The Response to Chemotherapy as Prognostic Marker in Multiple Myeloma

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Objectives: Even though the correlation between the degree of therapeutic response and overall survival was studied for a long time, there are still contradictory opinions. This study intends to evaluate the prognostic value of response to chemotherapy in terms of patient survival and depending on the type of therapy.
Material and method: The study analyses 110 patients diagnosed and treated between January 2006 and September 2012. Descriptive analysis of cases was performed and survival analysis was realised using Kaplan-Meier curves compared to logrank test.
Results: The median survival was 18 months when the patients were treated with vincristine + adriamycin + dexamethasone, 20 months with melphan + prednisone, 71 months with melphalan + cyclophosphamide + vincristine + prednisone ($p = 0.020$), 33 months with Bortezomib and 4 months with dexamethasone. A percent of 38.18% of patients responded near completely to therapy, partial response occurred in 29.09% of cases and no response/ refractory disease in 32.72%. The patients had a median survival of 62 months for near complete response to therapy, 20 months for partial response and 4 months for no response/ refractory disease ($p < 0.0001$). The time to disease progression was of 24 months regardless of the used therapy. The most common adverse effect was anaemia.
Conclusions: Lack of response to treatment is a negative prognostic factor in the evolution of multiple myeloma patients.

Keywords: multiple myeloma, survival, chemotherapy, prognostic factor

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Introduction

Multiple myeloma is a malignant proliferation of fully differentiated B lymphocytes that produce antibodies. For over 30 years, it was treated with a melphalan and prednisone combination, the median survival being of approximately 3 years. Nearly the same survival was present in case of patients treated with vincristine + adriamycin + dexamethasone (VAD) and melphalan + cyclophosphamide + vincristine + prednisone (VMPC). The median survival increased after the introduction of the Bortezomib therapy, being between 4 and 5 years. In case of high-dose chemotherapy and hematopoietic stem cell transplantation the median survival was 5 years, while without chemotherapy the median survivals would have been 6 months [1,2]. Diversification of therapeutic options has led to the extension of disease control, to prolonged survival and to improvements in the quality of life of patients [3].

The choice of therapy depends on patient age, performance status, disease stage, prognostic factors and possible side effects. The treatment algorithm has significantly evolved and improved in recent years [4]. The doses of conventional therapy get complete response in reduced proportion: MP in less than 5% and the high dose regimes of dexamethasone in less than 10% [5]. Criteria for complete response to chemotherapy comprise: the complete absence of monoclonal component to electrophoresis and immunofixation, bone marrow plasma cell infiltration below 5%, stable bone disease having confirmed results at 6 weeks. Patients with near complete response are those who have been detected with the absence of monoclonal component in electrophoresis, regardless of the immunofixation test, but present the remaining criteria of complete response [6,7].

Material and method

This study is retrospective and includes 110 patients diagnosed and treated in the Department of Hematology of the Medical Clinic I, County Emergency Clinical Hospital Tîrgu Mureș between January 2006 and September 2012. The age of the patients was between 30 and 90 years. The multiple myeloma diagnosis was established by cytological, immunological and radiological methods. The specific cytoreductive treatment consisted of applying the following polychemotherapies: VAD type (vincristine 0.4 mg/day + adriamycin 9 mg/m^2/day in continuous perfusion for 4 days + dexamethasone 20 mg/m^2/day per os on days 1–4, 9–12 and 17–20), combination MP (melphalan/alkeran 8 mg/m^2/day per os + prednisone 100 mg/day per os for 4 days), VMPC type (vincristin 1 mg/m^2/day on 1 day + melphalan 2–5 mg/m^2/day on days 2–5 + cyclophosphamide 100 mg/m^2/day on days 2–5 + prednisone 600 mg/m^2/day on days 2–5), Bortezomib (bortezomib 1.3 mg/m^2/day on days 1, 4, 8, 11 then a rest period of 10 days) and DXM (dexamethasone 40 mg/day on days 1–2, 4–5, 8–9, 11–12).

