Haematologica 1998; 83:708-713 original paper

Multiple myeloma index: verification of a new prognostic approach with evaluation of treatment response

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Abstract

Background and Objective. **Currently adopted prognostic criteria for multiple myeloma (MM) still lack reliable predictive ability to select subsets of patients for different therapies, in particular for intensive treatment protocols. In this work we aimed to test the prognostic value of the MM Prognostic Index (MMPI), developed in 1996 by Grignani *et al.* from Pavia University as a clinical and investigational tool.**

Design and Methods. **Ninety-three MM patients were eligible for the study. All received initial induction therapy based on a standard 6-month melphalan + prednisone (M+P) protocol. Clinical and laboratory parameters, conventional staging and bone marrow infiltration percentage and cytopathology (BMIC) were assessed at diagnosis, while treatment response (TR) was evaluated using criteria after induction therapy. Cox's multivariate survival analysis was applied on prognostic data.**

Results. **In our patients independent prognostic value was confirmed for British Medical Research Council staging, BMIC and TR, the three factors considered in MMPI. Risk classes obtained via MMPI identify patients with different outcomes; moreover, the index discriminates significantly among Stage II patients.**

Interpretation and Conclusions. **This new approach to MM prognosis is simple and reliable from the prognostic point of view; it refers not only to neoplastic mass, but also to intrinsic proliferative capacity of the malignant clone and to tumor-host interactions. We recommend its adoption in clinical practice and in the evaluation and design of therapeutic trials.**

Key words: multiple myeloma, prognosis, staging system, bone marrow pathology, treatment response

Currently adopted staging systems for multiple myeloma (MM) such as Durie and Salmon's,[1] Merlini-Waldenström-Jayakar's[2] and the British Medical Research Council's,[3] still lack sufficient reliability to determine individual patients' prognosis and therefore to be useful in the assessment of individual therapeutic choice. In order to provide a simple and reliable tool for selection of patients for different therapies and comparison of studies, Grignani *et al.* recently proposed a prognostic index for multiple myeloma.[4]

Briefly, this new approach to MM prognosis derives from multivariate survival analysis and is based on the integration of clinical and laboratory features at diagnosis, represented by disease stage according to the *British Medical Research Council* (BMRC) system,[3] bone marrow features such as cytopathology and infiltration percentage[5,6] and as an *ongoing* parameter, evaluation of initial response to conventional treatment schedule.[4,7]

In this work we aimed to verify this new prognostic approach on 93 eligible MM patients and compare its results with presently available staging systems.

Materials and Methods

In this study we considered 93 patients diagnosed as having multiple myeloma (MM) in two Varese hospitals during the last fifteen years. MM was diagnosed on the basis of the presence of at least two of the following criteria: (a) significant serum and/or urinary monoclonal component; (b) presence of skeletal lytic lesions; (c) 10% or more bone marrow plasma cells. All patients were staged according to currently adopted systems: Durie and Salmon's (DS, ref. #1), Merlini-Waldenström-Jayakar's (MWJ, ref. #2) and the British Medical Research Council's (BMRC, ref. #3); in particular, BMRC Stage I is defined by blood urea nitrogen (BUN) ≤ 48 mg/dL, hemoglobin (Hb) > 10 g/dL, and absence of or minimal entity symptoms, Stage III by Hb ≤ 7.5 g/dL or BUN > 61 mg/dL together with symptoms affecting patient's life and activities, while Stage II comprises those patients not fulfilling criteria for Stages I and III. Bone marrow aspirate and biopsy from all patients was used to know the degree of infiltration (plasma cell percentage) and cytologic subtype (plasma cells vs plasmablastic).[5,6] Stage I patients (according to DS staging system) received no treatment unless they had unfavorable clinical features (progressive bone lesions, anemia, recurrent infections) or until evidence of disease progression. Stage II and III patients were administered standard first-line chemotherapy based on melphalan (dose: 8

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Table 1. Response to treatment criteria for multiple myeloma proposed by Grignani *et al.* (1996).

