive care for all patients at the time of diagnosis. For example, 80% of the patients have a bone disease and up to 33% have kidney compromises. Complications arising during therapy should be appropriately treated. In all patients, particular attention to supportive care is essential to avoid early complications that may compromise the therapeutic outcome. *Myeloma Therapy* in guidelines includes a list of primary therapeutic regimens recommended for the transplant candidates and for the non-transplant group of patients, as well as a list of recommended agents for maintenance therapy. The list does not include all the regimens. Multiple myeloma panel, NCCN, has classified the regimens either as *preferred regimens* or *other regimens* based on a balance of efficacy and toxicity. Research on various first line regimens has focused on improving the CR rates in both transplant and non-transplant candidates. The NCCN panel has underlined the importance of response to first line therapy after two treatment cycles. Regimens based on Bortezomib may be useful in patients with kidney failure and in those with particular adverse cytogenetic characteristics, although are associated with increased herpes zoster incidence [7-11]. The risk of deep vein thrombosis (DVT) is low with bortezomib; even though, peripheral neuropathy and gastrointestinal disorders can be higher. Adverse events associated with Bortezomib are predictable, so the patient is monitored.

This paper aims to assess the response to first line treatment of patients included in the study and their correlation with the negative prognostic factors in multiple myeloma: age over 60 years, male gender, anemia,

email: adina.bucur@gmail.com, Phone: 0040-723786442; Costiluca 67@yahoo.ro

hypercalcemia, elevated levels of creatinine, Beta 2 microglobulin, hypoalbuminemia and Bence-Jones proteins type.

Experimental part

The study was conducted on a group of 105 patients admitted to the Hematology Department of the Municipal Emergency Clinical Hospital of Timisoara from 01 January 2013 until 31 December 2017. The study is retrospective for the period 2013-2015, so that medical records of patients admitted and diagnosed for the first time with multiple myeloma during that period were analyzed. The study became prospective starting with 2015 year and we included patients admitted to our clinic for first diagnosis.

The treatment protocol in our clinic consists in first line therapy before transplant, which may be VAD regimen administered according to the following protocol:

-Vincristine 0.4 mg daily, days 1-4,

-Doxorubicin – 9 mg/m^2 days 1-4, Dexamethasone 40mg/day, days 1-4, 9-12, 17-20 during odd cycles and days 1-4, 9-12 during even cycles

The cycle is repeated at 28 days.

Bortezomib - Dexamethasone 4-6-8 cycles is also used as first line therapy, as follows:

-Bortezomib 1.3mg/m^2, days 1,4, 8, 11

-Dexamethasone 40mg/day, days 1,2; 4,5; 8,9; 11,12.

The cycle is repeated at 21 days.

Statistical analysis

The data were collected from the medical records for each patient. Anthropometric, hematologic, biochemical and immunological parameters, type of treatment and response to treatment were analyzed. Statistical data processing was performed with the SPSS20.0 program. For descriptive statistics, the results were expressed in percentages and absolute values. The difference in treatment response depending on biological parameters was calculated using the Chi-squared test. Kaplan Meyer curve was used to calculate survival.

Results and discussions

We have included 105 patients who were admitted for first diagnosis to the Hematology Clinic of the City Clinical Hospital Timisoara, where they received chemotherapy according to the treatment protocol after the diagnosis of multiple myeloma was confirmed.

Twenty-seven patients received VAD regimen, while 78 underwent Bortezomib + Dexamethasone regimen as fist line therapy. When analyzing anthropometrical data, different gender distribution in the two groups of patients is seen, while a higher percentage of patients over 60 years is observed in both groups, with 77.7% in the VAD group (21 out of 27 patients) and 56.4% in the group treated with Bortezomib + Dexamethasone (44 out of 78 patients).

