REVIEW ARTICLE

Diagnosis and the current trends in multiple myeloma therapy*

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ABSTRACT

Multiple myeloma is still an incurable disease. In recent years the introduction of 3 novel drugs oriented on basic mechanisms of multiple myeloma cells proliferation and survival has improved patients' outcome. These drugs are: thalidomide, its new analog, lenalidomide, and proteasome inhibitor, bortezomib. All three are highly effective both in newly diagnosed and relapsed/resistant patients.

Multiple myeloma (MM) is an incurable disease that is characterized by the accumulation of clonal plasmocytes in the bone marrow. It accounts for 10–15% of all hematological malignancies and 1–2% of all cancers. The incidence of MM varies by race and age. It occurs in Europe in approximately 4 of every 100,000 individuals.[1] In Poland about 1000 new cases of MM are diagnosed yearly, however this number seems to be underestimated. To date, no single cause for myeloma has been identified.

In TABLE 1 diagnostic criteria for MM and in TABLE 2 the staging according Durie-Salmon proposal are shown.[1]

In 2006 Durie et al.[2] published the modified classification called Durie-Salmon Plus Staging System which intergrates new imaging techniques such as magnetic resonance imaging, whole body FDG-PET scanning and whole body computed tomography into routine staging.

Many authors use the new International Staging System (ISS) which is straightforward and based on the assessment of 2 blood tests, i.e., β_2-microglobulin and albumin levels.[3] The ISS is shown in TABLE 3. In TABLE 4 the major poor prognostic factors are listed.

Approximately 10–40% of patients are asymptomatic at diagnosis. About 50–70% of MM patients have bone pain due to lytic lesions and pathological vertebral fractures. Many patients suffer from frequent bacterial infections and anemia. ⅓ of MM patients show impaired renal function at the time of diagnosis. A hyperviscosity syndrome is a rare serious complication of MM.[4]

Treatment of myeloma Treatment of MM is an extremely complex process. In the last years the treatment of newly diagnosed MM patients has undergone significant changes.[5,6] The initial decision for newly diagnosed patients is based on whether a patient is a candidate for high-dose chemotherapy supported by stem cell transplantation.[7,8] Afterwards the options are often dependent on the previous treatment.

Autologous stem cell transplantation High-dose chemotherapy supported by autologous stem cell transplantation is associated with an increased complete remission (CR) rate and an increase in median overall survival compared to standard dose chemotherapy and it is now considered the treatment of choice for newly diagnosed MM patients <65 years. Until now this is a therapy that has clearly demonstrated a prolongation of overall survival compared with conventional chemotherapy.[5,6] In the past 20 years peripheral blood stem cell transplantation (PBSCT) has been widely used as a part of starting therapy in newly diagnosed MM and as a salvage therapy for patients with recurrent/resistant disease. Although PBSCT is superior to conventional therapy, it is still not a therapeutic option.[5]

Allogeneic stem cell transplantation Allogeneic stem cell transplantation is at present the only available option which is curative, however this approach involves a mortality of more than 20–30%. To diminish such a high percentage of mortality the French group IFM tested

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TABLE 1 Diagnostic criteria of multiple myeloma

Major criteria	Minor criteria
Plasma cells on tissue biopsy	Bone marrow plasma cells 10–30%
Bone marrow plasma cells >30%	Bone plasmacytoma
Monoclonal protein levels:	Monoclonal protein lower than in major criteria:
IgG >35 g/l	IgG <6 g/l
IgA >20 g/l	IgA >1 g/l
Light chain excretion in urine ≥1 g/24 h	IgM <0.5 g/l

To diagnose myeloma a minimum of 1 major and 1 minor or 3 minor criteria that must include the 2 first should be met

Abbreviations: IgA – immunoglobulin A, IgG – immunoglobulin G, IgM – immunoglobulin M