Patients were considered with near complete response to chemotherapy when the monoclonal component to electrophoresis was reduced by 100%, bone marrow plasma cell infiltration was less than 5% and stable bone disease having confirmed results at 6 weeks. Partial response to chemotherapy was established when monoclonal component of the serum dropped by over 50%, Bence Jones proteinuria decreased by over 90%, the presence of plasma

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Table I. The characteristics of patients with multiple myeloma (MM)

Characteristics	No. of patients	%
Sex: male/female	57/53	51.81/48.18
Residence: urban /rural	53/57	48.18/51.81
ECOG		
0–2	54	49.09
3–4	56	50.90
Sub-type of MM		
IgG-type MM	69	62.72
IgA-type MM	28	25.45
Micromolecular MM	10	9.09
Non-secretory MM	3	2.72
Clinical stage Salmon Durie		
Stage I	7	6.36
Stage II	18	16.36
Stage III	85	77.27
Hemoglobin <10 g/dl	66	60.00
Plasma cells >40%	55	50.00
Creatinine >2 mg/dl	40	36.36
Lytic bone lesions	87	79.09
Line therapy		
1	56	50.90
>1	54	49.09

cells in the bone marrow was below 5% and stable bone disease, results confirmed at 6 weeks. The staging was realized using the Salmon and Durie system.

A descriptive analysis of cases was performed. The survival was estimated using the Kaplan-Meier curves and compared using the logrank test. These were performed using Graph Pad Prism program, a p value <0.05 was considered statistically significant. Since the study was performed retrospectively, by analysing the data in the source documents, an informed consent was not available.

Results

The group included 51.81% men and 48.18% women, the average age being 64 years. Performance status (ECOG) of the patients between 3 and 4 was evaluated at a rate of 50.90%. At the time of diagnosis 77.27% of the patients were in the stage III according to the Salmon and Durie system. Depending on the type of secreted immunoglobuline, the most frequent was IgG, present in 62.72% of cases. The characteristics of patients are presented in Table I. Hypercalcemia was present in 31.81% of cases, low serum albumin occurred in 66.36% and Bence Jones proteinuria appeared in 56.36% of cases.

The patients received, as first-line of treatment, VAD type in 55 of cases, MP combination in 19 of cases, VMPC type in 15 of cases, Bortezomib in 13 of cases and DXM in 8 of cases. A single line of treatment received 56 patients, the rest of the patients received two or more lines of therapy. The maintenance therapy was administered to patients as follows: DXM to 83.33% of cases, Interferon to 9.52% of cases and Bortezomib to 7.14% of cases. A percent of 38.18% of patients responded near completely to therapy, 29.09% responded partially and 32.72% did not respond or had refractory disease.

The distribution of patients according to response to chemotherapy is presented in Figure 1.

The patients treated with VMPC type had a near complete response to therapy in nearly 60% of cases, those with Bortezomib in 53.84% of cases, those with MP combination in 36.84% of cases and those with VAD type in 34.54% of cases. DXM treated patients presented no response to therapy in a proportion of 87.5% of cases. Among the patients treated with VMPC type only 13.33% of cases showed no response to therapy.

The median survivals of patients, according to response to chemotherapy was 18 months in those treated with VAD type, 20 months in those treated with MP combination, 71 months in those treated with VMPC type ($p = 0.020$), 33 months in those treated with Bortezomib and 4 months in those treated with DXM (Figure 2).

The patients who were treated with VAD type and responded nearly completely, had a median survival of 40 months, those with partial response had a median survival of 17 months, and those who showed no response or disease progression had a median survival of 7 months ($p < 0.001$). In case of the patients who underwent a treatment with VMPC type with almost complete response, median

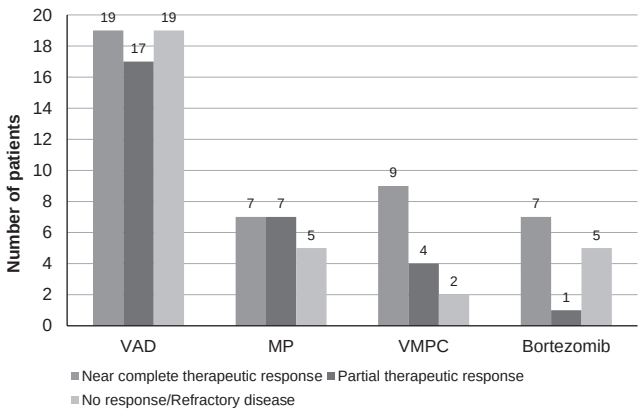

Fig. 1. Repartition of patients according to their response to therapy. VAD = vincristine + adriamycin + dexamethasone; MP = melphalan + prednisone; VMPC = vincristine + melphalan + prednisone + cyclophosphamide.

