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CORRESPONDENCE

Identification of clinical-biological features of newly diagnosed early relapse multiple myeloma patients eligible for autologous stem cell transplantation

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Abstract

A portion of multiple myeloma (MM) patients relapse early or do not respond to first line treatment. Identification of possible clinical and or biological features of these patients remains an unmet medical need. In this study we assesed the predictive markers for early relapse MM, defined as a progressive disease that occurred within 18 months, from autologoust stem cell transplantation (ASCT) in MM patients who did not have primary refractory disease. 74 consecutive MM patients were included in the study that received intensive therapy with ASCT. The study was able to identify the main features of newly diagnosed ER MM patients eligible for ASCT identifying the IgA isotype and the R2-ISS score system as the main predictive prognostic factors for ER in this cohort of MM patients.

KEYWORDS
autologous stem cell transplantation, early relapse, high risk, multiple myeloma

Despite many therapeutic advances [1], multiple myeloma (MM) remains an incurable hematological malignancy with a cohort of patients who relapse early or do not respond to first-line therapy including autologous stem cell transplantation (ASCT) [2–4].

Quite recently, early relapse (ER) after ASCT has been recognized as an independent risk factor for shorter overall survival (OS) [5, 6].

The proportion of patients relapsing early is stable over time at about 15%–20% [7] and they continue to have a median OS less than 3 years [8]. Consequently, clinical and/or biological features that identify patients at high risk for ER at diagnosis represent an unmet medical need [9, 10] and were investigated in this retrospective-observational and single-center study.

The primary endpoint of the study included the assessment of predictive markers for ER defined as a progressive disease that occurred within 18 months from ASCT in patients who did not have primary refractory disease (i.e., failure to achieve at least a partial response to initial therapy [15]). In the literature, most studies assessed 12 months post-ASCT as the cut-off between early and late relapse [5–10], however, other authors considered different thresholds for defining ER as 18 [11, 14] or 24 [12–14] months. The secondary endpoint of the study was to elucidate the impact of early post-ASCT relapse on the clinical course of the disease confirming its role as a major predictor of survival in the era of novel agents.

Only patients who received an upfront ASCT (both single or tandem) between 2011 and 2021 in the Hematology and Bone Marrow

TABLE 1 Description of cohort characteristics.

	Population $n = 74$	ER Cohort $n = 19$	Non-ER Cohort $n = 55$	p-Value
Age at diagnosis (y/o); median (range)	57.0 (38–71)	57.0 (38–68)	57.6 (42–71)	0.81
Male Sex; *n* (%)	43.0 (58.1)	12.0 (63.2)	31.0 (56.4)	0.65
IgA Isotype; *n* (%)	13.0 (24.0)	7.0 (43.8)	5.0 (12.8)	<0.05
Elevated LDH; *n* (%)	11.0 (14.8)	6.0 (31.6)	5.0 (9.1)	<0.05
Hypercalcemia; *n* (%)	9.0 (12.1)	5.0 (26.3)	4.0 (7.3)	<0.05
High Risk Cytogenetic; *n* (%)	11.0 (14.8)	6.0 (31.6)	5.0 (9.1)	<0.05
Amp/Gain 1q; *n* (%)	16.0 (21.6)	8.0 (42.1)	8.0 (14.5)	<0.05
Stage R-ISS III; *n* (%)	13.0 (17.5)	8.0 (42.1)	5.0 (9.1)	<0.001
Stage R2-ISS III-IV; *n* (%)	28.0 (37.8)	17.0 (89.5)	21.0 (38.2)	<0.001
Pis + IMiDs based-Induction; *n* (%)	67.0 (90.5)	18.0 (94.7)	49.0 (89.0)	0.46
Standard dose conditioning; *n* (%)	51.0 (69.0)	14.0 (73.6)	37.0 (67.2)	0.60
Tandem-ASCT; *n* (%)	28.0 (37.8)	9.0 (47.4)	19 (34.5)	0.32
PFS to transplant (months); median (range)	40.8 (3–115)	15.6 (3–18)	55.5 (19–115)	<0.001
Consolidation; *n* (%)	47.0 (63.5)	9.0 (47.3)	38.0 (69.0)	0.08
Maintenance; *n* (%)	51.0 (68.9)	12.0 (63.1)	39.0 (70.9)	0.52
IMIDs based-maintenance; *n* (%)	29.0 (39.1)	5.0 (26.3)	24.0 (43.6)	0.18
PIs based-maintenance; *n* (%)	14.0 (18.9)	6.0 (31.5)	8.0 (14.5)	0.10
Post-relapse EMD evolution; *n* (%)	11.0 (14.9)	9.0 (47.2)	2.0 (3.6)	<0.001
Post-relapse sPCL evolution; *n* (%)	4.0 (5.4)	3.0 (15.8)	1.0 (1.8)	<0.005
OS to diagnosis (months); median (range)	67.8 (17–154)	47.0 (17–135)	75.0 (28–154)	<0.001

Abbreviations: y/o: years old; LDH: lactate dehydrogenase; R-ISS: revised—international staging system; R2-ISS: revised 2 - international staging system; high-risk cytogenetics: the presence of del(17p) and/or t(4;14) and/or t(14;16); Amp/Gain 1q: the presence of gain or amplification of chromosome 1q; PIs: proteasome inhibitors; IMiDs: immunomodulatory drugs; PFS: progression-free survival; EMD: extra-medullary disease (it does not include paraskeletal plasmacytoma); sPCL: secondary plasma-cell leukemia; OS: overall survival.

