Original Study

Prognostic Value of Serum Paraprotein Response Kinetics in Patients With Newly Diagnosed Multiple Myeloma

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Abstract

Response kinetics is not well-established as a prognostic marker in multiple myeloma (MM). We developed a mathematical model to assess the prognostic value of serum monoclonal component (MC) response kinetics during 6 induction cycles in 373 newly diagnosed MM patients. The model calculated a "resistance" parameter that reflects the stagnation in the response after an initial descent, dividing the patients into two kinetics categories with significantly different progression-free survival (PFS).

Introduction: Response kinetics is a well-established prognostic marker in acute lymphoblastic leukemia. The situation is not clear in multiple myeloma (MM) despite having a biomarker for response monitoring (monoclonal component [MC]). **Materials and Methods:** We developed a mathematical model to assess the prognostic value of serum MC response kinetics during 6 induction cycles, in 373 NDMM transplanted patients treated in the GEM2012Menos65 clinical trial. The model calculated a "resistance" parameter that reflects the stagnation in the response after an initial descent. **Results:** Two patient subgroups were defined based on low and high resistance, that respectively captured sensitive and refractory kinetics, with progression-free survival (PFS) at 5 years of 72% and 59% (HR 0.64, 95% CI 0.44-0.93; $P = .02$). Resistance significantly correlated with depth of response measured after consolidation (80.9% CR and 68.4% minimal residual disease negativity in patients with sensitive vs. 31% and 20% in those with refractory kinetics). Furthermore, it modulated the impact of reaching CR after consolidation; thus, within CR patients those with refractory kinetics had significantly shorter PFS than those with sensitive kinetics (median 54 months vs. NR; $P = .02$). Minimal residual disease negativity abrogated this effect. Our study also questions the benefit of rapid responders compared to late responders (5-year PFS 59.7% vs. 76.5%, respectively [$P < .002$]). Of note, 85% of patients considered as late responders were classified as having sensitive kinetics. **Conclusion:** This semi-mechanistic modeling of M-component kinetics could be of great value to identify patients at risk of early treatment failure, who may benefit from early rescue intervention strategies.

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Introduction

The clinical landscape in multiple myeloma (MM) has significantly improved over the last 20 years[1] because of novel drugs and better tools for diagnosis and disease monitoring.[2] Response to therapy is a key element to evaluate treatment efficacy, which is critically associated with patients' survival. Standard response criteria rely on the evaluation of plasma cells in bone marrow[3-8] and monoclonal component (MC) in serum and urine.[9]

Response kinetics is a well-established prognostic marker in acute lymphoblastic leukemia,[10,11] while information about its value in MM is rather limited.[12-16]

Two studies have analyzed response kinetics in newly diagnosed MM[12,13] and a third one, at relapse.[14] Yan et al.[12] demonstrated that early responders (patients that reach their best response within the first 3 months) had significantly worse survival compared with late responders. Additionally, they defined 4 distinct response kinetics patterns with different outcomes. Patients with gradual and sustained remission ("U-valley" pattern) showed prolonged survival, whereas poor outcomes were observed in patients with rapid and transient responses ("roller coaster" pattern).

The Mayo Clinic group analyzed 840 patients treated between 2004 and 2015.[13] They found that patients harboring high-risk features, such as high tumor burden, high-risk cytogenetic abnormalities or ISS 3 were more likely to achieve an early response (in the first 2 cycles). However, the achievement of an early response (in the first 2 months) was not associated with a prolonged survival, suggesting that response kinetics has limited impact on long-term outcomes in the era of novel therapies.

In the context of RRMM patients, Garderet et al.[14] showed that patients achieving an early (0-4 months) VGPR or better response had significantly shorter duration of response and PFS when compared to those achieving a late response (> VGPR after 4 months). They suggested that patients with indolent disease and lower tumor proliferation would slowly respond to therapy, with favorable long-term outcomes.

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Mathematical approaches, such as semi-mechanistic models integrating relevant treatment and tumor related properties (ie, pharmacodynamics, proliferation, and resistance development) have been used to predict clinical outcomes based on the time course of circulating biomarkers. This has been reported in the setting of small cell lung cancer, nonfunctioning gastro-entero-pancreatic neuroendocrine tumors and breast cancer, among many other types of tumors.[17-20] However, to our knowledge, these semi-mechanistic models have not been explored in MM using serial assessment of the MC. Thus, we aimed to assess the prognostic value of serum MC response kinetics using population semi-mechanistic pharmacodynamic models, evaluated in NDMM patients treated in the GEM2012Menos65 clinical trial.

