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RESEARCH

The Albumin and Monoclonal Protein Ratio as Prognostic Marker for Multiple Myeloma in the Era of Novel Agents

Katalin Kádár · Krisztina Wolf · Judit Tábori · István Karádi · Judit Várkonyi

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Abstract Multiple myeloma (MM) is a heterogeneous disease group regarding prognosis, clinical course, and response to therapeutic interventions. Numerous prognostic factors have been identified however there was no consensus about the best prognostic indicators or the proper staging systems. In a previous study the A/M ratio containing albumin (A) and monoclonal component (M) emerged as reliable predictor of survival duration in patients treated with conventional chemotherapy. In the current retrospective study authors evaluated the prognostic role of this fraction in the era of novel agents. They assessed the A/M ratio prior treatment in 56 newly diagnosed MM patients from the aspect of the survival time. According to the results the A/M being <1 at the diagnosis indicated significantly poorer prognosis both at the 2 years (p=0,01) and at the 5 years (p=0,07) survival endpoints. These results proved that A/M ratio remained valuable marker for predicting prognosis in patients treated with proteosome inhibitor and antiangiogenic therapy as well. Authors recommend therefore applying this A/M ratio in further studies for the better pre-treatment stratification.

Keywords Multiple myeloma · Prognostic factors · Albumin · M-protein · A/M ratio

K. Kádár (✉)
Kútvölgyi Clinical Centre, Semmelweis University,
Kútvölgyi út 4.,
1125 Budapest, Hungary
e-mail: kadarka@kut.sote.hu

K. Wolf · J. Tábori · I. Karádi · J. Várkonyi
3rd Department of Internal Medicine, Semmelweis University,
Kútvölgyi út 4.,
1125 Budapest, Hungary

Introduction

It has been long observed that MM patients vary significantly in their clinical course like survival duration with a median of 3–4 years, but with a range from less than 6 months to more than 10 years [1, 2]. This variability reflects the heterogeneity of the myeloma cell biology and the influence of multiple host factors. Although during the disease course partial or complete remission can be achieved temporarily, MM is still not a curable disease. Finding suitable prognostic factors and hence the optimum staging system is an issue in clinical medical research. Numerous prognostic factors have been identified as having importance in the pre-treatment evaluation of patients [3–9]. Staging systems have been also developed to separate them into various risk groups with different outcomes [10–19]. However no consensus has been achieved so far. Some of these factors are not easily applicable in the everyday routine work, like plasma cell labelling index (PCLI), or others are expensive, like the genetic testing.

The aim of our study was to identify simple, accurate, reproducible and readily available laboratory parameters as prognostic factors, that effectively guide treatment decisions. In a previous study an A/M ratio, containing albumin (A) and monoclonal component (M) at diagnosis, emerged as a reliable predictor of survival duration in patients treated with conventional chemotherapy [20].The A/M ratio being lower than 1 correlated strongly with poor prognosis and in contrast to this A/M >1 predicted long survival. In the same work authors found that the initial WBC count $<4{,}5\times10^9$/l correlated with poor prognosis as well. Based on this experience they created an AMWBC score system containing the A/M ratio and the WBC count at diagnosis that can be useful to predict survival time (Table 1). In the current study we assessed the role of these prognostic features in the era of novel agents.

Table 1 AMWBC prognostic score index calculation

Score	0	1
A/M	≥1	<1
WBC	$\geq 4{,}5\times10^9$/l	$<4{,}5\times10^9$/l

0 score = good prognosis
1 score = intermediate prognosis
2 score = poor prognosis
A/M≥1 = 0 score
A/M<1 = 1 score
WBC≥$4{,}5\times10^9$/l = 0 score
WBC<$4{,}5\times10^9$/l = 1 score
Patient having A/M≥1 and WBC≥$4{,}5\times10^9$/l, the AMWBC score = 0
Patient having A/M<1 and WBC<$4{,}5\times10^9$/l, the AMWBC score = 2
Patients having either of factor 1, the AMWBC score = 1
Cited from: Várkonyi et al, POR 2008

Patients and Methods

In this retrospective analysis records of 126 consecutive patients in whom multiple myeloma was newly diagnosed between January 1996 and July 2006 were reviewed. To get enrolled in the study, patients were required to be originally diagnosed, followed, and treated in our university hospital. Patients were excluded if they had any other plasma proliferate disorders like monoclonal gammopathy of uncertain significance, smoldering myeloma or amyloidosis, or if they had a concomitant malignant disease at the same time when MM was diagnosed. Exclusion criteria were moreover to be transplanted during the clinical course. In case of light chain disease and non secretor myeloma the A/M ratio can not be interpreted, therefore these patients were not enrolled in the study as well. Finally 103 patients met all these criteria. From the total of the 103 patients 47 were given only convetional therapy and 56 persons were treated either with new treatment modalities like thalidomide, bortezomib alone or in combination with conventional agents. Patients' characteristics are summarized in Table 2. The pre-treatment A/M ratio, WBC count and the so called AMWBC score was determined in all cases, and correlated to the survival. Survival time was considered from the date of the diagnosis until the date of death, or the date of the last follow up. Surviving patients were censored at year 2 and at year 5 to be alive. Kaplan-Meier analysis was used for analyzing overall survival, and differences between groups were tested for statistical significance using the 2-tailed log-rank test [21].