TABLE 2 The Durie-Salmon staging system

Stage I (low cell mass: $<0,6 \times 10^{12}/m^2$)
All of the following:
hemoglobin value >10 g/dl
serum calcium value normal or ≤12 mg/dl
bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only
low M-component production rate (IgG value <5 g/l, IgA value <3 g/l, Bence-Jones protein <4 g/24 h)
Stage II (intermediate cell mass: $0.6–1.2 \times 10^{12}/m^2$)
Fitting neither stage I nor stage III
Stage III (high cell mass: $>1.2 \times 10^{12}/m^2$)
One or more of the following:
hemoglobin value <8.5 g/dl
serum calcium value >12 mg/dl
advanced lytic bone lesions (scale 3)
high M-component production rate (IgG value >7 g/l, IgA value >5 g/l, Bence-Jones protein >12 g/24 h)
Subclassification
A: relatively normal renal function (serum creatinine <2.0 mg/dl)
B: abnormal renal function (serum creatinine ≥2.0 mg/dl)

Abbreviations – see TABLE 1

nonmyeloablative allogeneic transplantation, but they failed to show the superiority of this strategy compared to classical allogeneic or double autologous transplantation.[9,10]

New drugs The introduction of novel drugs, i.e. thalidomide, lenalidomide and bortezomib, may change this scenario.[11-13] These agents can be used before or after PBSCT aiming to increase the CR and to prolong overall survival (OS).[14,15]

If a patient is not a candidate for an autologous transplant the best combination is melphalan, prednisone and thalidomide, as it was shown by the Italian and French myeloma study groups.[9,10] High-dose dexamethasone is often used in older patients who may be unable to tolerate thalidomide and melphalan.

Treatment for relapsed/refractory multiple myeloma

Therapy for relapsed/refractory diseases are usually based on combinations of new drugs like thalidomide, bortezomib and lenalidomide.[4,15]

In 2 large multicenter international trials the combination of lenalidomide (LEN) and dexamethasone (DEX) was evaluated in comparison to DEX alone. Both trials showed that a percentage of response to LEN/DEX was much greater. In the LEN/DEX group event-free survival was prolonged to 11 months compared to 5 months in the DEX group. This therapy has also shown the efficacy superior to DEX by prolonging time to progression (TTP) and OS.[16,17]

The combination of lenalidomide and dexamethasone as a frontline therapy produced a very high percentage of response – 91%.[12] Another new drug bortezomib, which is a proteasome inhibitor, was approved in the US and Europe for resistant/relapsed MM.[13] In multicenter clinical trials bortezomib was more effective than high-dose DEX. The benefits of bortezomib included a longer TTP, a higher CR rate and longer OS. Bortezomib was also very effective in the initial therapy.[18]

TABLE 3 International Staging System

Stage	Criteria	Median survival (months)
I	β_2-M <3.5 mg/l and albumin ≥3.5 g/l	62
II	β_2-M <3.5 mg/l and albumin <3.5 g/l or β_2-M 3.5–5.5 mg/l	44
III	β_2-M >5.5 mg/l	29

Abbreviations: β_2-M – β_2-microglobulin

TABLE 4 Selected poor prognostic factors in myeloma

Factors	Specification
Chromosomal abnormalities	del 13q t(4;14) t(14;16) t(11;14) monosomy of chromosome 13
Age	>65 years
β_2-microglobulin	≥3 mg/l
Albumin level	<3.5 g/l
Lactate dehydrogenase	≥190 UI
Heavy chain	immunoglobulin A
Platelets	<130 G/l
Bence-Jones protein	present
Plasma cell labeling index	>3%

Maintenance therapy In order to maintain remission, various therapies have been evaluated. A study performed at the Mayo Clinic in USA did not show any effects of maintenance or prolongation of OS.[8] By contrast, the study performed by the French IFM with pamidronate and thalidomide showed improvement in OS in patients treated with this combination.[19]

In the near future treatment strategies will be tailored based on prognostic factors, genetic background and host features. The addition of novel and conventional agents to the standard treatment with lenalidomide, thalidomide and bortezomib has changed a therapeutic paradigm in MM. Future studies will show whether high percentages of positive response to novel drugs will translate into the improvement of overall survival.

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