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R-ISS and NLR-ISS can Predict Time to Treatment in Smoldering Myeloma

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Abstract

Objectives: We recently identified the ratio between absolute neutrophils count and absolute lymphocyte count, NLR ≥ 2, combined to ISS as a predictor of progression free survival (PFS) and overall survival (OS) in patients younger than 65 years with symptomatic Multiple Myeloma (MM). We retrospectively examined the NLR-ISS in 165 consecutive smoldering Myeloma (sMM) accessed our Center between January 2004 and June 2014.

Methods: NLR was calculated using data obtained from the complete blood count (CBC) at diagnosis and subsequently correlated with time to treatment (TTT) for symptomatic MM. All patients underwent to bone marrow evaluation to estimate plasma cells infiltration (BMPC) and cytogenetic alterations detectable by FISH, Magnetic Resonance Imaging (MRI) to detect bone lesions, serum free-lite chain evaluation (sFLC). Patients with bone marrow plasma cells >60% or lytic lesions at MRI were excluded from further analysis.

Results: We identified 127 patients with sMM defined accordingly to the updated IMWG 2015 guidelines. The median NLR was 1.7 (range 0.6-10.5), lower than the value previously found for MM 1.9 (range 0.4-15.9, p=0.005. Higher NLR was independent from ISS stage, BMPC amount, high-risk FISH and sFLC.

Using NLR ≥ 2 we could not predict TTT. Indeed, in univariate analysis only BMPC ≥ 30% (p=0.003), albumin <3.5 g/dL (p=0.008), beta-2 microglobulin >3.5 g/L (p=0.0001), ratio of uninvolved/involved sFLC (p=0.0002), immunoparesis (p=0.016) and LDH (p<0.0001) could predict TTT. In multivariate analysis, these three parameters were independent (p<0.0001). In multivariate analysis, LDH and beta-2 microglobulin were weak but significant independent predictors of outcome. Since both are part of R-ISS, we applied ISS, R-ISS and NLR-ISS to identify TTT at 60 months. R-ISS resulted the strongest system to distinguish patients in stage I and stage II with TTT at 60 months respectively 92% and 62.7% (p=0.0002). NLR-ISS could distinguish patients in stage I and stage II with TTT at 60 months respectively 91.9% and 67.8% (p=0.007).

Conclusion: We could not confirm previously proposed parameters to predict time to treatment using the new definition of sMM. However, ISS and its improved variants R-ISS and NLR-ISS were able to identify patients in stage I with excellent outcome at 60 months. Prospective larger series are needed to use R-ISS to identify high-risk sMM.

Keywords: Smoldering multiple myeloma; ISS; R-ISS; NLR-ISS

Introduction

More than fifty years ago, Alexanian et al. described twenty patients affected by Multiple Myeloma (MM) with low tumor mass disease who were asymptomatic, with a hemoglobin level greater than 10 g/dL, and with not more than 3 lytic bone lesions or compression fractures or recurrent infection. These patients were defined as having an indolent MM [1]. Since then, the two terms of Smoldering and Indolent myeloma were variably used in an undefined manner until 2003 when the IMWG defined smoldering MM (sMM) as BMPC ≥ 10% and/or M protein level ≥ 30 g/L and lack of end organ damage (CRAB-hypercalcemia, renal failure, anemia, and bone lesions) [2].

SMM is distinguished from MGUS based on the level of serum M protein and the percentage of clonal BMPCs. SMM accounts for about 15% of all the patients with newly diagnosed MM [3] and the risk of progression to symptomatic MM is higher compared to MGUS patients (10% per year versus 1% per year, respectively) [4,5].

The disease definition of sMM was recently updated to exclude patients with bone marrow plasma cells of 60% or higher, serum involved/uninvolved FLC ratio of ≥ 100, and those with 2 or more focal lesions (typically indicating focal bone marrow abnormalities) on magnetic resonance imaging [6]. Such patients have an approximately 40% per year risk of progression and are now considered as MM [6].

