Risk assessment for multiple myeloma: the role of bone marrow transplantation

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ABSTRACT

The Durie/Salmon staging system continues to be used worldwide in patients with multiple myeloma. However, in recent years, new systems have been proposed. The International Myeloma Foundation performed a retrospective study with 11,179 patients and proposed an *International Staging System* utilizing serum levels of β2 microglobulin and albumin. In addition, current research has focused on the usefulness of cytogenetic and molecular data as prognostic factors. Preliminary data suggest that these parameters are powerful discriminators of a poor prognostic group of myeloma patients. Indeed, these prognostic indexes have been utilized in clinical trials, with interesting and encouraging results.

Multiple myeloma (MM) is a malignant clonal plasma cell disorder accounting for 1% of all cancers and 10% of hematological malignancies.[1] The main characteristic of the disease is the clonal proliferation of plasma cells, and the production, in the majority of cases, of a monoclonal heavy and/or light chain immunoglobulin (M-protein).[2] This disease occurs in older population, with median age at presentation of 65 years.[3] Fewer than 2% of MM patients are under 40 years old at diagnosis.[4] The survival of MM patients varies from a few months to more then ten years, depending on characteristics related to the disease itself (plasma cells abnormalities, tumor mass, stromal factors), as well as to host factors.[5,6] These risk factors for the development and progression of disease have been considered to be critical in the comparison of outcomes within and between different clinical trials. This strategy of assessing the patient according to the presence of risk factors is important on an individual basis, because it can predict the outcome. In addition, it adequately stratifies the patients in clinical studies.[7-10]

Clinical, biological and molecular factors adversely influence the outcome, and prognostic models have been developed trying to stratify patient into groups of different survivals.[5,7;10-12]

Prognostic assessment

The prognostic assessment has been based on risk factors, and can be divided in:
Clinical factors:
1. age distribution: poorer survival in older patients;
2. performance status

Factors related to the biology of the malignant clone:
1. cytogenetic abnormalities: 2. proliferation index (high proliferative activity)
Tumor mass and organ damages:
1. renal failure (creatinine); 2. high serum levels of β2-microglobulin and C-reactive protein.

Since the development of the Durie/Salmon staging system 3 decades ago, new prognostic models that include these three groups of characteristics have been proposed.[12] The Durie/Salmon staging system takes into account clinical and laboratorial parameters, trying to estimate the tumor mass, and consequently the prognosis. Analyzing the presence of four factors at diagnosis (anemia, M protein, calcium and lytic bone lesions) and presence of high serum creatinine levels, this system divided MM patients in three defined groups, with three different survival curves.

Looking for other prognostic markers, the level of β2microglobulin showed to be an interesting prognostic factor because it correlates with tumor mass and renal dysfunction. The cutoff of 6 mg/L of β-2-microglobulin was able to divide MM patients in two groups of different prognoses.[13] In 2003, The International Myeloma Foundation suggested another staging system that incorporates the β-2-microglobulin. This system is easier than the Durie/ Salmon, and still predicts the outcome.[10] This staging system, called *International Staging System* (ISS), was based on only two variables (β2-microglobulin and albumin), and was able to define three prognostic groups with different median survivals (Table 1).

Table 1. International Staging System (ISS).

Stage	Criteria	Median survival (months)
I	Serum B2 microglobulin <3,5 mg/L and serum albumin >35g/L	62
II	Neither I or III	45
III	Serum β2 microglobulin >5,5 mg/L	29

The comparison between these two staging systems showed that the ISS is better to define patients in stage I and II than Durie/ Salmon, and that patients in stage III of the ISS have worse prognosis than stage III of Durie/Salmon.[10]

The ISS has been validated on different settings of patients and treatments of MM, including a recent analysis among 487 Brazilians patients diagnosed during the past 7 years.[14]

The C-reative protein is another marker of tumor mass that has been used as prognostic factor. It has a good correlation with tumor growth, and it is independent of the B2 microglobulin levels. Another index score that incorporates this marker is under study.[15]

Other factors that correlate with the outcome include plasma cell morphology, type of bone marrow infiltration, expression of adhesion molecules (CD56), high proliferative activity, and angiogenesis.[16-20]

Recently, various cytogenetic abnormalities present in the myeloma clonal cells were studied, and were strong prognostic factors. By conventional cytogenetic analysis, at least 39% of MM patients exhibit cariotypic abnormalities.[21] With the use of tests with greater sensitivity, such as FISH analysis, several abnormalities have been described, in a greater proportion of patients.[22] Deletions/monosomy of chromosome 13, non-hyperdiploidy, and certain balanced translocations (including chromosome 14) are predictors of poor outcome.[23-25] The deletion or monosomy of chromosome 13 represents the most prevalent abnormality, accounting for 50% of the abnormalities observed. This abnormality occurs in 45% of patients with MM analyzed by molecular technique (FISH analysis),[24,26,27] and its presence is independently associated with poorer survivals and duration of complete remission.[21]

With the addition of all these new molecular profiles to clinical variables, new staging systems may be even more powerful to identify prognostic groups.

