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The Prognostic Value of Classical Immunoparesis in Multiple Myeloma

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ABSTRACT

Multiple myeloma (MM) is a very heterogeneous hematological malignancy characterized by the proliferation of clonal plasma cells in bone marrow, leading to a decrease in normal plasma cells. The immune system plays a key role in both the pathogenesis and the prognosis of MM. A wide range of immune dysfunctions can be demonstrated in most patients at diagnosis. The presence of suppression of uninvolved immunoglobulins, also called classical immunoparesis (CIP), can be demonstrated in the majority of newly diagnosed MM (NDMM) patients, although its prognostic impact remains controversial in previous studies. Our population-based study confirms that CIP is present in most NDMM patients. It is associated with several well-known prognostic factors, including the International Staging System, being more frequent in late stages. Median overall survival in CIP+ patients was 62.4 months (CI 95%, 52.1-72.7), whereas it was not reached for those CIP- (p=0.150). Despite the absence of statistical significance, the multivariate Cox proportional hazards model endorses CIP as an independent and strong prognostic factor for overall survival in NDMM, besides age, performance status, total serum cholesterol, and the presence of 1q gain. More comprehensive studies, including complete immune profiling, are warranted to establish the role of CIP in the context of the current and emerging prognostic factors in NDMM.

Keywords: Multiple Myeloma, Prognosis, Immunoparesis, Classical Immunoparesis, Overall Survival.

INTRODUCTION

Multiple myeloma (MM) is a very heterogeneous and complex multistep malignancy [1]. Most newly diagnosed MM (NDMM) patients are virtually preceded by a precursor disease, mainly monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM) [2].

The current definition of MM [3] is based on the demonstration of 10% or more clonal bone marrow plasma cells (cPC) or a biopsy-proven plasmacytoma and at least one of the so-called MM-defining events. MM defining events are divided into two groups: evidence of end-organ damage attributed to the underlying cPC proliferative disorder (hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesions) and the presence of a biomarker of malignancy (60% or more cPC, 100 or more involved/uninvolved serum-free light chain ratio, or more than one focal lesion on magnetic resonance imaging). A monoclonal protein (M protein) secreted by the cPC can be shown in blood and/or urine in most patients. The M protein can be an intact immunoglobulin (Ig) leading to the most frequent type of MM, the intact Ig MM (IIMM). Sometimes only a free light chain (FLC) can be demonstrated, the so-called light chain MM (LCMM). More rarely, some patients secrete M protein in quantities below "measurable," and others have no detectable M protein by standard methods, constituting the oligosecretory MM and the non-secretory (NSMM) subtypes, respectively.

Despite tremendous progress being made in recent years, our knowledge about the pathogenesis of MM remains limited. In addition to genetic mutations and clonal evolution, a loss of effective immune surveillance may drive malignant transformation. The complex interaction of cPC with the bone marrow microenvironment contributes to expanding the immunosuppressive cell populations [4]. Consequently, a progressive increase in M protein (the involved Ig in IIMM or the involved FLC in LCMM) and a decrease in the uninvolved Igs (uIgs) are expected in untreated MM patients. This reduction below the lower limit of normal for one or more uIgs is termed classical immunoparesis (CIP) to differentiate it from the immunoparesis (IP) measured by the Heavy/Light Chain (HLC) assay, which measures the uninvolved pair of the same isotype (isotype-matched IP) or other isotypes [5]. The CIP may be present in approximately 25%, 50%, and more than 80% of MGUS [6], SMM [6,7], and MM patients [8-13], respectively. CIP has been associated with the risk of transformation to MM of precursor diseases, the risk of infection, and a poor outcome in MM in terms of overall survival (OS) in some studies. On the other hand, the potential recovery of the IP after treatment is interpreted as a reconstitution of the immune system, and it has been related to a better outcome in MM [14].

MM remains a largely incurable and challenging disease. Recent efforts have been focused on immunotherapy in order to reach not only deeper and more lasting responses but also to achieve a reconstitution of the immune system. A complete roadmap should be implemented to make the dream of curing MM come true [15].