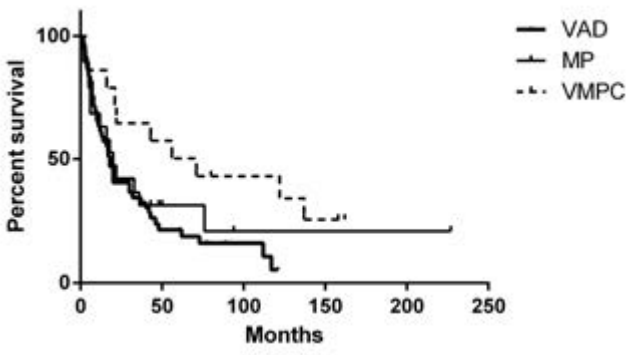

Fig. 2. Survival curve of patients with multiple myeloma depending on the type of therapy. VAD = vincristine + adriamycin + dexamethasone; MP = melphalan + prednisone; VMPC = vincristine + melphalan + prednisone + cyclophosphamide.

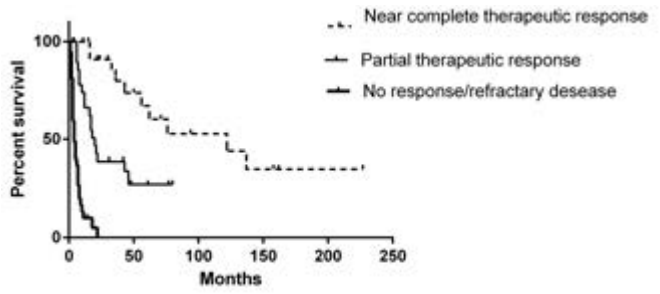

Fig. 3. Survival curve of patients with multiple myeloma depending on their response to therapy. VAD = vincristine + adriamycin + dexamethasone; MP = melphalan + prednisone; VMPC = vincristine + melphalan + prednisone + cyclophosphamide.

Table II. Treatment complications in multiple myeloma patients depending on the type of therapy

Complication	VAD (n = 55) %	VMPC (n = 15) %	MP (n = 19) %	Bortezomib (n = 13) %
Anemia	34.54	26.66	10.52	30.76
Thrombocytopenia	5.45	13.33	10.52	7.69
Neutropenia	12.72	20.00	5.26	7.69
Infection	9.09	13.33	10.52	15.38
Peripheral neuropaty	10.09	6.66	5.26	15.38
Trombosis	1.81	6.66	10.52	7.69
Gastrointestinal disorders	9.09	13.33	10.52	15.38
Hemorrahage	9.09	–	–	–

survival was 137 months. However, the median survival was 22 months in case of patients with partial response, and 3.5 months in case of nonresponsive patients / refractory disease ($p < 0.001$). The patients treated with combination MP had a median survival of 76 months if they showed a near complete response rate, 18 months when they responded partially, and 5 months if the patients presented no response / refractory disease ($p = 0.013$).

The patients treated with Bortezomib had an undefined median survival in case of near complete and partial response to therapy, and 3 months if the patients presented no response / refractory disease ($p = 0.003$).

When the patients responded almost completely regardless of therapy used, the median survival was 62 months, it was 20 months in those with partial response and 4 months in those without response / disease progression ($p < 0.0001$) (Figure 3).

The time to disease progression was of 24 months regardless of the used therapy. In patients with near complete response to treatment the median survival time to disease progression was 15 months for VAD type therapy, it was 39.5 months for VMPC type therapy and 33 for months MP combination ($p = 0.166$). In case of the patients treated with Bortezomib, the time to disease progression was undefined.

The most common adverse effects were anaemia (26.36%), neutropenia (10.90%), bacterial or viral infections (10.00%), gastrointestinal disorders (10.00%), peripheral neuropathy (9.09%), thrombocytopenia (7.27%), thrombosis (4.54%), and haemorrhage (4.54%) (Table II).