Data presented recently by the Intergroupe Francophone du Myelome (IFM 99) showed a high incidence of cytogenetic abnormalities, in agreements with other studies, but they were able to identify three groups of patients with different median overall survivals, according to beta2-microglobulin levels and the presence of t(4;14) or del(17p). The best overall survival was observed among patients with β2-microglobulin levels <3 mg/L and absence of t(4;14) or del(17p). This

profile was observed in 35% of patients. Patients with the worst overall survival (median 2 years) comprised 15% of patients, and included beta2-microglobulin >3 mg/L and the presence of either t(4;14) or del (17q). The other 50% of patients belonged to an intermediate group.[26]

Clinical applicability

The rational of staging a patient is to quickly identify high risk patients, and target the most appropriated therapy for each case. Unfortunately, this is not yet standard of care, but it is a matter of several clinical trials worldwide.[7,25,27-30] A recent study of the IFM based the treatment of MM on the staging of the patients. It suggested dividing patients in two groups, according to β2-microglobulin levels and the presence of chromosome 13 deletion. High risk patients were those with β2 >3 mg/L and the presence of del 13 by FISH analysis.

Patients without these high risk criteria were treated with two consecutive stem cell transplants conditioned with melphalan 140 mg/m^2 and 200 mg/m^2 (IFM 99-02). Patients classified as high risk were enrolled in treatment strategies that included higher doses of chemotherapy (200 and 220 mg/m^2 of melphalan), followed by two autologous stem cell transplants (IFM 99-04) or one autologous and one HLA-identical sibling dose-reduced allogeneic transplant (IFM 99-03). These approaches had an impact in overall survival. The IFM 99-04 showed that in high-risk patients, the dose intensity of melphalan at 420 mg/m^2 led to encouraging results, but the addition of anti-IL6 monoclonal antibody to the second conditioning regimen did not improve the outcome.[25] The IFM 99-04 showed that maintenance with thalidomide after the autologous transplant resulted in an improvement in the event free survival (EFS) in patients without deletion of chromosome 13 and in those with a β-2 microglobulin > 2.5 mg/L. However, this benefit of thalidomide was not observed among patients with deletion of 13 or with β2-microglobulin <2.5. No impact in the overall survival was observed with this maintenance approach.[28]

Treatment based on risk assessment has been also prospective studied by Brazilians researchers. The treatment protocol includes a stratification based on the presence of deletion of chromosome 13 and β2-microglobulin >2.5 mg/L (high risk). For patients without high risk criteria, an induction remission with

chemotherapy is followed by a single autologous peripheral blood transplant using melphalan 200 mg/m^2. Patients are then randomized to receive maintenance treatment with dexamethasone with or without thalidomide. For high risk patients, the protocol consists of a first autologous transplant with melphalan 200 mg/m^2, followed by a second transplant with the same conditioning regimen, or a non-myeloablative allogeneic transplant if the patient has a matched donor. After the second transplant, patients are randomized to receive maintenance treatment with chemotherapy (DCEP) ±thalidomide. Data on the first 107 patients enrolled in this study showed that most patients present with MM in advanced stages (73% Durie/Salmon III, and 45% ISS stage III), and deletion of chromosome 13 was observed in 45% of patients.[27]

Conclusions and recommendations

Staging patients according to prognostic factors has been the subject of several researches and has been used to guide clinical trial protocols. In the future, this approach is hoped to help in defining treatment regimens on a patient basis, with a favorable impact on the prognosis.

The recommendation of recent guidelines on the management of MM[4] includes:

1. The International Prognostic Index based on serum albumin and β2-microglobulin in preference of Durie/Salmon staging system.

2. Evaluate prognosis before starting treatment with, as a minimum, serum levels of β2-microglobulin and albumin. Cytogenetic and/or FISH analysis may be helpful if available.

3. At present there is no evidence to support using prognostic factors to choose therapy in individual patients.

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