A major prognostic system used in active MM is the International Staging System (ISS) which was developed using survival data from patients treated from 1981 through 2002 [7]. The ISS combines serum 2-beta-microglobulin and albumin levels to classify patients into three groups with different overall survival (OS) outcomes. Recently, in combination with lactate dehydrogenase levels and high-risk chromosomal aberrancies detected by FISH, revised- ISS (R-ISS) can identify patients with high risk of early MM - related death [8].

Since ISS does not take into account the role of the tumor microenvironment in sustaining MM recurrence and long-term survival in MM is associated with a distinct immunological profile [9,10], we recently investigated the neutrophil to lymphocyte ratio (NLR) in active MM patients treated up-front with novel agents [11].

We found that NLR-ISS could predict at diagnosis three groups (very-low, standard-risk and very-high risk) with the 5-year estimates for PFS at 39.3%, 19.4% and 10.9% and 95.8%, 50.9% and 23.6% for OS [11].

SMM is a biologically and clinically heterogeneous disease. Unfortunately, at this time, there is no single pathologic or molecular feature that can reliably distinguish patients with sMM who have only premalignant plasma cells from those with a clonal malignant disease. The evaluation of the risk of progression to symptomatic disease, actually based on some parameters derived from retrospective studies to be validated in prospective series [12].

The only two models validated in prospective interventional trials, respectively from Mayo Clinics (based on serum M protein and the extent of bone marrow involvement [4]) and the Spanish group (based on presence on an aberrant plasma cell immunophenotype in >95% of clonal PCs and immunoparesis [13]) do not overlap and there are many patients that are differently classified according the two models. Dispenzieri and colleagues have shown that the prognostic value of the initial Mayo Clinic model can be improved by adding the serum FLC ratio as a variable [14].

The aim of our study was to define in a single-center retrospective series of sMM patients identified according the new IWMG criteria the prognostic meaning of clinical variables available in the routinely clinical practice and ISS, R-ISS and NLR-ISS to predict time to first treatment for progression in active myeloma.

Material and Methods

Patients

Our retrospective analysis included 165 sMM patients evaluated at the AOUP Vittorio Emanuele, Catania between January 2004 and June 2014. All patients provided written informed consent before entering the study, performed in accordance with the Declaration of Helsinki. Ten patients were excluded for presence of bone lesions at MRI or plasma cell infiltration greater than 60%, considered as active MM according to the last recommendation consensus.

Twenty-eight patients were excluded for lack of FISH analysis, due to artefact in samples or insufficient material, or missing sFLC evaluation. Thus, the analysis was limited to a cohort of 127 patients with median follow-up of 50.7 months (range 26.2-110.4).

In all patients, complete blood count (CBC) and routine biochemical examinations were taken at diagnosis and NLR was calculated using data obtained from the CBC differential count.

Statistical methods

Logistic regression was used to evaluate the time to first treatment for active MM (TTT) from the time of inclusion in the study.

Independent variables were the following: age, β2-microglobulin and albumin levels, ISS, lactate dehydrogenase (LDH) relative to normal levels and adverse cytogenetics defined as t (4;14) or del (17p) by fluorescent in situ hybridization (FISH) as part of R-ISS, serum involved/uninvolved free light chain ratio, NLR, myelomatous bone marrow infiltration and dosage of immunoglobulins. Immunoparesis was defined as reduction of two uninvolved immunoglobulin isotypes.

Qualitative results were summarized in counts and percentages. Descriptive statistics were generated for the analysis of results and a p-value under 0.05 was considered significant.

The Kaplan–Meier method was used to estimate progression-free survival (PFS) and OS. PFS was defined as the maximum time from either the start of diagnosis or the start of treatment date to the occurrence of death from any cause, disease progression or relapse, or censored at the date of last contact.

All analyses were performed using Graph Pad Prism version 6.00 for Windows, Graph Pad Software, San Diego California USA, www.graphpad.com, except proportional hazards model analyses which were performed using R programming language (R 2.15.0, Vienna, Austria).

Results

We identified 127 patients with sMM defined accordingly to the updated IMWG guidelines [6]. Baseline characteristics of patients are listed in Table 1.

