Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk

Multiple Myeloma (MM) management and survival have dramatically improved in the last decade, notably with triple combinations including one immunomodulatory drug (IMiD) and one proteasome inhibitor (PI) for induction treatment, and high dose therapy (HDT) plus autologous stem cell transplantation (ACST) in younger patients. However, while some patients experience long remission and even cure for rare cases, prognosis is still poor for high-risk MM patients. Early relapse (ER) after treatment has been recognized as an independent risk factor of resistance to rescue treatments and shorter overall survival (OS).[1,2] Heterogeneity in treatment response duration may be influenced by several patient or disease related features such as frailty, age, comorbidity, clinical stage and cytogenetic abnormalities. Among the high-risk chromosomal changes described in MM, those established and on which there is general consensus are del(17p) and t(4;14). These abnormalities impact nega-

tively both, progression free survival (PFS) and OS, and affect respectively around 8% and 15% of newly diagnosed multiple myeloma (NDMM) patients.[3,4]

Given the current availability of particularly effective salvage therapies,[5] we wondered if an ER after first line intensive treatment is still associated with poor OS in both high-risk and standard-risk patients. To address this issue, we retrospectively analyzed clinical and cytogenetic data of a large and homogeneous cohort of NDMM patients treated by intensive chemotherapy followed by ACST, and consolidation.

The Toulouse Ethics Committee approved the study and written informed consent was obtained for all patients included. Clinical data were obtained from 2,627 patients followed >18 months or having relapsed, and for whom diagnosis of MM was established between April 1, 2004 and August 17, 2018. Patients who had primary refractory disease were not included. All patients received an intensive approach with either a doublet-based induction (38%) including PI or a triplet-based (62%) including a PI and an IMiD, followed by ASCT and consolidation by same regimen as induction. Twelve percent of the cohort also received an IMiD-based mainte-

Table 1. Description of patients' characteristics and their association to early relapse.

Variable	No relapse within 18 months n=2,131 n (%)	Early relapse (≤18 months) n=496 n (%)	P	OR [CI 95%]	P
		Univariable analysis		Multivariable analysis n=1,224	
Sex			0.711		
Male	1,198 (58)	286 (58)			
Female	883 (42)	203 (41)			
Missing	50	7			
Age			0.422		
<60 y	1,208 (57)	291 (59)			
≥60 y	923 (43)	205 (41)			
ISS			<0.0001		
1	633 (36)	88 (22)		1.00	
2	757 (43)	181 (45)		1.83 [1.18-2.82]	0.007
3	387 (22)	136 (33)		2.36 [1.46-3.80]	<0.001
missing	354	91			
Cytogenetic			<0.0001		
standard risk	1,560 (85)	300 (67)		1.00	
high risk*	268 (15)	145 (33)		3.66 [2.51-5.34]	<0.001
missing	303	51			
Treatment			0.001		
doublet	755 (35)	215 (43)		1.16 [0.82-1.65]	0.395
triplet	1,376 (65)	281 (57)		1.00	
Best response			<0.0001		
VGPR/CR	1,134 (84)	128 (57)		0.24 [0.17-0.35]	<0.001
SD/RP	223 (16)	95 (43)		1.00	
Missing	774	273			
Maintenance			0.362		
No	1,879 (88)	430 (87)			
Yes	252 (12)	66 (13)			