Here we report a single-center population-based prospective observational study in a large series of MM patients to assess the prognostic impact of baseline CIP in terms of OS and early mortality.

MATERIALS AND METHODS

All NDMM diagnosed at the University Hospital Virgen de las Nieves in Granada, Spain, between 2013 and 2019, covering a reference population of 327,751 inhabitants (annual official report, 2012), that fulfilled the International Multiple Myeloma diagnostic criteria and had baseline serum Igs available have been included in the study. All patients were enrolled in the MM clinical registry that was created in 2011, as well as in the population-based Granada Cancer Registry, working since 1985. The follow-up was carried out until December 31, 2020.

All common baseline prognostic variables were recorded, including a comprehensive comorbidity assessment, as previously described [16].

The presence of baseline CIP was defined as a reduction in the level of one or more uIgs less than the lower limit of the normal range (IgG 700, IgA 70, and IgM 40 mg/dL, respectively, in our clinical laboratory) at the moment of diagnosis.

Comparisons of quantitative variables according to CIP status were performed using the t-Student test or the Mann-Whitney non-parametric test, depending on the result of the normality test on the variable. For the comparison of qualitative variables, the chi-square test was used. Quantitative variables were represented by mean and standard deviation.

According to Kaplan-Meier methodology, OS was estimated in months (m) with their 95% confidence intervals (95% CI). Log-rank test was used to analyze the statistical significance of differences between groups. Early mortality was defined as mortality in the first six months.

Cox proportional hazards were used to calculate hazard ratios (HR) for each variable. For multivariate analysis, factors with prognostic significance at 0.15 level were introduced into a Cox proportional hazards model (backward analysis). All P-values were two-sided. No imputation for missing data has been used.

Analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20.0 software (SPSS Inc., IBM Corp., Armonk, NY, USA).

RESULTS

264 MM patients have been included in the MM clinical registry during the period of study, 242 (91.7%) NDMM and 22 (8.3%) SMM. The median age was 67 years (range, 36-93; IQR, 58-76). 197 (81.4%) NDMM and 14 (63.6%) SMM were CIP positive. One hundred forty-two patients were men (53.8%). Clinical characteristics of patients are shown in Table 1.

Table 1: Clinical characteristics of multiple myeloma patients.			
Variable	**n**	**%**	**CIP, %**
MM	264	100	
-NDMM	242	91.7	197 (81.4)
-SSM	22	8.3	14 (63.6)
Age, years Median, range	67(36-93)		
Sex			
-Men	142	53.8	78.2
-Women	122	46.2	82
Subtype			
-IgG	144	54.5	77.8
-IgA	60	22.7	90
-IgD	5	1.9	80
-IgM	1	0.4	-
-CLMM	47	17.8	78.7
-NSMM	6	2.3	50
-Biclonal	1	0.4	-
ISS			
-I	74	28	71.6
-II	67	25.4	77.6
-III	117	44.3	87.2
-Missing	6	2.3	-

CIP: classical immunoparesis; CLMM: light chain MM; Ig: immunoglobulin; ISS: International Staging System; MM: multiple myeloma; NDMM: newly diagnosed MM; NSMM: non secretory MM; SMM: smoldering MM.

The comparative association of CIP positive versus negative patients with other prognostic variables is represented in Table 2. Other variables such as serum creatinine, lactate dehydrogenase, total cholesterol, platelet count, and chromosome one cytogenetic abnormalities did not reach statistical significance.

Table 2: Association of classical immunoparesis (CIP) with other quantitative prognostic variables*.			
Variable	**CIP+**	**CIP-**	**p**
Age, years	67.2 / 11.9	63.3 / 11.1	0.033
Albumin, g/dL	3.5 / 0.7	3.8 / 0.7	0.016
Hemoglobin, g/dL	11.1 / 2.2	12.6 / 2.3	<0.001
ANC, x10^3/µL	3.9 / 2.4	5.7 / 9.1	0.013
cPC (BM), %	25.4 / 21.1	15.2 / 20.2	0.002
BMI, Kg/m^2	28.0 / 4.1	26.8 / 4.4	0.091