Characteristic	Patients N=127 (100%)
Median age, years (range)	63 (26-86)
Males, N (%)	62 (49)
Paraproteins (isotype), N (%)	
Immunoglobulin G	107 (84)
Immunoglobulin A	16 (12)
Immunoglobulin D-M	4 (4)
Light chain only	0 (0)
Immunoparesis N (%)	52 (41)
sFLC involved/uninvolved ratio (range)	2.3 (0.4-42.6)
Paraprotein g/dL (range)	1.2 (0.15-3.7)
Plasma cells in the bone marrow (range)	15 (10-55)
WBC, cells/mmc (range)	6130 (3000-13500)
ANC, cells/mmc (range)	4615 (1290-10170
ALC, cells/mmc (range)	2819 (970-5380)
NLR (range)	1.7 (0.6-10.5)
Cytogenetics (FISH, IWMG criteria)	
No chromosomal aberrancies	86 (68%)
Standard risk chromosomal aberrancies	35 (27%)
High risk chromosomal aberrancies(del17p, t(4;14) t (14;16))	6 (5%)
Serum albumin, g/dL (range)	3.9 (2.2-4.9)
Beta-2 microglobulin, mg/L (range)	2.3 (0.2-7.4)
LDH U/L (range)	280 (123-560)

Table 1: Characteristics at diagnosis of 127 sMM.

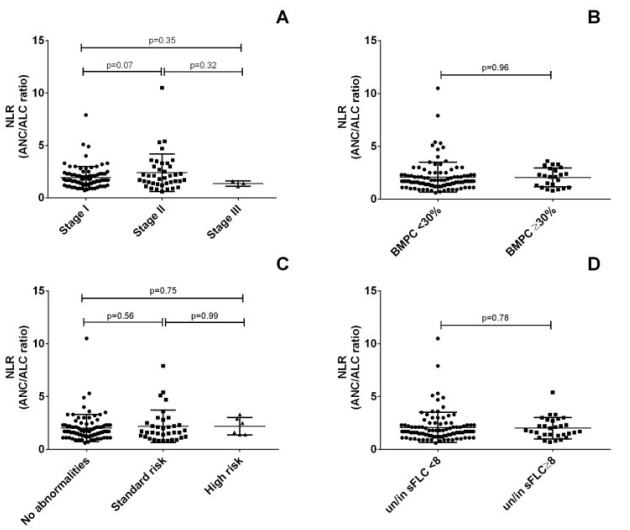

Figure 1: NLR in sMM patients based on ISS stage (A); plasma cells infiltration in bone marrow (B); FISH (C) and sFLC (D).

Median age was 63 (range 26-86). The largest part of patients was I stage according to ISS, IgG isotype. 52/127 (41%) patients carried immunoparesis. Median plasma cells infiltration was 15 % (range 10-55).

An abnormal karyotype was observed in about one third of cases. High-risk chromosomal abnormalities were observed in 6/127 (5%) patients.

By definition, beta-2 microglobulin and albumin to assess ISS stage, FISH and LDH to assess R-ISS and NLR levels were available for all the patients.

The median NLR was 1.7 (range 0.6-10.5), lower than the value previously found for MM 1.9 (range 0.4-15.9, p=0.005, [11]).

As previously shown for active MM at diagnosis [11], a higher NLR did not correlate with ISS stage, plasma cell infiltration or an adverse karyotype, neither uninvolved/involved sFLC ratio ≥ 8 (Figure 1).

In univariate analysis only BMPC ≥ 30% (p=0.003), albumin <3.5 g/dL (p=0.008), beta-2 microglobulin >3.5 g/L (p=0.0001), ratio of uninvolved/involved sFLC (p=0.0002), immunoparesis (p=0.016) and LDH (p<0.0001) could predict time to treatment (TTT) at 60 months (Table 2).

In multivariate analysis, LDH and beta-2 microglobulin were weak but significant independent predictors of outcome (Table 3).

Since both are part of R-ISS, we applied ISS, R-ISS and NLR-ISS to identify TTT at 60 months (Figure 2).

R-ISS resulted the strongest system to distinguish patients in stage I and stage II with TTT at 60 months respectively 92% and 62.7% (p=0.0002).