Materials and methods

Study design

Four hundred and fifty-eight newly diagnosed MM patients were included in the GEM2012Menos65 clinical trial conducted by the Spanish Myeloma Group.[21] Patients with Bence Jones (n = 69) MM and non-secretory disease (n = 6) and incomplete data regarding serum MC during the 6 induction cycles (n = 10) were excluded from the analysis. Accordingly, 373 patients were evaluated in this post-hoc study.

Trial design and primary analysis were recently published.[21] In brief, patients were uniformly treated with 6 induction cycles with bortezomib + lenalidomide + dexamethasone (VRD), followed by autologous stem cell transplant (ASCT) conditioned with either Melphalan 200mg/m2 or Busulfan + melphalan and posttransplant consolidation with 2 additional cycles of VRD followed by maintenance with lenalidomide +/- ixazomib.

The following characteristics, documented at diagnosis, were analyzed: MC concentration, hemoglobin, creatinine, calcium, albumin, beta-2-microglobulin, lactate dehydrogenase categorized as high and normal, the International Staging System (ISS), and cytogenetics. High-risk cytogenetics was defined by the presence of at least one of the following abnormalities detected by iFISH: t(4;14), t(14;16) and/or del(17p).

For the purpose of this study, we analyzed the sequential measurements of MC each cycle, during the 6 induction cycles and minimal residual disease status after consolidation. We also determined in which cycle each patient achieved their best response and further classified them as early responders if they reached their best response within the first 4 cycles or late responders if it was after 4 cycles. Finally, we determined which patients displayed rises in the MC that did not qualify as progressive disease (PD) at any time during the induction. Kinetics of response were correlated with both the response and the minimal residual disease (MRD) obtained after consolidation, defined according to the International Myeloma Working Group (IMWG) 2016 criteria.[9]

Population semi-mechanistic pharmacodynamic modelling of the M-component

In the clinical setting, we expect an MC decline after each treatment cycle, more quickly in some patients than others. Nonethe-

less, occasionally there is a stagnation in this decrease (stabilization) or even, the MC slightly increases without qualifying as PD, or shows overt progression in the following cycles. We estimated that these different dynamics of MC reduction are the result of several factors. First, the expected positive treatment's effect on the tumor leading to MC reduction. Second, factors that generate resistance to therapy that may account for progressively diminished efficacy of the treatment, which translates into slower MC reduction and stagnation in the response. This resistance may be due both to intrinsic tumor's characteristics and to external factors. Finally, the tumor's proliferative capacity, which makes the MC steadily increase over time. Dynamic interaction between all these factors could explain the different MC kinetics. Thus, we designed a mathematical model to calculate these parameters for each patient. Serum concentrations of the MC that were measured at the time of diagnosis and after each induction cycle were plotted individually for each patient and analyzed through the nonlinear mixed effects modeling approach implemented in the software NONMEM 7.4 using the first order conditional estimation with the laplacian option.

Model building: in order to characterize the MC reduction curve and calculate the proposed parameters for each patient we developed the following ordinary differential equation:

$$\frac{dM}{dt} = \lambda - D_{Effect} \times e^{-\gamma \times t} \times M$$

Where dM/dt stands for the rate of change of the MC in serum. Treatment's effect is represented by the D_{Effect} parameter. Since values of drug concentration were not available for correlation with the MC it was assumed as a constant variable in the model. The tumor's resistance is represented in the formula by the gamma (γ) parameter, which can predict the moment when the slope of the M-component reduction decreases to a half. Such a moment accounts for an eventual stagnation of patients' response measured by the MC. Finally, the tumor's proliferative capacity is represented by the lambda (λ) parameter, a zero-order rate constant, that estimates the MC daily increase if the treatment variable (D_{Effect}) had no effect. The initial condition of the system was set up at the value of the MC-component at diagnosis.

Data were logarithmically transformed for the analysis. Levels of MC below the quantification limit (0.009 g/dL) were treated as censored information. Inter-individual variability (IIV) associated with the parameter of the model (see below) was described with an exponential model preventing negative values for the individual parameters. An additive error model in the logarithmic scale accounted for the residual variability.

Model selection. Selection between competing models was based on the (i) visual inspection of the goodness of fit plot, (ii) minimum value of the objective function approximately equal to -2 × Log(likelihood) (-2LL), where a drop of 3.84 points in -2LL between 2 nested models differing in one parameter is considered significant at the 0.05 level, and (iii) precision of model parameters computed as the ratio between the standard error and the estimate of the parameter (RSE). Model candidates with parameters presenting RSEs greater than 50% were rejected.