It was also found that most patients in both groups (55.5% in VAD group, 55.1% in Bortezomib group) had anemia (Hg < 10 g/dl). Thrombocytopenia is less common in both treatment groups. ESR over 40mm/h is seen in over 70% of the patients in VAD group and more than 85% in the Bortezomib group. Inflammation factors (fibrinogen, FAS, LDH, PCR) are beyond normal values in less patients in both groups. Changes in the parameters of kidney function is found in less than half of the patients. Hypercalcemia, which is considered a negative prognostic factor, is present in 7.4% of the patients treated with VAD and in 34.6% of the patients on Bortezomib. Hypoalbuminemia is seen in 37% of the patients in the VAD group and in 44.9% of those receiving Bortezomib, while increased values of Beta 2 microglobulin are found in over 50% in both groups, as well as the presence of Kappa chains. Elevated D-dimer values are seen in 51.9% of the patients on VAD and 41% of those in the Bortezomib + Dexamethasone group. Immunoglobulins are present in most patients in both groups.

The International Staging System (ISS) was used for staging the disease:

-Stage I: Beta 2 microglobulin < 3.5 mg/L and albumin ≥ 3.5g/dL

-Stage II: values that cannot be included in stages I or III

-Stage III: Beta 2 microglobulin ≥5.5 mg/L

Most patients enrolled in both groups had stage III disease at the time of diagnosis.

The response to treatment was evaluated as complete remission, partial remission, refractory disease or relapse. A significant percentage of patients receiving bortezomib and dexamethasone as first line treatment were found to have a complete or partial response and stable disease (74.4%), with no deaths recorded during therapy. In the VAD group, 44.4% of patients had progressive disease, while 3 patients died during treatment. The response to treatment is found to be better in the bortezomib and dexamethasone group, the difference between the two groups reaching statistical significance.

The response to treatment is statistically significantly influenced by some of the parameters considered to be negative prognostic factors, namely low level of serum albumin, the patients with albumin levels under 3.5 g/dL having a negative response to treatment compared with those with higher levels. Total protein values lower than 64g/L and higher than 83g/L also correlated with a negative response to treatment compared with patients showing normal levels of this parameter. Level of Beta 2 microglobulin > 3mg/dl is also a negative prognostic factor and it is statistically significantly correlated with a negative response to treatment (refractory or relapsed disease). Other negative prognostic factors present in patients included in this study are male sex, age over 60 years, Hg < 10g/dL, platelets < 150000/mm^3, CRP positive, creatinine > 2mg/dL, hypercalcemia > 10mg/dL and presence of cells in the peripheral smear.

At survival analysis, patients treated with bortezomib and dexamethasone were found to have a mean survival of 29.462 ± 2.037 months, while those receiving VAD had a mean survival of 22.481 ± 3.328 months.

Multiple myeloma is a neoplastic plasma cell dyscrasia in which patient survival ranges from a few months to several years [12,13] and is influenced by several factors.

The majority of patients included in the study group were aged over 60 years at the onset of disease. Most of them were in their sixth decade of life, which is in line with the data in the literature (average age at diagnosis is 60 years) [14-16].

In our group of 105 patients, 55 patients were female and 50 were male, although in the literature multiple myeloma mainly affects male gender (M/F ratio = 1.5) [17-19].

Many prognostic factors for MM were proposed and analyzed in the literature, but not all have been shown to be useful in classifying patients into risk groups in order to personalize the chemotherapy regimen.

Factors identified in various studies that negatively affect survival are older age, severe bone lesions, low hemoglobin levels, platelet depletion, hypercalcemia, decreased plasma albumin levels, elevated plasm a bone marrow