NLR-ISS could distinguish patients in stage I and stage II with TTT at 60 months respectively 91.9% and 67.8% (p=0.007).

		n	PFS @ 60 months (SE)	p value
Age	>65 years	59	81.1 (0.6)	0.82
	< 65 years	68	76.6 (0.6)	
Serum Albumin	<3.5 g/dL	17	53.9 (1.4)	0.008
	>3.5 g/dL	110	82.4 (0.4)	
Serum Beta-2 microglobulin	>3.5 mg/L	35	55.7 (0.9)	0.0001
	<3.5 mg/L	92	88.0 (0.4)	
NLR	>2	52	75.2 (0.7)	0.4
	<2	75	80.8 (0.6)	
Immunoparesis	yes	52	61.8 (0.9)	0.016
	no	75	85.4 (0.5)	
sFLC involved/uninvolved	>8	30	55.2 (0.9)	0.0002
	<8	97	86.1 (0.4)	
BMPC	>30%	23	56.4 (0.2)	0.003
	<30%	104	83.1 (0.4)	
LDH	>UPN	19	34.7 (1.4)	<0.0001
	<UPN	108	85.9 (0.4)	
High-risk chromosomal abnormalities by FISH	yes	6	66.7 (2.7)	0.26
	no	121	79.2 (0.4)	

Table 2: Time to treatment at 60 months in sMM according to the largest accepted prognostic factors: age, serum albumin, serum beta-2 microglobulin, NLR, immunoparesis, sFLC, bone marrow plasma cell infiltration (BMPC), LDH and high-risk chromosomal aberrancies detected by FISH.

Covariate	HR	SE	p-value	95% CI
Serum albumin	1.15	0.54	0.79	0.39 to 3.3
Serum beta-2-microglobulin	3.42	0.44	0.0054	1.44 to 8.11
BMPC	1.23	0.53	0.67	0.46 to 3.39
sFLC_ratio	1.84	0.49	0.25	0.66 to 5.16
LDH	3.71	0.46	0.008	1.41 to 9.76
Immunoparesis	1.13	0.51	0.81	0.43 to 3.01

Table 3: Coefficients and Standard Errors of Cox proportional-hazards regression to predict time to treatment at 60 months in sMM.

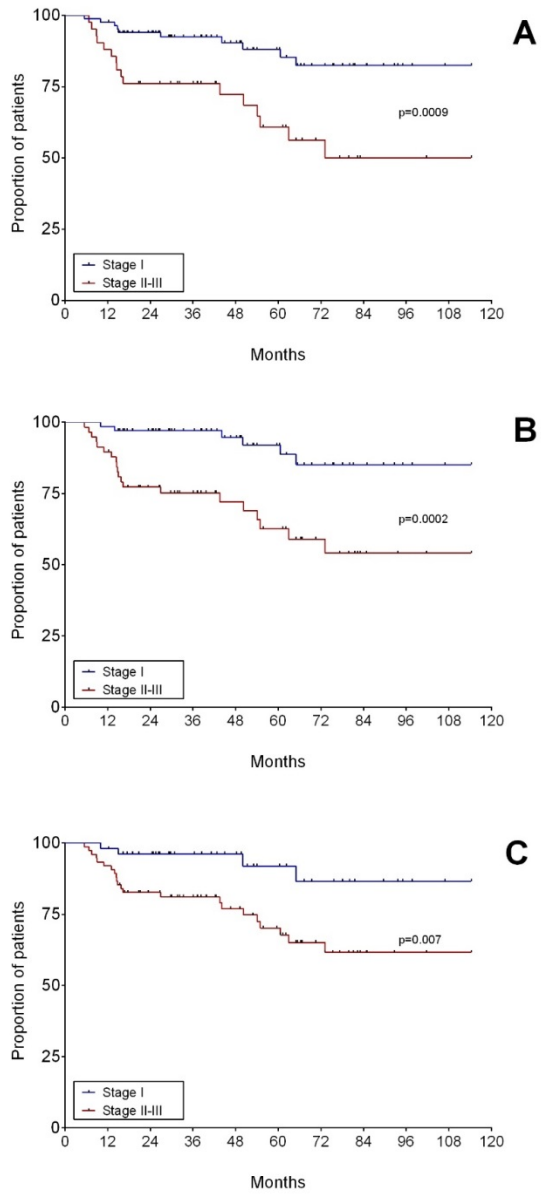

Figure 2: Time to treatment in sMM according to ISS (A); R-ISS (B) and NLR-ISS (C).