Model evaluation. The selected model was evaluated using simulation-based model diagnostics as visual predictive checks. One thousand simulations, with the same design characteristics as the original one, were done. For each simulated study and time of measurement, the 5th, 50th and 95th percentiles of the simulated values were computed. Then the 90% prediction intervals of the aforementioned percentiles were calculated and plotted together with the corresponding percentiles obtained from raw data.

Statistical analysis

Figure 1 shows some features of the semi-mechanistic model including its schematic representation, model performance at the individual level, and the impact on the M-component kinetics of different degrees of proliferation and resistance.

We defined two groups for the resistance and two for the proliferation parameters, depending on their magnitude through ROC analysis in relation to PFS: low (< 0.001 for resistance and < 0.0004 for proliferation) and high (≥ 0.01 for resistance and ≥ 0.0004 for proliferation). The D_{effect} parameter was not considered for analysis since its values were assumed as a constant variable in the model due to lack of values of drug concentration.

We performed Kaplan Meier survival analysis for PFS using the log-rank test to determine significant differences. Later, patients that progressed during the induction cycles were excluded for the analysis. Univariate analysis was performed using independent-samples Kruskall-Wallis test, chi-squared or Fisher's exact test, as appropriate, for the independent variables previously mentioned, only with the categorized resistance variable. All the statistical analysis was done with the SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics, Version 26.0. Armonk, NY: IBM Corp).