Results

Our results show that those patients who had A/M<1 at diagnosis have significantly poorer prognosis either at the 2 years (p=0,006) and at the 5 years (p=0,005) survival endpoint as well in the total of 103 patients (Fig. 1). The same significant difference was observed in the 56 patients treated with the novel agents (p=0,01 and p=0,07 respectively) (Fig. 2). In our present study in the group of the 56 patients who received novel treatment modalities, there was no significant correlation between the initial lower WBC count and the survival time (Fig. 3). When the patients were selected according to the so called AMWBC score system, three group emerged that showed statistical difference only at the 5 years survival period (p=0,056). However, further analysing this result, the poor prognostic group (AMWBC score=2) identifies 67% of those patients who live not more than one year; 81% of patients in the intermediate prognostic group (AMWBC score=1) live longer than two years, and 80% of the good prognostic group (AMWBC score=0) patients live 55 months (Fig. 4).

Table 2 Patients' characteristics

	All patients (n=103)	Patients treated with novel agents (n=56)
Male	36 (35%)	16 (29%)
Female	67 (65%)	40 (71%)
Mean age	67,76 years (45–89)	66,87 years (46–89)
IgG	74 (72%)	47 (84%)
IgA	27 (26%)	9 (16%)
IgM	1 (0,9%)	0 (0%)
IgD	1 (0,9%)	0 (0%9
kappa	74 (72%)	44 (79%)
lambda	29 (28%)	12 (21%)
Mean survival	46,5 months (1–204)	50,7 months (1–205)

Discussion

Availability of expanding therapeutic modalities in MM underlines the importance of the best selection of patients for targeted treatments based on their risk categories. There has not been so far consensus on the proper and widely acceptable prognostic indicators that help making the best pre-treatment decision. According to our results the A/M ratio seems to be appropriate for this purpose and can be one of those features that have remarkable prognostic significance. According to our results the patient subgroup having A/M<1 at diagnosis have significantly poorer prognosis while A/M >1 refers on longer survival. Both parameters of the fraction have already been used in previous clinical staging systems but only one by one. Bladé et al. used the albumin and the BUN as an important prognostic marker [10]. The M-component referring on the amount of the tumour mass is a good tool for monitoring the effectiveness

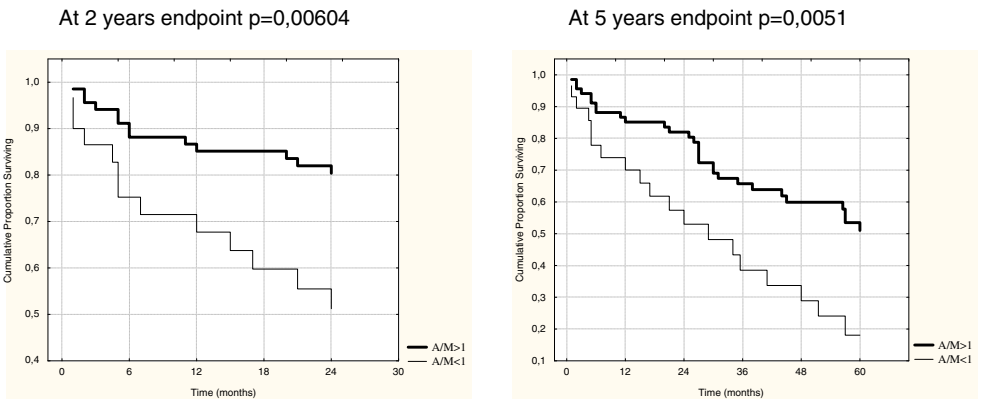

Fig. 1 A/M ratio and survival in all MM patients ($n=103$)

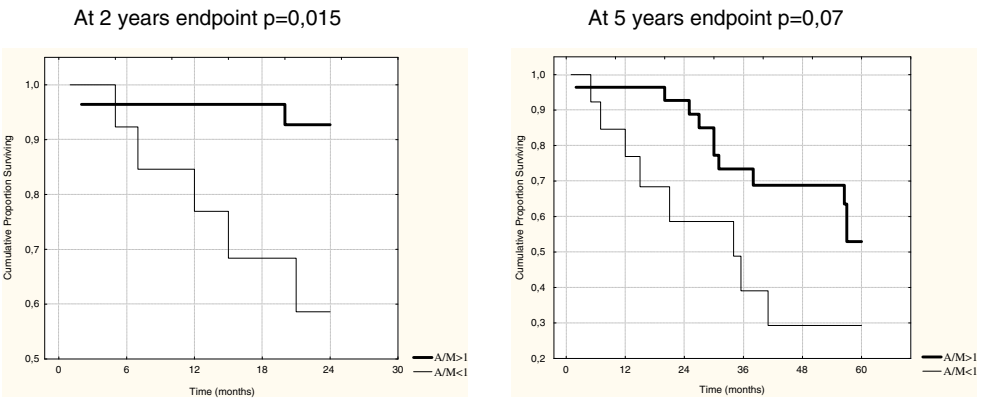

Fig. 2 A/M ratio and survival in MM patients treated with novel agents ($n=56$)