Table 1
BASELINE CHARACTERISTICS

Parameter	Value	VAD (N=27)	Bortezomib+dexamethasone (N=78)
Sex	M F	15 (55.6%) 12 (44.4%)	35 (44.9%) 43(55.1%)
Age	<40 years 41-60 years 61-75 years >75 years	1 (3.7%) 5 (18.5%) 10 (37%) 11 (40.8%)	2 (2.6%) 32 (41%) 35 (44.9%) 9 (11.5%)
Hg (g/dl)	<7 7-10 10-12 >12	5 (18.5%) 10 (37%) 7 (25.9%) 5 (18.6%)	9 (11.5%) 34 (43.6%) 22 (28.2%) 13(16.7%)
Platelets (mm^3)	<50000 50000-100000 1000000-150000 >150000	3 (11.1%) 1 (3.7%) 4 (14.8%) 19 (70.4%)	2 (2.6%) 12 (15.4%) 13 (16.7%) 51 (65.3%)
ESR (mm/h)	<40 40-80 80-120 >120	6 (22.2%) 5 (18.5%) 7 (25.9%) 9 (33.3%)	8 (10.3%) 16 (20.5%) 30 (38.5%) 24 (30.8%)
Fibrinogen (mg/dl)	238-498 >498	19 (70.4%) 8 (29.6%)	59 (75.6%) 19 (24.4%)
FAS (U/L)	<40 40-130 >130	5 (18.5%) 15 (55.6%) 7 (25.9%)	7 (9%) 39 (50%) 32 (41%)
LDH (U/L)	81-234 >234	11 (40.7%) 16 (59.3%)	36 (46.2%) 42 (53.8%)
CRP (mg/L)	negative positive	14 (51.9%) 13 (48.1%)	51 (65.4%) 27 (34.6%)
Creatinine (mg/dl)	<1 1-2 >2	11(40.8%) 3 (11.1%) 13 (48.1%)	43 (55.1%) 15 (19.2%) 20 (25.7%)
Urea (mg/dl)	21-43 >43	12 (44.4%) 15 (55.6%)	49 (62.8%) 29 (37.2%)
Serum Ca (mg/dl)	<8.6 8.6-10 >10	9 (33.3%) 16 (59.3%) 12 (7.4%)	17 (21.8%) 34 (43.6%) 27 (34.6%)
Serum K (mmol/L)	3.4-4.4 >4.4	20 (74.1%) 7 (25.9%)	63 (80.8%) 15 (19.2%)
Albumin (g/dl)	<6.4 6.4-8.3 >8.3	10 (37%) 11 (40.7%) 6 (22.3%)	35 (44.9%) 27 (34.6%) 16 (20.5%)
Beta 2 microglobulin (mg/L)	<3.5 3.5-5.5 >5.5	5 (18.5%) 6 (22.2%) 16 (59.3%)	14 (17.9%) 18 (23.1%) 46 (59%)
Proteins (g/L)	<59.8 59.8-72.4 >72.4	5 (18.5%) 7 (25.9%) 15 (55.6%)	8 (10.3%) 31 (39.7%) 39 (50%)
Chains	Kappa Lambda	15 (55.6%) 12 (44.4%)	54 (69.2%) 24 (30.8%)
Peripheral smear	absent present	18 (66.7%) 9 (33.3%)	33 (42.3%) 45 (57.7%)
D-dimers (ng/ml)	0-243 >243	13 (48.1%) 14 (51.9%)	46 (59%) 32(41%)
IgA (g/L)	present absent	19 (70.4%) 8 (29.6%)	62 (79.5%) 16 (20.5%)
IgG (g/L)	present absent	27 (100%) 0 (0%)	72 (92.3%) 6 (7.7%)

Treatment		Stage			Total
		I	II	III	
VAD	Count	4	6	17	27
	Percent	14.8%	22.2%	63.0%	100.0%
Bortezomib	Count	11	15	52	78
	Percent	14.1%	19.2%	66.7%	100.0%

Table 2
DISEASE STAGING

		Response					Total
		RP	RC	BS- plateau phase	BP	Deaths	
VAD	Count	3	3	6	12	3	27
	Percent	11.1%	11.1%	22.3%	44.4%	11.1%	100.0%
Bortezomib	Count	24	21	13	20	0	78
	Percent	30.8%	26.9%	16.7%	25.6%	0.0%	100.0%