Criteria	
(A):	reduction in MC
(B):	decrease in bone marrow plasma cells ≥ 20% as evaluated on bone marrow imprints before and after treatment
(C):	a ≥ 2 g/dL rise in hemoglobin levels in anemic patients (Hb < 11 g/dL), sustained for more than 4 months
(D):	return of serum calcium and blood urea nitrogen to normal values
(E):	elevation of serum albumin to 3 g/dL or higher (in absence of other causes of hypoalbuminemia)
(F):	no evidence of skeletal lytic lesions progression
Definitions	
Complete response (CR):	>50% reduction of MC + more than half other criteria fulfilled
Partial response (PR):	25-50% reduction of MC more than half other criteria fulfilled
No response (NR):	Other than CR and PR; no evidence of progression
Progression (PROG):	>25% increase in MC and/or ≥ 20% increase in bone marrow infiltration degree and/or worsening of laboratory parameters (hemoglobin, serum calcium, blood urea nitrogen) and/or skeletal lesions

MC: monoclonal component.

Table 2. Assessment of multiple myeloma risk classes according to Grignani *et al.* (1996).

Points = BMRC + BMIC + treatment response

Values for variables cited in equation:

BMRC: 0 if Stage I, 1 if Stage II, 2 if Stage III disease;
BMIC: 0 if bone marrow infiltration < 40% and favorable cytology, 1 if infiltration >40% or unfavorable cytology (plasmablasts), 2 if both infiltration > 40% and unfavorable cytology;
Treatment Response: 0 if positive (complete or partial remission), 1 if negative (no response or progression).

Points obtained are then categorized as follows:

0–1	First risk class
2	Second risk class
3–5	Third risk class

Table 3. How to obtain multiple myeloma prognostic index (MMPI) for each patient.

$$MMPI = 0.5 \times BMRC + 0.5 \times BMIC + 1.5 \times \text{treatment response}$$

Values for variables cited in equation:

BMRC: 1 if Stage I, 2 if Stage II, 3 if Stage III disease;
BMIC: 1 if bone marrow infiltration < 40% and favorable cytology, 2 if infiltration >40% or unfavorable cytology (plasmablasts), 3 if both infiltration > 40% and unfavorable cytology;
Treatment response: 1 if positive (complete or partial remission), 2 if negative (no response or progression).

MMPI values are then categorized as follows:

2.5–3	First prognostic group
3.5–4	Second prognostic group
> 4	Third prognostic group

mg/m^2/die) + prednisone (50 mg/m^2/die). Melphalan+prednisone (MP) cycles, lasting a week each, were repeated every 4-6 weeks until response or disease stabilization. When disease relapse was observed after remission, patients were re-treated according to the same MP schedule; if refractory or showing evidence of progressive disease, and suitable for age and other pathologies, patients received polychemotherapy according to standard M2, Alexanian's or VAD protocols. Patients underwent restaging (including bone marrow re-evaluation), and response to treatment was evaluated using criteria published by Grignani *et al.*[4] after 6 months of initial MP therapy and categorized as complete remission (CR), partial remission (PR), no response (NR) or progression (PROG) (Table 1).

Assessment of multiple myeloma risk classes and prognostic index according to Grignani *et al.* was carried out as shown in Tables 2 and 3, respectively). Follow-up was considered interrupted on August 31st, 1997.

Actuarial survival curves were plotted according to Kaplan and Meier,[8] and comparison between them was obtained via log-rank test.[9] In order to assess independence of the prognostic value of the various factors, Cox's proportional hazards method[10] was applied. Statistical calculations were carried out using the STATA software package.

Results

Our series comprised 93 patients, of whom 46 were males and 47 females; mean age at diagnosis was 67 years (range 33-94 years, SD 15.4 years). Monoclonal component was IgG isotype in 61 patients, IgA in 27; 2 cases produced only urinary Bence-Jones (BJ) light chains and 3 cases were classified as non-secretory myeloma.

At the end of the follow-up period, 84 out of 93 patients (90.3%) were dead. Median survival of the whole series was 38 months. According to the BMRC system, thirty-nine patients (41.9%) were diagnosed as having stage I disease, 43 (46.3%) stage II, and 11 (11.8%) stage III. The BMRC staging system identified groups with different outcomes (Figure 1, $p < 0.001$): median survivals were 64 months for stage I, 30 months for stage II and 12 months for stage III. Durie-Salmon's staging system, too, identified three