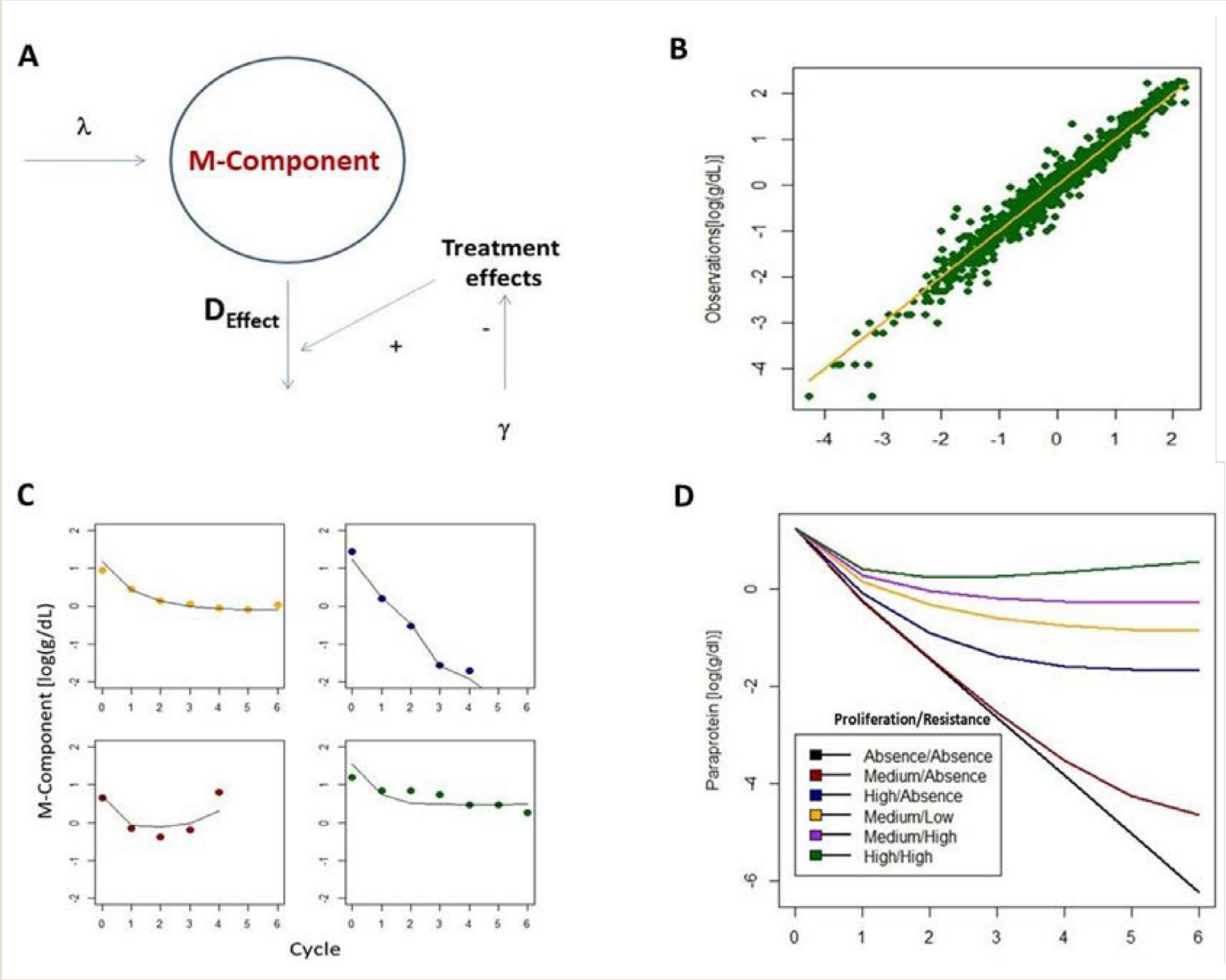
Results

We established two categories for both the *resistance* and *proliferation* parameters using the cut-off described in Materials and Methods: high (≥ 0.01 for resistance and ≥ 0.0004 for proliferation) and low (< 0.001 for resistance and < 0.0004 for proliferation). Initially, the combination of these parameters, which included all patients necessary to develop the model, allowed to establish 4 kinetics categories. Nonetheless, after excluding the standard progressions (according to IMWG criteria) detected during the 6 induction cycles (38/373; 10.2%) only the resistance parameter retained significant association with PFS, so we proceeded using only this parameter, that categorized patients into two categories: low resistance that reflects "sensitive kinetics" and high resistance that reflects "refractory kinetics" and we will use these two terms along the study.

Accordingly, the sensitive kinetics group included 215/335 (64.2%) patients while within the refractory kinetics category there were 120/335 (35.8%) patients. Although neither group reached the PFS median, patients with sensitive kinetics had significantly longer PFS than those with refractory kinetics (72% and 59% at 5-years), which translated into a 36% reduction in risk of progression for the sensitive kinetics group (HR 0.64, 95% CI 0.44-0.93; $P = .02$) (Figure 2).

Univariate analysis (Table 1) did not show an association between the kinetics patterns and baseline disease characteristics, except for

Figure 1 A, Schematic representation of the semi-mechanistic model used to describe the time profiles of the M-component. B, Measured values versus predictions. Solid line is the line of unity. C, M-component profiles of 4 patients chosen at random (measured, points; predicted, lines). D, Simulated profiles of M-component representing patients with same value at diagnosis, same sensitivity to treatment effects, and different magnitude of proliferation and resistance. Low, medium, and high, refer to the 2.5th, 50th, and 97.5th percentiles of the respective parameter distributions.



an unexpected higher proportion of high-risk cytogenetics cases within the sensitive kinetics group (22.8% vs. 13.3%). Interestingly, patients with high-risk cytogenetics and sensitive kinetics (n = 49) did not have a significantly different PFS from patients with standard cytogenetics and refractory kinetics (n = 62) (median PFS 58 months [95% CI 47-69] vs. NR; $P = .53$).

We found a significant correlation between kinetic profiles and depth of response measured after consolidation (Figure 3). Among patients with sensitive kinetics (n = 215), 174 (80.9%) reached CR, 35 (16.3%) VGPR, 1 (0.5%) PR, 1 (0.5%) SD, and 4 (1.9%) PD; and 147 patients (68.4%) reached negative MRD status. Within the refractory kinetics group (n = 120), only 36 patients reached CR (31.6%), 60 VGPR (50.9%), 19 patients PR (14.9%), 1 (0.8%) SD and 4 (2.6%) PD. Within this cohort, only 25 patients (20.8%) reached negative MRD status.

Next, we sought to determine whether the kinetic profiles had any subsequent impact on PFS for patients that reached CR or negative MRD status after consolidation. Within patients who reached CR those who displayed sensitive kinetics (174/210, 82.8%) had significantly better PFS than those with a refractory kinetics (36/210, 17.2%) (median NR vs. 54 months [95% CI 45-62]; $P = .02$) (Figure 4), with a 45% reduction in risk of progression or death (HR 0.55; 95% CI 0.32-0.95; $P = .03$). By contrast the kinetics profile did not significantly modify the outcome for patients that reached negative MRD status after consolidation ($P = .46$).

We then analyzed the correlation of the kinetic profiles with the time to best response. We defined early responders as those who achieved their best response within the first 4 cycles and late responders as those who achieved it during the last two. Accordingly, 185/335 (55.4%) patients were classified as early responders and 150/335 (44.6%) as late responders. There was a higher propor-

Figure 2 Survival plot for PFS comparing the two response kinetics profiles. PFS = progression-free survival.