Transplant Unit of Maggiore University Hospital (Parma, Italy) within 6 months of the initial diagnosis were enrolled. Patients who were progression-free at the last visit required at least 19 months of follow-up from ASCT to be included in the study. Patients who did not receive a novel agent with induction were excluded, as were patients with primary refractory disease who proceeded to an allogeneic stem cell transplantation following their relapse.

Definitions of response and progression were used according to the International Myeloma Working Group response criteria. All statistical analyses were done by SPSS Statistics. The characteristics of cohorts were summarized using the median value for continuous variates and the frequency for categorical ones. The chi-square test and t-test were used to identify differences between groups for categorical and continuous variables, respectively. Kaplan-Meier curves with log-rank tests were used to analyze survival data. The bivariate logistic analysis was conducted to recognize independent factors predicting ER. Subsequently, multivariate analysis was performed using the Cox proportional hazards regression model to confirm the validity of bivariate logistic analysis for survival data and to identify factors associated with worsened progression-free survival (PFS) from ASCT. For all statistical analyses two-sided p-value of < 0.05 was considered to be significant. The cohort characteristics are summarized in Table 1.

All 74 consecutive patients included in the study received intensive therapy with either a doublet-based induction ($n = 7$, 9.5%) including a proteasome inhibitor (PI) or a triplet-based ($n = 67$, 90.5%) including a PI and an immunomodulatory drug. A total of 19 (25.5%) patients experienced ER, with a median time to relapse of 15.6 (range: 3–18) months versus 55.5 (range: 19–115) months of the non-ER cohort ($n = 55$; 74.5%). Most of the ER patients ($n = 18$; 94.7%) had induction therapy with dexamethasone in combination with thalidomide and bortezomib; among these nine (47.4%) patients received further 2–3 cycles of consolidation by the same regimen as induction. Fourteen (73.6%) ER patients received the standard conditioning regimen as melphalan given at 200 mg/m^2 divided over 2 days, in only five (26.4%) patients melphalan was dose reduced to 100–140 mg/m^2 because of advanced age, renal impairment or poor performance status according to the Eastern Cooperative Oncology Group status scale. Nine (47.4%) ER patients underwent tandem transplantation based on patient consent, presence of high-risk cytogenetic abnormalities, and/or post-ASCT response lower than very good partial response. Regarding maintenance therapy, five (26.3%) ER patients continued with lenalidomide but in six (31.5%) ER patients bortezomib-based maintenance was preferred in view of high-risk disease features [17, 18]. Univariate statistical analysis identified as possible predictive markers for ER at