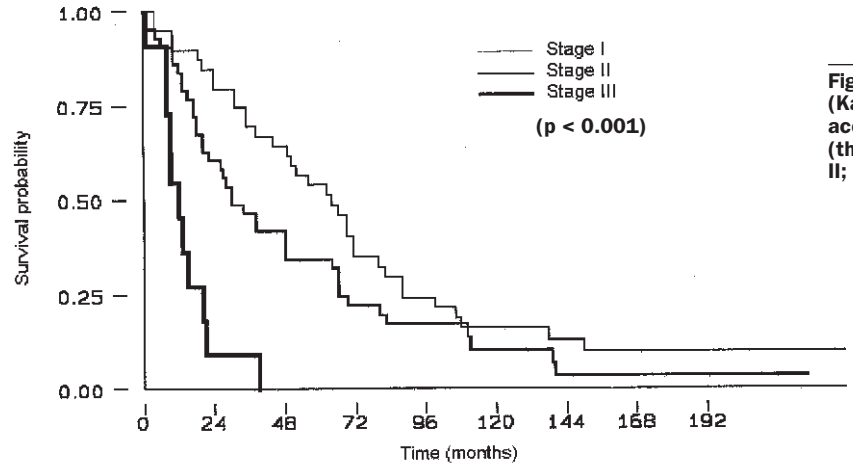

Figure 1. Actuarial survival probability (Kaplan-Meier plot) of 93 MM patients according to BMRC staging system (thin line: Stage I; medium line: Stage II; thick line: Stage III).

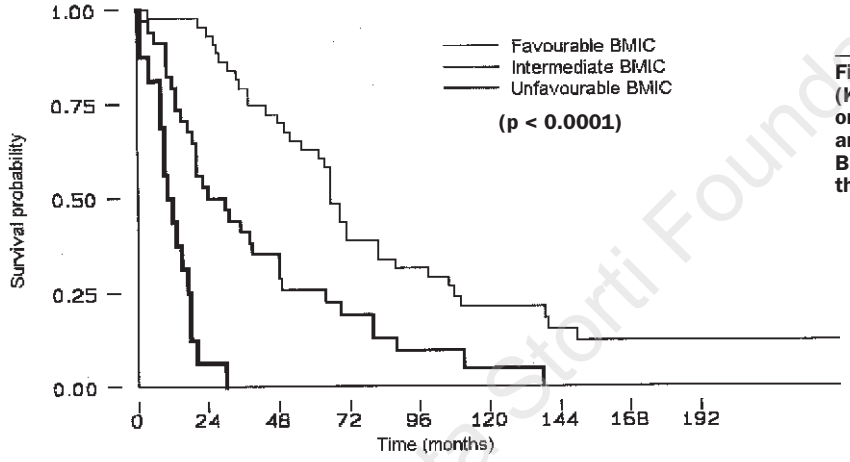

Figure 2. Actuarial survival probability (Kaplan-Meier plot) of 93 MM patients on the basis of bone marrow infiltration and cytopathology (thin line: favorable BMIC; medium line: intermediate BMIC; thick line: unfavorable BMIC)

groups of patients different with respect to prognosis: median survivals were 66 months, 38 months and 13 months for Stages I, II and III respectively ($p < 0.001$). In our series, all three staging systems considered confirmed their prognostic value: the BMRC's showed the best chi-square value ($\chi^2 = 28.35$) compared to Merlini's (16.44) and Durie-Salmon's (14.39).

Bone marrow showed unfavorable cytological features (presence of plasmablasts) in 33 cases (35% of the whole); plasma cell infiltration percentage (BMI%) ranged from 10% to 94% (mean 36.9±14.1%); at diagnosis 33 cases (35%) showed high levels of infiltration (over 40%). Of the patients with plasmablastic MM, nearly half showed high degrees of infiltration (48.4% versus 28.3%); of the cases with elevated BMI%, a similar percentage had unfavorable cytology (Table 4). Bone marrow infiltration plus cytopathology (BMIC), a newly composed parameter proposed to sum the prognostic value of the two most important features of bone marrow examination, retained high prognostic value: median survivals were 66, 24 and 12 months for *favorable* (43 patients), *intermediate* (34) and *unfavorable* (16) BMIC, respectively (Figure 2, $p < 0.0001$). Treatment response (TR) was positive in 64 patients (68.8%) with 39 CRs and 25 PRs and negative in 29 cases (31.2%) with 5 NRs and 24 PROGs. These two groups had very different outcomes (Figure 3, $p < 0.0001$): median survivals were 66 months for responders (CR+PR) and 12 months for unresponsive patients (NR+PROG).