Discussion

The current definition of high-risk sMM [6] includes bone marrow clonal plasma cells ≥ 10% and <60% (otherwise active MM is identified) and any one or more of the following: i) serum M protein ≥ 30g/L [4]; ii) IgA isotype [4]; iii) immunoparesis with reduction of two uninvolved immunoglobulin isotypes [4,12]; serum involved/uninvolved free light chain ratio ≥ 8 (but less than 100, otherwise active MM is identified) [13,14]; iv) progressive increase in M protein level (Evolving type of SMM) [15]; v) bone marrow clonal plasma cells 50-60% [4]; abnormal plasma cell immunophenotype (≥ 95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes [14]; vi) chromosomal aberrancies detected by FISH t (4;14) or del 17p or 1q gain [16,17]; vii) increased circulating plasma cells [14]; viii) magnetic resonance imaging (MRI) with diffuse abnormalities or 1 focal lesion [18,19]; ix) PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction [20].

A recent study indicates that the risk of progression is extremely high (approximately 90% at 2 years) when the BMPC is ≥ 60%, and these patients are now considered as MM. The amount of BMPC is evaluated on either the bone marrow aspirate or biopsy examination, and in case of discrepancies the higher of the two values should be used [6].

Bone disease detectable by (MRI) is able to predict TTP in sMM. However, patients with more than one focal lesion at MRI should no longer consider as sMM but as MM according to the current IMWG criteria [6].

In the study of 93 patients with SMM, Perez-Persona and colleagues found 60% of patients with SMM have an aberrant immunophenotype similar to MM [14]. The risk of progression in such patients was significantly higher compared to those, who had a lower rate of aberrancy in the detected BMPC population; median TTP was 34 months versus not reached for patients with 95% or greater versus less than 95% aberrant PC, respectively. Among the clinical variables we could not include immunophenotyping and circulating PC in our analysis because not routinely available in our center.

Thus, risk-scores actually available are based on retrospective series that included about 10-15% of subjects currently considered symptomatic MM. Despite the effect of such changes on the estimates is considered minimal for the low proportion of patients upstaged from SMM to MM [4], we used in our analysis the new, most stringent definition of sMM. Moreover, each model appears to identify unique patients as high risk, with some but not complete overlap [21] justifying the need of additional models easily reproducible in large scale in both retrospective and prospective series.

In multivariate analysis only serum albumin and LDH were independent factors able to predict time to treatment, suggesting applying the actual scores for MM risk stratification, ISS and R-ISS. In this study NLR was not a predictor of outcome in univariate analysis, but our previous observations showed that its prognostic impact should be limited to young patients, in which compromised immune system has not yet altered by advanced age [11]. Thus, we tested NLR-ISS because ISS and NLR are easily available for all patients at diagnosis. NLR-ISS could distinguish patients in stage I with excellent outcome, with TTT at 60 months of 91.9%.

R-ISS was the best prognostic score, able to distinguish patients in stage I and stage II with TTT at 60 months respectively 92% and 62.7%.

The standard of care for SMM is observation until development of symptomatic MM, but there are ongoing attempts to give early-treatment to high-risk sMM patients that have an approximately 50% risk of progression within 2 years [22]. The Spanish group has recently showed the superiority of combination of lenalidomide and low-dose dexamethasone (Rd) versus observation in a phase III clinical trial enrolling 120 patients with high risk sMM [23]. In general, novel agents will be tested in the setting of high-risk sMM for their low toxic profile and high response rate. Thus, largely applicable models that

could identify easily patients that could benefit of early treatment enrolling in a clinical trial are needed. Our analysis shows that R-ISS and NLR-ISS could help to identify the setting of high-risk sMM.

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