Table 3
THE RESPONSE TO FIRST LINE TREATMENT

Chi-Square Tests

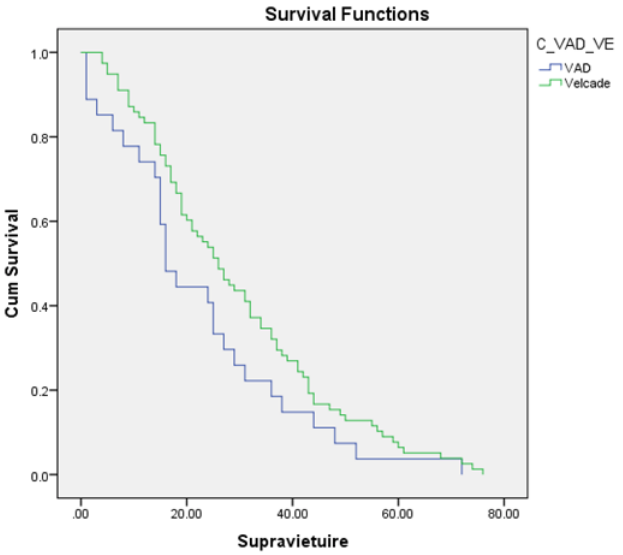
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	16.544[a]	4	.002
Likelihood Ratio	16.749	4	.002
Linear-by-Linear Association	11.996	1	.001
N of Valid Cases	105		

Parameter	Value	RP	RC	BS	BP	Deaths	P-value
Sex	M F	13 14	9 15	8 11	18 14	2 1	.018
Age	<60 years >60 years	10 17	12 12	6 13	11 21	1 2	.019
Hg (g/dl)	<10 >10	12 15	9 15	12 7	22 10	3 0	.003
Platelets (mm^3)	<150000 >150000	3 24	3 21	4 15	5 27	3 0	.020
CRP (mg/L)	negative positive	17 10	15 9	13 6	20 12	0 3	.010
Creatinine (mg/dl)	<2 >2	20 7	20 4	14 5	17 15	1 2	.010
Serum Ca (mg/dl)	<10 >10	18 9	18 6	14 5	24 8	2 1	.020
Albumin (g/dl)	<6,4 >6.4	10 17	6 18	10 9	19 13	0 3	.030
Beta 2 microglobulin (mg/L)	<5,5 >5.5	9 18	14 10	8 11	12 20	0 3	.008
Proteins (g/L)	<72.4 >72.4	11 16	17 7	9 10	13 19	1 2	.050
Peripheral smear	absent present	12 15	16 8	8 11	14 18	1 2	.050

Table 4

Treatment	Mean[a]			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
VAD	22.481	3.328	15.959	29.004
Bortezomib	29.462	2.037	25.469	33.454
Overall	27.667	1.756	24.225	31.109

Table 5
OVERALL SURVIVAL



cells, elevated serum creatinine, high serum β2 microglobulin and increased C-reactive protein. [20-22].

Results of the 22 clinical and laboratory tests associated with anthropometric parameters recorded at the time of diagnosis in all patients, meaning age, sex of patients, bone marrow cells, myeloma immunological type, hemoglobin, platelets, calcium, albumin, immunoglobulin, ALAT, ASAT, lactate dehydrogenase, creatinine, urea, uric acid, β2M, CRP, ESR and bone involvement, were published in other studies as well [23,24].

Only some of the factors analyzed in our study statistically significantly influenced the response to treatment and the duration of survival, i.e.: age over 60 years, hemoglobin <10g/dL, platelets under 150000/mm^3, creatinine >2mg/dL, serum calcium >10mg/dL, increased C-reactive protein, low serum albumin levels, high levels of Beta 2 microglobulin, total serum protein, as well as presence of cells in the peripheral smear.

The mean survival time was 29.462 ± 2.037 months in patients treated with bortezomib and dexamethasone versus of 22.481 ± 3.328 months in those receiving VAD.

Conclusions

A long list of useful prognostic factors for MM can be found in the literature, although no single factor can accurately predict the survival of these patients. This is why a number of factors easily to be ascertained at the time of diagnosis are analyzed and are helpful in predicting the risk of adverse response to treatment. Out of these factors, beta2M and CRP, circulating monoclonal plasmids count and bone marrow plasma cell labelling index are mandatory. Defining a panel of negative prognostic factors that influence the evolution and response to multiple myeloma treatment would allow for tailoring of personalized therapies for each patient.