Survival analysis according to Grignani's risk classes (MMRC) resulted in a significant differentiation between three prognostic classes (Figure 4, $p < 0.001$): 51 patients (54.8%) belonged to risk class I, 13 (13.9%) to class II, 29 (31.2%) to class III. Median survivals were 66 months for class I patients, 48 months for class II and 13 months for class III. Survival analysis according to Grignani's prognostic index (MMPI) showed essentially similar distribution among prognostic groups with respect to that among risk classes. A significant differentiation was observed between the three prognostic groups: median survivals were 66 months for Group I patients, 48 months for Group II

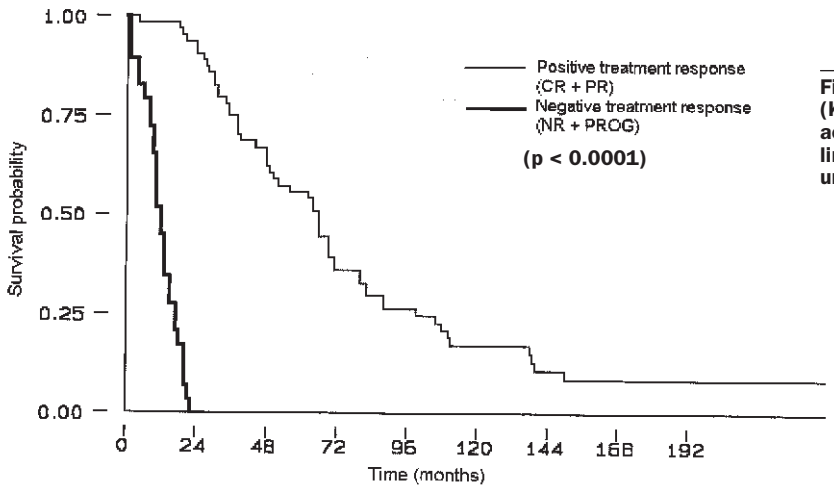

Figure 3. Actuarial survival probability (Kaplan-Meier plot) of 93 MM patients according to treatment response (thin line: responsive – CR+PR; thick line: unresponsive – NR+PROG)

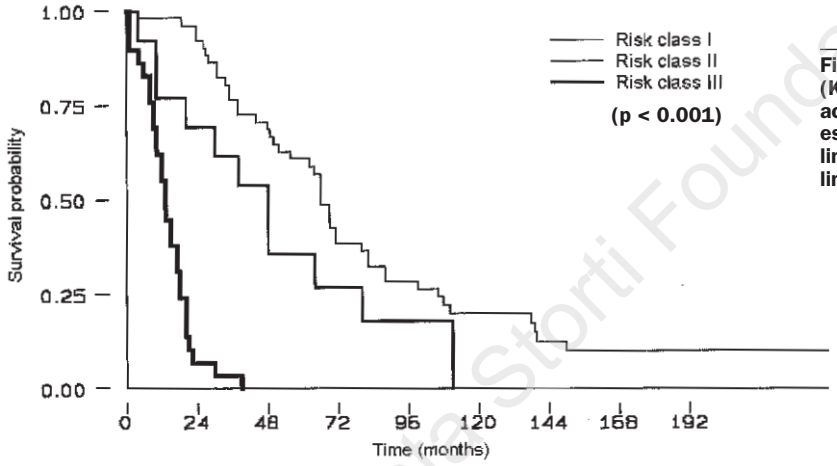

Figure 4. Actuarial survival probability (Kaplan-Meier plot) of 93 MM patients according to Grignani *et al.*'s risk classes (thin line: class I- Low risk; medium line: class II – intermediate risk; thick line: class III – high risk).

Table 4. Relationship between bone marrow infiltration (BMI%) and bone marrow cytopathology (plasmablastic vs. plasmacytic) distributions and roles in determination of BM infiltration-plus-cytopathology (BMIC) parameter.

Bone marrow % infiltration	*Plasmacytic M*		*Plasmablastic MM*		*Total*
Low (<40%)	43*	71.7%	17°	52.6%	60
Elevated (≥ 40%)	17°	28.3%	16#	48.4%	33
Total	60*	100%	33*	100%	93

(Symbol)	*BMIC*	*No. cases (%)*
*	Favorable	43 (46.2%)
°	Intermediate	34 (36.6%)
#	Unfavorable	16 (17.2%)

and 12 months for Group III ($p < 0.001$).

Cox's multivariate survival analysis in our patients confirmed the independence of the prognostic value of BMRC staging, of the BMIC parameter and, when added to the first model tested, of response to treatment. None of the other parameters tested (including age, sex, monoclonal component entity and isotype, light chain, number of bone lesions, hemoglobin, platelets, white blood cells, serum creatinine and calcium, significant Bence-Jones urinary excretion) reached statistical significance (Table 5).