Discussions

The correlation between the degree of the therapeutic response and the overall survival of patients treated with standard chemotherapy has been studied for a long time, however there are contradictory opinions. In this study, the patients who responded almost completely to therapy, had a better survival than patients with partial or no response regardless of the therapy used. We used almost complete response to therapy because the absence of monoclonal component was performed by electrophoresis and the immunofixation was not performed in order to confirm. The results of the study on 628 patients revealed that those who showed complete response had a median survival of 5.1 years and those with partial response 3.3 years [8]. Complete response is an independent predictor for long-term of outcome regardless of age and stage of disease [9]. A phase III study in 1555 previously untreated patients, who had a median survival of 33 months, revealed that the best measure of the impact of therapy on the survival duration of patients is actually the first period of the disease progression and not the magnitude of response [10].

The treatment with MP combination has been considered, by many clinicians, as one of the primary standard therapies for initial treatment with a response rate between 50 and 60% having a median survival between 2 and 3 years [11]. Patients treated with MP combination, representing 17.27%, had a median survival of 20 months. A study conducted on a group of 1027 patients, who were treated at a rate of 57%, illustrated that median survival was of 31 months in case of the patients treated with MP combination, and patients treated with other regimens had a median of 38 months [12]. The addition of Bortezomib in combination with MP significantly benefits the patient survival [13]. In our study, only 13 patients underwent a treatment with Bortezomib having almost completely response 53.84% and no response 38.46%, with a median survival of 33 months. The time to disease progression was undefined, because 7 (87.5%) patients were in this period. The most common adverse effects were: anaemia 30.76% of patients, infection 15.38% of patients, peripheral neuropathy 15.38% of patients and gastrointestinal disorders 15.38% of patients. These results are explained by the small number of patients who received treatment with Bortezomib and because the therapy was recently introduced.

A study conducted on a group of 32 previously untreated patients, who received Bortezomib in 10 patients and the combination of Bortezomib with DXM in 22 patients, achieved a therapeutic response rate of 88% and the most common adverse effects were neuropathy in 31% of patients, constipation in 28% of patients, and myalgias in 28% of patients [14].

Bortezomib is a factor of improvement of prognosis in young and old patients, being used in both cases: as a sin-

gle agent and in combination therapy. It became the centrepiece in the initial therapy as well as in relapse, subcutaneous administration being less neurotoxic [15,16,17,18].

Patients treated with VAD type had a median overall survival below 18 months. In a study performed on 67 previously untreated patients and 31 patients relapsed / refractory disease, the authors achieved an overall response rate of 84%, with a median survival of 36 months for those previously untreated and 10 months for relapse / refractory disease [19]. VAD therapy, administered on the basis of rapid intravenous infusion, is an efficient induction regimen for previously untreated patients with a response rate of 67% but with neurotoxicity of 18% [20]. Rajkumar said that it was time to finally say goodbye to VAD type, being replaced with new innovative therapies [21].

In case of the patients with multiple relapses and/or ineligible for high dose of therapy, DXM alone increases life expectancy. A randomized study conducted on 488 patients showed a significantly better progression-free survival of disease for those treated with melphalan-prednisone, associated with lower morbidity in contrast to DXM regime. This indicates that the MP combination standard remains a good choice for older patients, when factors such as efficiency and comfort are followed [22]. A higher rate of complete response has been obtained with new therapeutic agents, but the benefit of complete response was not identical in all patients [23]. Treatment options should be customized according to patient comorbidities, because new therapeutic agents have different toxic effects [24].

Conclusions

A percent of 38.18% of patients responded near completely to therapy, partial response occurred in 29.09% of cases and no response/refractory disease in 32.72% of cases.

The median survival was of 18 months if the patients were treated with VAD type, 20 months with MP combination, 71 months with VMPC type ($p = 0.020$), 33 months with Bortezomib and 4 months with DXM.

The patients had a median survival of 62 months when they responded near completely to therapy, 20 months in case of partial response and 4 months for no responsive patients/ refractory disease ($p < 0.0001$).

The time to disease progression was 24 months regardless of the used therapy, 15 months for VAD type therapy, 39.5 months for VMPC type therapy, 33 months for MP combination and it was undefined in case of Bortezomib.

The most common adverse events were anaemia, neutropenia, bacterial or viral infections, gastrointestinal disorders, peripheral neuropathy, thrombocytopenia, thrombosis and haemorrhage.

Lack of response to treatment is a negative prognostic factor in the evolution of MM patients.

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