* high risk means presence of del(17p) and/or t(4;14). ISS: injury severity score ; VGPR : very good partial response; CR : complete response; SD: stable disease; RP: partial response.
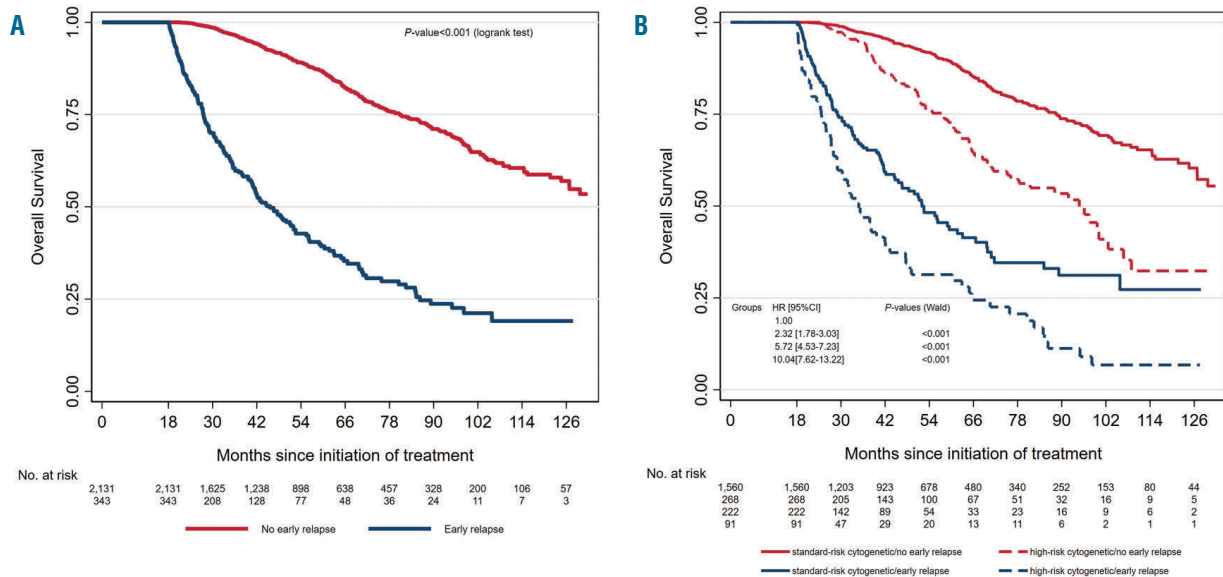
Figure 1. Kaplan-Meier overall survival curves for patients according to early or no early relapse. Landmark analysis at 18 months. (A) Patients with no early relapse (ER) (n=2,131) *versus* patients with ER (n=343). (B) Patients with no ER and standard-risk cytogenetic (n=1,560, red line) *versus* patients with no ER and high-risk cytogenetic (n=268, red dashed line) *versus* patients with ER and standard-risk cytogenetic (n=222, blue line) *versus* patients with ER and high-risk cytogenetic (n=91, blue dashed line). High-risk cytogenetic was defined by the presence of t(4;14) and or del(17p) in more than 55% of plasma cells.

nance. Depth of response and progression were determined based on criteria defined by the International Myeloma Working Group.[6] Relapse was considered early if it occurred within 18 months of starting initial therapy, which is equivalent to relapse within 12 months from ASCT.[1,2] Survival analyses were performed using Landmark analysis at 18 months after initiation of treatment to reduce the guarantee time bias, reducing the cohort to 2,474 patients (n=153 excluded because followed <18 months, see the *Online Supplementary Figure S1*). The data was summarized by frequency and percentage for categorical variables and by median and range for continuous variables. The association of parameters with ER was tested with the χ^2 or Fisher's exact test for univariable analyses, and logistic regression models for multivariable analyses. Survival rates were estimated by the Kaplan-Meier method. Univariable and multivariable analyses were performed using Logrank test and Cox proportional hazards model. Tests were two-sided and *P*-values <0.05 were considered significant. Statistical analyses were conducted using Stata®, version 13.

Bone marrow samples were obtained at diagnosis and shipped overnight to a central laboratory. Upon receipt, plasma cells were isolated from bone marrow using CD138+ MAC-Sorting (Miltenyi Biotec, Paris, France). Post-sorting purity was checked as previously described and only samples with ≥70% plasma cells after sorting were kept for the cytogenetic analysis. Plasma cells were analyzed by fluorescence *in situ* hybridization for t(4;14)(p16;q32) and del(17p13) determination using specific probes from Abbott Molecular (Paris, France). Only deletions 17p present in ≥55% plasma cells were taken into account.[7] For some patients, single–nucleotide polymorphism (SNP)-array was also performed (Affymetrix, Santa Clara, CA. USA) using the Cytoscan® array.