Discussion

Survival duration for multiple myeloma (MM) patients can vary from a few months to many years: physicians would like to have a more precise prediction of survival for the individual patient. It is reasonable to consider more aggressive and toxic therapy for patients with prognostic factors indicating a short survival:[11,12] in particular, during the last few

Table 5. Multivariate survival analysis according to Cox's proportional hazard method. Only significant parameters in univariate analysis are displayed. Highly significant *p* value are underlined.

Prognostic covariate	*Model 1 (p value)*	*Model 2 (p value)*
BMIC	0.000	0.013
Disease stage (BMRC)	0.001	0.030
Response to treatment (TR)		0.000

years various studies described results of bone marrow transplantation (BMT) procedures in MM. High-dose chemotherapy followed by autologous BMT is certainly feasible and efficient, improving response rates, event-free end overall survival according to some authors,[13-16] while peripheral blood stem-cell rescue also yields promising results.[17-19] Meanwhile, small groups of younger patients have undergone allogeneic BMT with interesting outcomes but very high toxicity rates.[20-22]

The multiple myeloma prognostic index (MMPI) with risk classes represents a truly new approach to MM prognosis, and is undoubtedly interesting because it deals with all aspects of tumor study. In our series, all three staging systems considered confirmed their prognostic value: the British Medical Research Council's had the best chi-square value compared to Merlini's and Durie-Salmon's, so the first choice seems appropriate. BMRC staging, while simple to use in everyday clinical practice, generally discriminates different risk groups well: it requires estimating neoplastic mass plus making a consideration of tumor-host interactions by means of symptoms and impact on renal function (renal failure being one of the main causes of death of patients). In our patients, only a small group (11.8%) had Stage III disease, while the vast majority fell in Stage I and II: MMPI helped to discriminate very high-risk cases among patients with clinical intermediate-stage disease: among our 43 BMRC stage II patients, 26 patients with MMPI class I or II had a median survival of 65 months, versus 15 months for 17 patients with MMPI class III (χ^2= 39.4; p < 0.0001).

The creation of a new parameter, bone marrow infiltration plus cytology (BMIC), which retains an important independent prognostic value is undoubtedly interesting, and is evidently related to biological malignancy grade. As we saw earlier, BMIC identifies three groups with very different prognoses. Differently from clinical stage, BMIC is related both to tumor mass (infiltration percentage) and to intrinsic biological tumor features (cytological atypia). Some authors have previously demonstrated prognostic values of BM histo- and cytological features,[23,24] but this information is not currently taken into consideration in assessment of individual prognosis and therapeutic approach. Recently, histologic grading was demonstrated to be significantly linked to a new prognostic factor directly reflecting intrinsic proliferative activity, the plasma cell labeling index (PCLI%), defined as the percentage of monoclonal plasma cells in S-phase measured by bromodeoxyuridine incorporation, and to serum β_2- microglobulin (β_2M) levels:[25] both PCLI% and β_2M hold independent prognostic value in multivariate analysis.[26,27]

Treatment response (TR) obviously correlates with overall survival,[28,29] and is a good indicator of those still poorly understood molecular and cellular events that render a tumor composed mostly of cells either responsive or non-responsive to chemotherapy: TR, too, thus reflects intrinsic malignancy and provides an evaluation of response to further, more aggressive therapies. Moreover, response to conventional chemotherapy and duration of therapy needed for achievement of remission are the most powerful predictive factors for survival in MM patients undergoing myeloablative high-dose chemotherapy followed by autologous BMT[13,15] or peripheral bood stem-cell rescue.[18]

Our results confirm that the two different versions of Grignani's prognostic index (risk classes and prognostic groups) identify patients' prognosis in the same way, as clearly visible from estimates of median survivals (see earlier). We support its authors in recommending widespread use of this new clinical and experimental tool for the assessment of MM patients' prognosis. In particular, risk classes could be applied in clinical practice, while the MM index offers sharp quantitative assessment of risk and could, therefore, be employed as a complex but global covariate in a Cox's proportional hazards analysis applied to a therapeutic trial, so reducing the number of patients necessary to evaluate a new therapeutic proposal.

Contributions and Acknowledgments

RB was responsible for the idea and supervision of the study and directed diagnostic evaluation and therapeutic management of all patients. MT and MEB participated in the clinical management of patients and collected data for the study. MT, in particular, helped in statistical calculations. The three of them contributed to discussion of findings, writing and revising the paper. RB is first and corresponding author in view of his position as head of the Department, and MT follows because of his clinical experience and work in the design and statistical analysis of the study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received February 4, 1998; accepted May 15, 1998.

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