*Mean and standard deviation values are shown. ANC: absolute neutrophil count; BM: bone marrow; BMI: Body mass index; CIP: classical immunoparesis; cPC: clonal plasma cells

The presence of CIP is significantly higher in NDMM (81.4%) versus patients with SMM (63.6%), p=0.046. Regarding ISS, we found a significantly elevated percentage with each stage, p=0.026 (Figure 1). With respect to the subtype, the higher percentage of CIP is demonstrated in the IgA subgroup. CIP is associated with some well-known negative prognostic factors. Patients with CIP are significantly older than those without CIP. Their absolute neutrophil count, mean albumin, and hemoglobin are significantly lower, whereas their mean cPC infiltration in bone marrow is higher. With respect to the body mass index, there is only a discrete trend to overweight in patients with CIP.

At the end of the follow-up, 97 NDMM CIP+ patients (40.1%) have died, being infection associated with mortality in 45.8% of cases. Median OS in CIP+ patients was 62.4 m (CI 95%, 52.1-72.7), whereas it was not reached for those CIP- (p=0.150) (Figure 2). We also did not find statistically significant differences with respect to early mortality according to CIP.

Univariate and multivariate Cox proportional hazards analyses are shown in Table 3. Remarkably, CIP is the variable with the strongest hazard ratio and associated p-value among the five variables included in the final model. On the other hand, this model emphasizes the negative impact of 1q gain, which is the most frequent cytogenetic abnormality in NDMM.

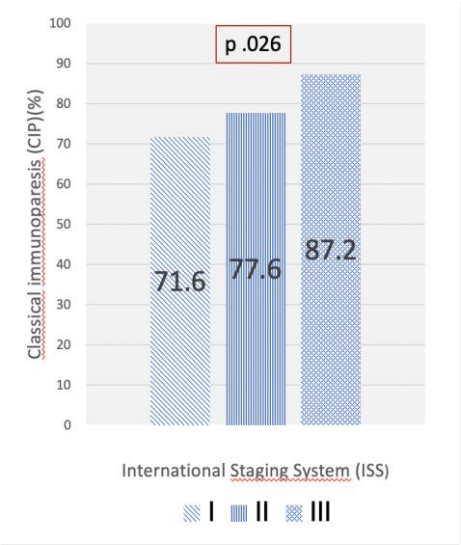

Figure 1: Presence of classical immunoparesis (%) according to the International Staging System.

Table 3: Univariate and multivariate Cox Proportional hazards analysis for overall survival.

	Univariate Analysis			Multivariate Analysis		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.06	1.04-1.08	<0.0001	1.06	1.01-1.10	0.024
ISS	2.10	1.59-2.79	<0.0001	-	-	-
ECOG	1.71	1.43-2.06	<0.0001	1.77	1.17-2.69	0.007
sCr	1.14	1.07-1.22	<0.0001	-	-	-
Hb	0,84	0.77-0.92	<0.0001	-	-	-
CMs	1.26	1.14-1.40	<0.0001	-	-	-
HD	2.76	1.80-4.23	<0.0001	-	-	-
RD	2.32	1.46-3.69	0.001	-	-	-
LDH	1.00	1.00-1.00	0.015	-	-	-
sChol	0.99	0.99-0.99	0.019	0.99	0.98-0.99	0.006
LD	2.14	1.17-3.91	0.025	-	-	-
Plt	0,99	0.99-1.00	0.035	-	-	-
CRP	1.00	1.00-1.01	0.060	-	-	-
1q gain	1.82	0.93-3.56	0.078	2.39	1.01-5.65	0.047
BMPC	1.01	1.00-1.02	0.086	-	-	-
1p del	2.31	0.89-5.98	0.118	-	-	-
CIP	1.50	0.85-2.64	0.141	10.28	3.29-32.15	<0.0001

BMPC: bone marrow plasma cells (by next-generation flow); CIP: classical immunoparesis; CMs: number of comorbidities; CRP: C-reactive protein; del: deletion; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; HD: heart disease; ISS: International Staging System; LD: liver disease; LDH: lactate dehydrogenase; Plt: platelets; RD: respiratory disease; sChol: serum cholesterol; sCR: serum creatinine.