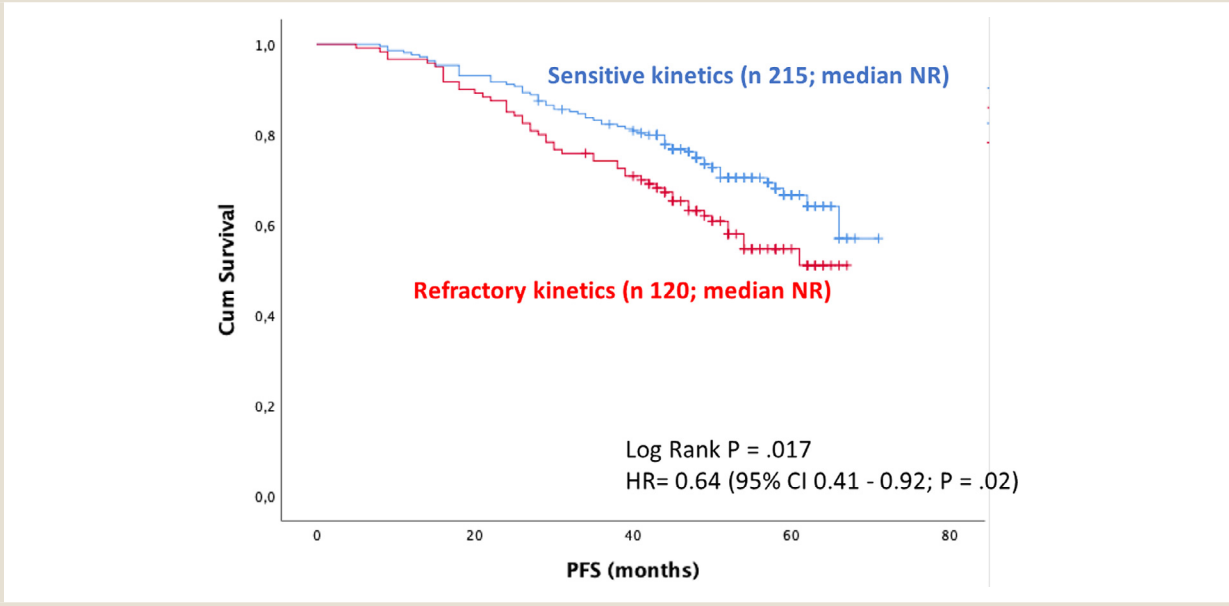


Table 1 Baseline Characteristics for the 2 Response Kinetics Patterns

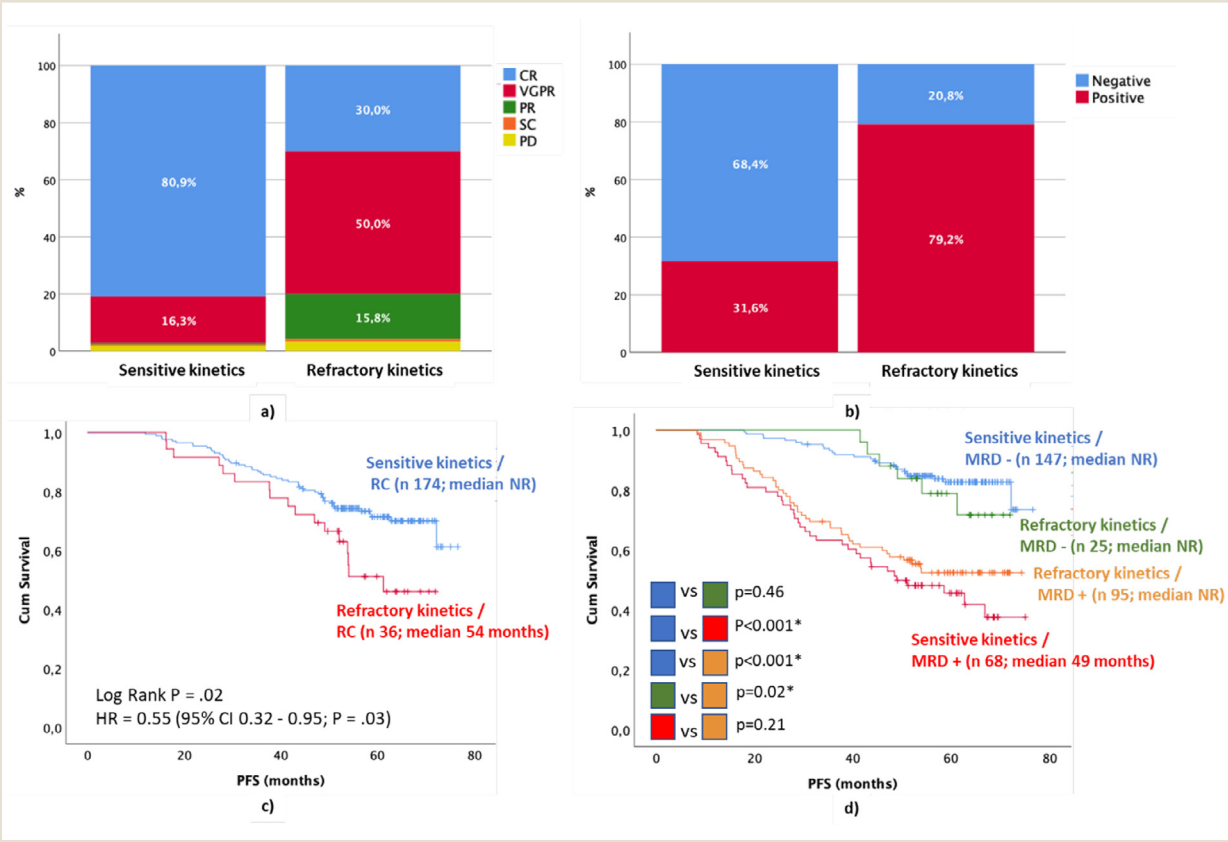
		Sensitive Kinetics (n = 215)	Refratory Kinetics (n = 120)	Valor *P*
Hemoglobin		10.9 (11.9)	10.9 (8.8)	.82
Creatinine		0.85 (1.58)	0.89 (1.46)	.38
Albumin		3.71 (3.6)	3.7 (3.15)	.94
B2M		3.4 (14.5)	3.4 (17.4)	.86
LDH	Normal	180 (83.7%)	101 (84.2%)	.85
	High	25 (11.6%)	15 (12.5%)	
ISS	I	87 (40.5%)	52 (43.3%)	.36
	II	86 (40%)	38 (31.7%)	
	III	39 (18.1%)	29 (24.2%)	
Cytogenetics	Standard	84 (39.1%)	62 (51.7%)	.02
	High-risk	49 (22.8%)	16 (13.3%)	
	Missing data	81 (37.7%)	43 (35.8%)	