Amongst the 2,627 patients, 496 (18.9%) experienced an ER. The remaining 2,131 patients (81.1%) had either not relapsed at the time of analysis, or relapsed but after 18 months. A description of patients' characteristics and their association to ER is given in Table 1. According to both univariable and multivariable analyses, patients with an injury severity score (ISS) score of 2/3, poor response to treatment and high-risk cytogenetics were more at risk of ER, whereas sex, age (including >65 years, *data not shown*) and presence of maintenance had no significant effect (Table 1). For this last point, it is noteworthy that only 12% of the patients were concerned, which is not surprising considering the relatively recent approval. A doublet-based treatment was more at risk of ER, but not independently (Table 1). The median follow up was 52.1 months (95% confidence interval [CI]: 50.3-54.0) and the 5 years OS was 79.7% (range: 77.6-81.6). According to univariable analysis, poor response to treatment (*P*=0.004), age ≥60 years at diagnosis (*P*=0.006), doublet based treatment (*P*<0.001), ISS 2 and 3 (*P*<0.001), high-risk cytogenetics (*P*<0.001) and ER (*P*<0.001) (see Figure 1A and *Online Supplementary Table S1*) were significantly associated with reduced OS, whereas sex and maintenance were not found associated to OS (*P*=0.098 and *P*=0.230, respectively). According to multivariable analysis (see the *Online Supplementary Table S2*), the independent factors significantly associated with reduced OS were: (i) doublet-based treatment (hazard ratio [HR] 1.54 (range: 1.18-2.00), *P*=0.0029; (ii) ISS 2 (HR 1.72 (range: 1.24-2.38), *P*=0.001) and ISS 3 (HR 1.89 (range: 1.33-2.68), *P*=0.0003); (iii) high-risk cytogenetics (HR 2.05 (range: 1.54-2.72), *P*<0.0001); and (iv) ER (HR 4.40 (range: 3.54-5.81), *P*<0.0001, see Figure 1A). Figure 1B represents the prognostic association of ER and cytogenetic risk.

Response to treatment has been a major prognostic factor in MM. It can be defined by at least three dimensions: rapidity, depth and duration. Fifteen years ago, Durie *et al.* showed that the underlying dominant predictor for OS is time to progression, ahead of depth of response to

induction treatment.[8] The Mayo Clinic has been the first to specifically describe the adverse prognostic impact of an ER after autologous transplant.[1] Given the current availability of efficient salvage therapy, we wondered if an ER after intensive first line still negatively impacts survival. We demonstrate here that ER is still strongly associated with reduced survival after an intensive first line treatment, confirming three recent studies obtained with smaller cohorts,[2,9,10] and that achieving at least a very good partial response (VGPR) is associated with lower risk of ER (adjusted overall response [OR] 0.24 [range: 0.17-0.35], P<0.001). Significant progresses has been recently made for response evaluation, and high sensitivity minimal residual disease may better predict ER.[11] High-risk cytogenetics was also associated with ER (adjusted OR 3.66 [range: 2.51-5.34], P<0.001), as suggested by previous studies. For instance t(4;14) has been shown to induce a chemotherapy sensitive disease, characterized by a high OR rate, but patients achieved short PFS after transplantation.[12] Very recently, revised-ISS has been shown to be predictive and prognostic for relapse within 24 months after ASCT,[13] confirming that some initial characteristics are associated with higher probablity to experiment short PFS. But importantly, we observed that not all patients with ER were included in high-risk cytogenetic group, since 12.5% of standard-risk patients experienced an ER (vs. 25.4% of high-risk cytogenetic group, see Table 1). Of note, these patients died sooner than those belonging to the high-risk cytogenetics and no ER subgroup (Figure 1B). More recently, other cytogenetic factors have been described to negatively impact patient 'survival such as 1q gain and del(1p32), or positively such as trisomy 5.[14] When this information was available (840, 820 and 830 patients, respectively, see the *Online Supplementary Figure S2* and *Online Supplementary Table S3*), we observed that 1q gain and del(1p32) were also associated with more likely ER whereas trisomy 5 was protective. Nevertheless, 14.7% of the patients without any of these four adverse prognostic factors (del(17p), t(4;14), 1q gain and del(1p32)) experienced ER after their first line treatment. A weakness of our study is that we did not include lactate dehydrogenase levels, these data being only available for patients diagnosed from 2015 onward.[15] We also did not include the t(14;16), since in our experience it does not represent an independent prognostic parameter. Despite this, explanations are still unknown to define those patients. Our data could be the starting point to subsequently identify new genomic changes or immune dysfunctions associated with ER, in order to better identify this subgroup from diagnosis. In addition, a patient initially considered to be of favorable risk may also acquire high risk abnormalities such as deletion 17p between treatment and relapse, underlying the need to also establish cytogenetic risk at relapse.

In conclusion, despite efficient post-relapse treatment, ER is strongly associated with reduced survival in both high- and standard-risk cytogenetic groups, and should be included in high-risk MM definition. Our data confirms that the prognosis established at diagnosis is a dynamic data which can evolve according to response to treatment, raising the question about the merit of current risk-adapted therapy and underlying the need to explore mechanisms of relapse. In addition, this study suggests that despite important progresses in salvage therapy, the first line of treatment must be the most efficient as possible.

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