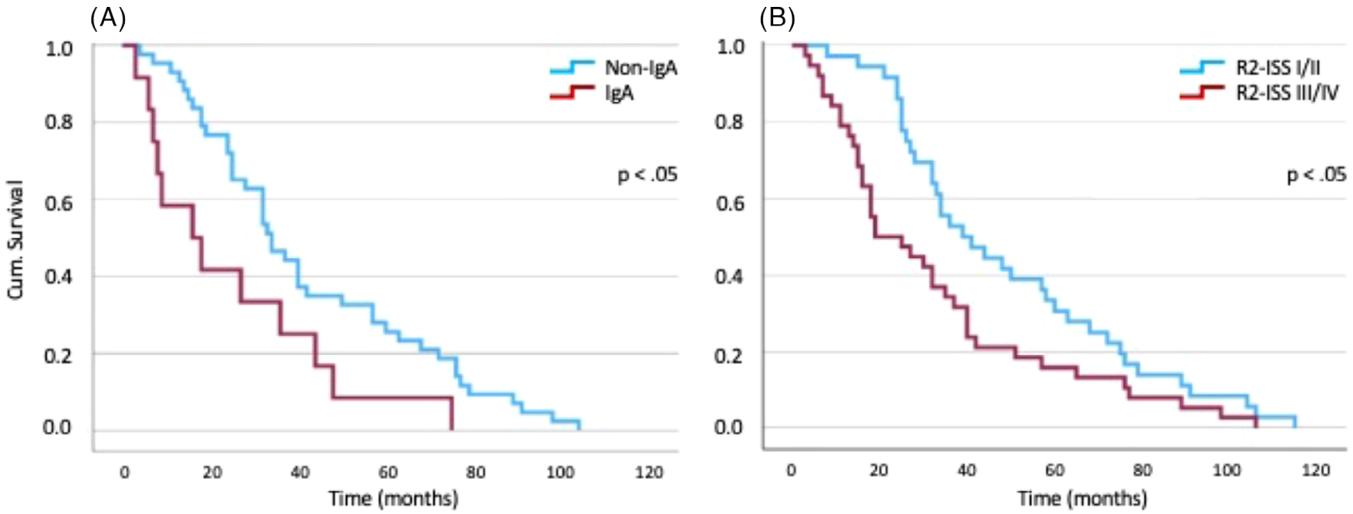

FIGURE 1 Kaplan-Meier progression-free survival curves from autologous stem cell transplantation (ASCT) according to isotype and revised 2 - international staging system (R2-ISS) stage. Landmark analysis at 18 months after ASCT. (A) Patients with IgA isotype ($n = 13$, red line) versus patients with non-IgA isotype ($n = 61$, blue line). (B) Patients with R2-ISS stage III or IV ($n = 29$, red line) versus patients with R2-ISS stage I or II ($n = 45$, blue line).

diagnosis: immunoglobulin A (IgA) MM ($p < 0.05$), elevated serum lactate dehydrogenase (LDH) level ($p < 0.05$), C-CRAB criteria ($p < 0.05$), high-risk cytogenetic aberrations ($p < 0.05$), stage R-ISS III ($p < 0.001$), gain or amplification of chromosome 1q ($p < 0.05$) and stage R2-ISS III or IV ($p < 0.001$). It also showed how ER patients were affected by diseases that more easily evolved extramedullary ($p < 0.001$), justifying the worse prognosis of this specific MM patient setting. First, bivariate logistic analysis and then Cox regression confirmed IgA isotype ($p < 0.05$) and higher stage according to R2-ISS ($p < 0.001$) as effectively independent predictive risk factors for ER. Furthermore, according to Cox regression analysis, both IgA isotype ($p < 0.05$) and stage R2-ISS III or IV ($p < 0.05$) with the presence of gain or amplification of chromosome 1q ($p < 0.05$) and the presence of an increase in serum LDH ($p < 0.05$) were all associated with shorter PFS from ASCT. Time-to-event analysis displayed a median PFS from the transplant of 24.7 (range: 11–106) months and 32.5 (range: 3–106) months for those with IgA MM and stage R2-ISS III or IV, respectively. In the group of patients with IgA isotype the median OS from transplant was 49.5 (range: 10–129) months, while the median OS from diagnosis was 58.0 (range: 17–135) months without statistically significant differences compared to counterpart (Figure 1). In the group of patients with stage R2-ISS III or IV the median OS from transplant was 48.2 (range: 10–107) months, while the median OS from diagnosis was 56.5 (range: 17–116) months. Finally, in the ER cohort the median OS from diagnosis was 47.1 (range: 17–135) in comparison with the 75.0 (range: 28–154) months of the non-ER cohort (Figure 1).

The two mains limitation of this study is the lack of biological data other than fluorescence in situ hybridization, however despite molecular genomics analysis is currently ongoing in some countries, nowadays there is no evidence on the prognostic impact and effective role of the main recurrent mutations in early relapse MM patients. The second is the small cohort of MM patients analyzed due to the monocentric feature of our study. However, the advantage of monocentric study is the minor variability of the biological and clinical data collection in comparison with multicentric ones.

In conclusion, this study was able to identify the main features of newly diagnosed ER MM patients eligible for ASCT identifying the IgA isotype and the R2-ISS score system as the main predictive prognostic factors for ER in this cohort of patients. Future multicentric studies will be necessary to corroborate these findings (Figures S1–S5).

AUTHOR CONTRIBUTIONS

Lorenzo Cillo enrolled patients, collected the data, contributed to statistical analysis, and wrote the paper. Anna Benedetta Dalla Palma designed the study and contributed to statistical analysis. Matteo Scita, Federica Librale, and Matia Bernardi contributed to patient enrollment. Stefania Ricci managed the patient's clinical data. Gabriella Sammarelli performed the cytogenetic analysis. Mario Pedrazzoni did the statistical analysis. Nicola Giuliani designed the study, contributed to statistical analysis, and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

Nicola Giuliani received research funding and honoraria from Amgen, Bristol-Myers Squibb, Takeda, Celgene, Millennium Pharmaceuticals, and Janssen Pharmaceuticals. The other authors declare no conflict of interest.

FUNDING INFORMATION

The authors did not receive support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript. No funding was received for conducting this study.

DATA AVAILABILITY STATEMENT

The data from this study are available on request from the corresponding author, Nicola Giuliani.

ETHICS STATEMENT

This study was approved by our local Ethic Committee on July 19, 2022, and it was conducted according to the Helsinki Declaration.

PATIENT CONSENT STATEMENT

All the participants signed a written informed consent.

CLINICAL TRIAL REGISTRATION

The clinical trial has been registered on the SIRER platform with the SIRER ID: 4579–011968.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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