Abbreviations: ISS = International Staging System; LDH = lactate dehydrogenase.

tion of late responders within the sensitive kinetics group (127/215 [59.1%] vs. 22/120 [18.3%], $P < .001$) as compared to the refractory kinetics group, whereas there was a higher proportion of early responders (98/120, 81.7%) among patients with refractory kinetics. Of interest, patients with sensitive kinetics who were late responders had significantly longer PFS than those with sensitive kinetics who were early responders ($P = .008$), with PFS rates at 5 years of 81.1% versus 64.8%, respectively. No significant differences were observed between early and late responders among patients with refractory kinetics (data not shown).

Finally, we analyzed the correlation between the kinetic profiles and patients that displayed an increase in the MC not qualifying for disease progression as per IMWG at any time during the induction. Accordingly, 100/335 (29.9%) presented a rebound in the MC, while 235/335 (70.1%) did not. Patients that presented a rebound at any time during the induction had a significantly shorter PFS as compared to patients without MC rebound, with a median PFS of 61 months versus NR, respectively ($P = .002$) (Figure 4). Interestingly patients with sensitive kinetics included a much lower proportion of rebounds (19/215, 8.8%) as compared to the refractory kinetics category (81/120, 67.5%) ($P < .001$).

Figure 3 A) Serum MC component response after consolidation among the response kinetics profiles. B) MRD status after consolidation among the response kinetics profiles C) Survival plot for PFS with the response kinetics profiles among patients that reached CR after consolidation. D) Survival plot for PFS with the integration of the response kinetics profiles and MRD status after consolidation. MC = monoclonal component; MRD = minimal residual disease; PFS = progression-free survival; CR = complete response.