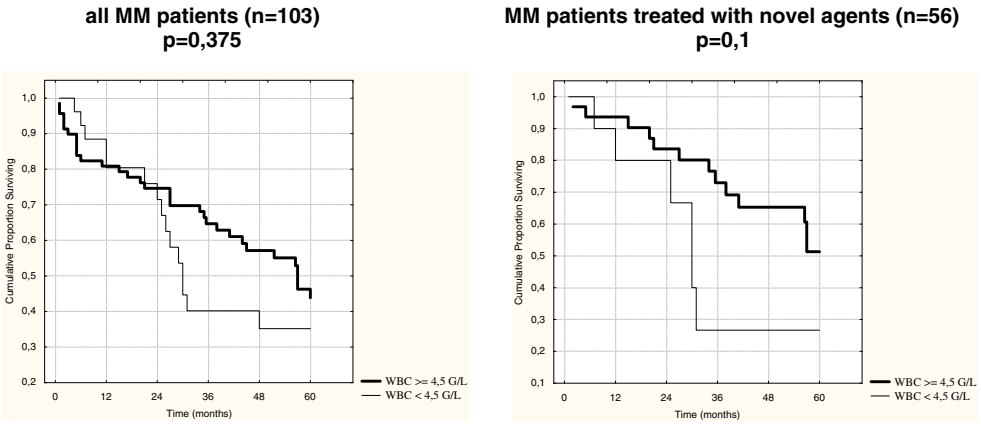

Fig. 3 Initial WBC count and survival at 5 years endpoint

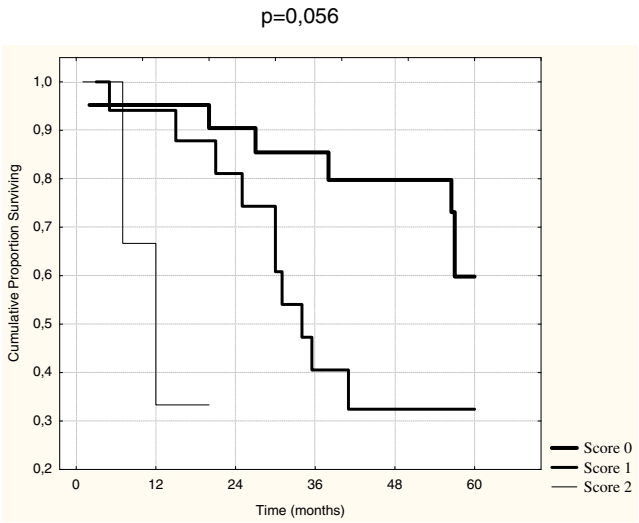

Fig. 4 Survival at 5 years endpoint according to the AMWBC score in patients treated with novel agents (n=56)

of the therapy and it was incorporated in the Durie Salmon model [12]. The most frequently used International Staging System (ISS) is based on the albumin and the beta-2 microglobulin level, however renal failure devaluates its significance [14]. In the previous study that served as a model for our present work, Várkonyi J et al proved for the first time in the literature the A/M ratio as a reliable prognostic marker in newly diagnosed patients treated with conventional chemotherapy [20]. Both markers reflect the effect of the IL-6 cytokine having central role in the pathomechanism of the disease: increasing the amount of the monoclonal protein produced by the plasma cells proliferating in the bone marrow, and inhibiting the albumin synthesis in the liver in the same time. Expressing this dual effect in the form of fraction provides more featured description of the disease.

In our present study we could confirm the prognostic role of the A/M ratio both in the case of all the 103 patients (47 of them were treated only with conventional therapy) and in those 56 patients who were treated both with conventional and novel agents. In contrast, there was no significant correlation between the initial lower WBC count alone and the survival time neither at the 2 years, nor at the 5 years survival endpoints. In the model study coexisting myelodysplastic syndrome (MDS) was suspected as a reason of the initially low WBC count in myeloma that was shown to be independent from the bone marrow infiltration rate. The favourable influence of the new therapeutic modalities had been introduced in both MM and MDS might neutralize the prognostic role of the WBC in the score and this would support the previous hypothesis. In the era of the novel biological agents authors recommend applying the A/M ratio in further studies for the better pre-treatment stratification and they consider that A/M and AMWBC score both useful to separate the poor prognostic group of patients who requires more aggressive therapy.

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