References

1.HANAHAN D, WEINBERG RA. Hallmarks of Cancer: The Next Generation. Cell. 2011;144(5):646–74[PubMed]

2.WALKER BA, WARDELL CP, CHIECCHIO L, SMITH EM, BOYD KD, NERI A, et al. Aberrant global methylation patterns affect the molecular pathogenesis and prognosis of multiple myeloma. Blood. 2011;117(2):553–62[PubMed]

3.KYLE RA, RAJKUMAR SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2008;23(1):3–9 [PMC free article] [PubMed]

4.LANDGREN O, KYLE RA, PFEIFFER RM, KATZMANN JA, CAPORASO NE, HAYES RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412–7 [PMC free article] [PubMed]

5.WALKER BA, WARDELL CP, LOPEZ-CORRAL L, HUMPHRAY S, MURRAY L, ROSS M, et al. Whole Genome Sequencing Illuminates the Genetic and Biological Features Underlying the Transition of SMM to MM. ASH Annual Meeting Abstracts. 2011;118(21):296

6.***Home-ClinicalTrials.gov [Internet]. [cited 2014 Jan 24]. Available from: http://www.clinicaltrial.gov/

7.SIEGEL RL, MILLER KD, JEMAL A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29. [PubMed]

8.BRENNER H, GONDOS A, PULTE D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111:2521–2526. [PubMed]

9.KUMAR SK, RAJKUMAR SV, DISPENZIERI A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516–2520. [PMC free article] [PubMed]

10.PALUMBO A, ANDERSON K. Multiple myeloma. N Engl J Med. 2011;364:1046–1060. [PubMed]

11.DEBES-MARUN CS, DEWALD GW, BRYANT S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia 2003;17:427-36.

12.HURT EM, WIESTNER A, ROSENWALD A, et al. Overexpression of cmaf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. Cancer Cell 2004;5:191-9.

13.LAHUERTA JJ, MARTINEZ-LOPEZ J, SERNA JD, et al. Remission status defined by immunofixation vs. electrophoresis after autologous transplantation has a major impact on the outcome of multiple myeloma patients. Br J Haematol. 2000;109:438-446.

14.ALMEIDA JJ, MATEO GG, ORFAO AA, et al. An immunophenotypic pattern characteristic of MGUS is achieved following autologous stem cell transplant in multiple myeloma [abstract]. Blood. 2000; 96:421a.

15.BLADE J, SAN MIGUEL JF, FONTANILLAS M, et al. Increased conventional chemotherapy does not improve survival in multiple myeloma: long-term results of two PETHEMA trials including 914 patients. Haematologica. 2001;2:272-278.

16.JACOBSON JL, HUSSEIN MA, BARLOGIE B, et al. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. Br J Haematol. 2003;122: 441-450.

17.SIROHI B, POWLES R. Multiple myeloma. Lancet. 2004;363:875-887.

18.MACLENNAN IC, TOELLNER KM, CUNNINGHAM AF, et al. Extrafollicular antibody responses [review]. Immunol Rev. 2003;194:8-18.
19.MITSIADES CS, MITSIADES N, MUNSHI NC, ANDERSON KC. Focus on multiple myeloma. Cancer Cell 2004;6:439-44.
20.HIDESHIMA T, BERGSAGEL PL, KUEHL WM, ANDERSON K. Advances in biology of multiple myeloma: clinical applications. Blood 2004;104:607- 18.
21.BERGSAGEL PL, KUEHL WM. Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol 2005;23:6333-8.
22.ZENT CS, WILSON CS, TRICOT G, et al. Oligoclonal protein bands and Ig isotype switching in multiple myeloma treated with high-dose therapy and hematopoietic cell transplantation. Blood. 1998;91: 3518-3523.
23.DAVIES FE, FORSYTH PD, RAWSTRON AC, et al. The impact of attaining a minimal disease state after high-dose melphalan and autologous transplantation for multiple myeloma. Br J Haematol. 2001; 112:814-819
24.SAMPATH D, PUNNOOSE E, BOGHAERT ER, BELMONT L, CHEN J, PEALE F, et al. Expression of Bcl-2 Pro-Survival Family Proteins Predicts Pharmacological Responses to ABT-199, a Novel and Selective Bcl-2 Antagonist, in Multiple Myeloma Models. ASH Annual Meeting Abstracts. 2012;120(21):5028

Manuscript received: 11.08.2018