Discussion

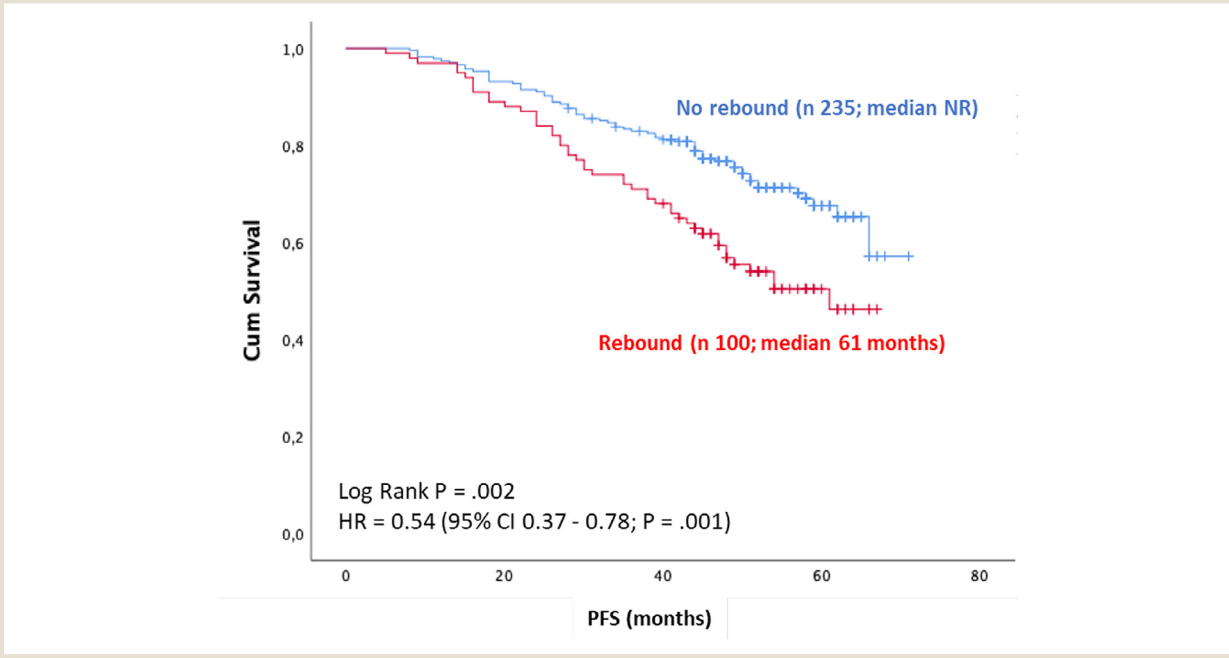
Depth of response to induction therapy is one of the most relevant prognostic factors in MM.[7,9] However, the relevance of response kinetics has not been carefully evaluated, despite the fact that MM has a unique biomarker (the MC) for follow-up. Moreover, intriguingly some data suggests that early responders may have a worse outcome as compared to slow responders,[13] and that early response with early relapse may be associated with an adverse outcome.[12]

Clinicians usually recognize the stagnation in the decrease of the MC, after a rapid reduction during initial cycles, as an adverse kinetic pattern, since this may reflect treatment resistance.[22] Moreover, minimal rebound in the M-component (below the 25% cut-off of increase defined as disease progression by IMWG criteria) may also alert of an impending disease progression.[23] Using a semi-mechanist model, we have analyzed the kinetics of response and defined an independent parameter, "*resistance,*" for each patient. The structure of the model is similar to that previously developed by Claret et al. in 2009[24] during the longitudinal analysis of solid tumors, and recently applied to the time course of M-protein in patients with MM who received isatuximab as a single agent or in combination.[25] Yet there are some differences. For example, we described disease proliferation with a linear model rather than exponentially as Koiwai et al.,[25] since according to the data shown by these authors, individual profiles presented an initial increase in M-protein values, a phenomenon that did not occur in our original data.

Using this resistance parameter, we have defined two different patterns of response kinetics associated with different outcomes in terms of PFS. Thus, patients corresponding to the sensitive kinetics group, showed a significantly longer PFS as compared to the refractory kinetics group (72% and 59% at 5-years) with a 36% reduction in risk of progression for the sensitive kinetics group.

There are frequent debates about the relevance of an early response in MM.[12] Our study based on a prolonged induction, with 6 cycles before transplant, represents a unique opportunity to evaluate this question. Interestingly, overall, 128 (85%) of patients considered as late responders were classified as having sensitive kinetics in our model and the median PFS was not reached in this cohort, being clearly superior to that of early responders with sensitive kinetics ($P = .008$). These findings reflects that the stagnation in the

Figure 4 Survival plot for PFS comparing patients that presented an increment in the MC not qualifying as PD at any point during the induction with those who did not present it. MC = monoclonal component; PD = progressive disease; PFS = progression-free survival.



response, identified by our *resistance* parameter, should probably be considered as a negative prognostic factor and may favor the design of early rescue interventions in curative oriented clinical trials.