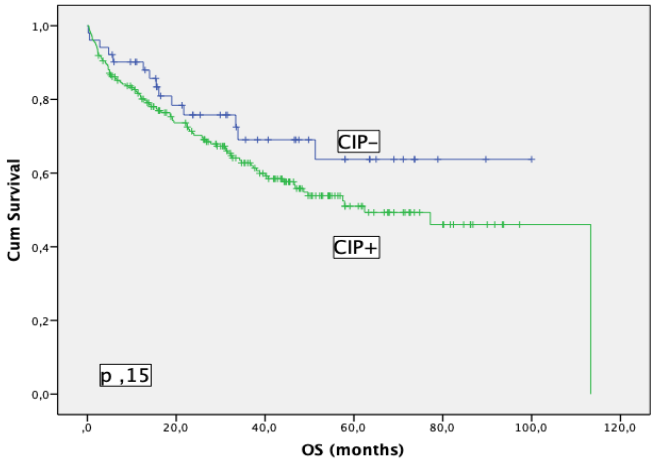

Figure 2. Overall survival according classical immunoparesis status in multiple myeloma.

DISCUSSION

The prognosis in MM depends on four categories of variables, those related to the biology of the disease, those associated with the characteristics of the patient, the stage, and the response to the treatment. The first is the largest group, given that the number of laboratory-based prognostic factors is continuously growing. The CIP belongs to this group.

Quantitatively, the percentage of CIP+ patients of SMM in our study is somewhat higher than the reported by Pérez-Persona E et al. (52%) [6], and the pointed out in the cohort of the Czech Myeloma Group by Hájek R and colleagues (51.5%) [7]. This is probably due to the small number of SMM in our series. On the other hand, the percentage of CIP+ NDMM in our study is similar to the previously reported by other groups, usually greater than 80% [5].

The prognostic value of CIP in NDMM remains controversial, provided that some studies can show statistically significant differences in OS [8,10,12], but others are not [9,11,13]. However, some studies use different cut-offs for CIP, changing the above baseline definition. Overall, the deeper the immunosuppression, the higher the prognostic impact.

Our study was performed in a university hospital with a specific monoclonal gammopathies unit and a MM clinical registry associated with a consolidated population-based cancer registry [16,17]. The analysis highlights the importance of CIP and confirms its association with other well-known negative prognostic factors in NDMM. Nonetheless, as it happens in other studies, we do not find statistically significant differences in median OS, even though the curves are clearly separated from the beginning. Interestingly, the multivariate analysis for OS shows that CIP is an independent prognostic factor besides age, performance status measured by the ECOG (Eastern Cooperative Oncology Group) score, total serum cholesterol, and the presence of 1q gain by fluorescence in situ hybridization. Our study emphasizes the need to establish a comprehensive approach to analyze OS, including Cox proportional hazards analysis.

This study has some limitations. First the relatively small sample size. Second, using an incomplete cytogenetic panel in the first four years of the study precludes a complete assessment of cytogenetic risk. Third, a complete clinical evaluation of infection is lacking; however, infection remains a key cause of mortality in our cohort.

A consolidated body of evidence shows that the HLC assay is a better tool to assess IP than conventional methods [5]. As Koulieris and colleagues [13] stated a decade ago, the HLC assay may conceivably replace “classical” total Ig quantitative measurements in the future. Moreover, the impact of the HLC assay to predict the risk of severe infection and even early mortality has been recently reported [18].

CONCLUSION

In conclusion, our data suggest that CIP is an independent and strong prognostic factor in MM that should be included in the baseline workup and monitoring of both NDMM and SMM. When IP is measured by conventional methods (CIP), it is present in most patients at the moment of diagnosis, and it is associated with a higher tumor burden. Despite this, we recommend that more specific alternatives such as the HLC assay should be used instead.

The immune profiling may play a crucial role in the outcome of MM [19], but probably only a complete immune evaluation will successfully predict survival in MM patients [20].

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