The proportion of patients that reached either CR or negative MRD status after consolidation was significantly higher among those with sensitive kinetics (80.9% vs. 30% and 68.4% vs. 20.8%, respectively). Furthermore, the resistance parameter identifies that patients who reach a CR and have sensitive kinetics have significantly better PFS than those that reach CR but have refractory kinetics. However, achievement of MRD negative status is able to abrogate the negative prognostic impact of refractory kinetics. This would further support the value of MRD negativity as a highly relevant clinical endpoint.[26]

Cytogenetics is one of the most relevant prognostic parameters at baseline.[27] Intriguingly in our series, the frequency of adverse cytogenetics was not higher among the high resistant kinetics category, albeit there was a high proportion of missing data. Nevertheless, of note, the resistance parameter modulates the prognostic impact of cytogenetics, turning patients who have standard cytogenetics but refractory kinetics into a subgroup with adverse prognosis.

Even though this study was based on data from a large randomized trial (GEM2012menos65) of patients uniformly treated, with external audit, and long-term follow-up, a potential limitation is that we only used this one series of transplant-eligible patients, with only measurable serum MC that received 6 cycles of induction treatment for the development and evaluation of the model. Additionally, MC measurements were not made in a central laboratory. Further studies are warranted to validate this model in other cohorts, especially in transplant-ineligible patients and in patients that have received more novel therapies such as monoclonal antibodies (antiCD38 or bispecific antibodies) or CAR-T cell therapies.

In conclusion, this semi-mechanistic model based on the M-component kinetics has the capacity to identify two different groups of patients with different response kinetics and different survival. Our goal would be to implement the model in the clinic with the help of a simple calculator. It might be particularly attractive to determine the utility of the model in non-transplant treatment approaches that are usually based on a prolonged/continuous number of cycles. This tool, based on the response kinetics during the first initial 6 cycle, could be of great value to identify patients at a risk of early treatment failure, before fulfilling IMWG criteria of disease progression. In this setting, an early detection/prediction of treatment failure would avoid unnecessary physical and financial toxicity. Moreover, this may offer a window of opportunity to overcome the dismal prognosis of early progressions, through early rescue intervention strategies incorporating new immunotherapeutic approaches, in a setting of low tumor burden and potentially less compromised patient condition.

Clinical practice points

What is already know about this subject?

- Although information about the relevance of response kinetics as a prognostic marker in MM is limited, some studies have analyzed its use and found that early responders (best response within the first 3 months) had significantly worse survival compared with

late responders, and defined several response kinetics patterns, such as patients with gradual and sustained remission ("U-valley" pattern) that showed prolonged survival, whereas poor outcomes were observed in patients with rapid and transient responders ("roller coaster" pattern).

- Mathematical approaches have been used to predict clinical outcomes based on the time course of circulating biomarkers for some solid tumors with success.

What are the new findings?

- Our mathematical model calculated a "resistance" parameter that reflects the stagnation in the response after an initial descent and, accordingly, defined 2 patient subgroups based on low and high resistance that respectively captured sensitive and refractory kinetics, with significantly different progression-free survival (PFS) at 5 years.
- There was significant correlation between resistance and depth of response measured after consolidation, with a greater proportion of CR and negative MRD among patients with sensitive kinetics.
- The resistance parameter modulated the impact of reaching CR after consolidation. Refractory kinetics patients with CR had significantly shorter PFS than those with sensitive kinetics and CR.

How might it impact on clinical practice in the foreseeable future?

- These results might allow to implement the model in the clinic with the help of a simple calculator.
- This tool could be of great value to identify patients at a risk of early treatment failure, before fulfilling IMWG criteria of disease progression. An early detection/prediction of treatment failure would avoid unnecessary physical and financial toxicity.

Authorship

Contribution: P.R-O, L-E.T-A, B.P and J.S-M conceived the manuscript. J-I.T. developed the semi-mechanistic model. L-E.T-A performed statistical analysis. P.R-O, L-E.T-A, J-I.T and J.S-M wrote the manuscript. L.R and J.B designed the clinical trial. All authors contributed in the enrollment and treatment of the patients included in the clinical trial, reviewed the manuscript and provided final approval.

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Disclosure

L-E.T-A has nothing to declare. P.R-O declares honoraria for lectures from and membership on advisory boards with Celgene-BMS, Janssen, Amgen, GSK, Kite Pharma, Oncopeptides, Sanofi, Abbvie and Takeda. Consultancy for Celgene, Janssen and GSK. A.J-U. declares no conflict of interest. R.R. declares honoraria from Becton-Dickinson, Sanofi and The Binding Site. FdA declares honoraria from Janssen, Celgene, Amgen, GlaxoSmithKline and Takeda J.S-M has received honoraria from consulting or Advisory Role: Amgen (Inst), Celgene (Inst), Takeda (Inst), Bristol-Myers Squibb (Inst), MSD (Inst), Novartis (Inst), Sanofi (Inst), Janssen (Inst), Roche (Inst), AbbVie (Inst).

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