TO THE EDITOR:

Early detection of treatment failure and early rescue intervention in multiple myeloma: time for new approaches

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There is currently no uniform approach on whether multiple myeloma (MM) patients experiencing a biochemical relapse should be treated immediately or whether therapy should be delayed until clinical relapse. The International Myeloma Working Group (IMWG) states that treatment is indicated when patients develop symptomatic relapse, a rapidly rising paraprotein level, or extramedullary disease. It is also emphasized that asymptomatic patients with biochemical relapse showing a slow rise in paraprotein level can be managed with a watch-and-wait approach.[1] However, there is a high degree of heterogeneity among patients in biochemical relapse treated in clinical practice and in clinical trials. Indeed, the inclusion criteria of pivotal studies leading to the approval of new drugs for relapsed/refractory MM (RRMM) primarily specified that patients needed to meet the criterion of progressive disease (PD) rather than clinical relapse (Table 1).[2-13] Thus, the numbers of patients with symptomatic vs biochemical relapse may vary across studies. A phase 3 trial comparing carfilzomib and dexamethasone vs bortezomib and dexamethasone for relapsed multiple myeloma patients showed that patients with biochemical relapse had better outcomes than those with symptomatic relapse at time of enrollment, though the impact of more aggressive disease biology in the later cannot be excluded.[14] The Mayo Clinic reported similar findings in a retrospective study comparing overall survival (OS) from start of first-line therapy, which was superior in patients starting second-line treatment of biochemical vs symptomatic relapse (125 vs 81 months, $P = .001$).[15] This could pose a challenge in the interpretation of data across clinical trials. We therefore propose in this commentary a review of the IMWG criteria[6] and management recommendations for relapse/progression in MM, with the aims of adapting them to new scenarios arising from advances in MM[16] and creating a framework for harmonized approaches in patients with biochemical relapse.

Acceptance of the IMWG criteria for diagnosis, response, and progression in patients with MM has decisively contributed to the harmonization of the language of clinical research and to improving comparability between trials. The diagnostic criteria for MM were updated in 2014,[17] driven in part by the identification of new myeloma-defining events that trigger the initiation of treatment. The response criteria were updated in 2016[6] as a consequence of the greater efficacy of new therapies and the existence of deeper levels of remission defined by minimal residual disease (MRD) assessment. By contrast, the core of the definitions established in 1998[18] for relapse and PD remain in force today because only a few minor modifications were proposed in 2006,[19,20] 2011,[21] and 2016.[15] Delayed treatment until disease recurrence reaches clinical significance was probably appropriate when conventional chemotherapy and autologous stem cell transplantation (ASCT) formed the basis of treatment. At that time, rescue treatment options were very limited, and the aim was to benefit patients by sparing them the effects of subsequent treatment between first signs of relapse and open symptomatic progression. The median time between biochemical and clinical relapse is ~5 to 6 months, but ~25% of patients with biochemical relapse do not show symptomatic progression after 2 years.[19,20] Thus, many clinicians consider that treatment can be delayed until clinical relapse, at least in standard-risk patients that at the time of biochemical relapse, do not show evidence of disease evolution into a high-risk

Table 1. Inclusion criteria in phase 3 clinical trials in RRMM leading to the approval of new drugs or drug combinations

Trial (clinicaltrials.gov identifier)	Experimental arm	Inclusion criteria (from clinicaltrials.gov, study protocol, or primary publication)	RRMM patients in biochemical relapse, n (%)
PANORAMA1[2] (NCT01023308)	Panobinostat, bortezomib, dexamethasone	Measurable* RRMM; primary refractory or bortezomib-refractory myeloma not eligible	Unknown
ENDEAVOR[3] (NCT01568866)	Carfilzomib, dexamethasone	MM with relapsing or progressing disease and measurable disease*	117 (12.6)[14]
ASPIRE[4] (NCT01080391)	Carfilzomib, lenalidomide, dexamethasone	Symptomatic MM, relapse or progressive disease, and measurable disease*	None (per protocol)
ELOQUENT-25 (NCT01239797)	Elotuzumab, lenalidomide, dexamethasone	Documented progression from most recent line of therapy and measurable disease*	Unknown
TOURMALINE-MM1[6] (NCT01564537)	Ixazomib, lenalidomide, dexamethasone	Symptomatic MM at diagnosis and RRMM with measurable disease,* not necessarily symptomatic	Unknown
CASTOR[7] (NCT02136134)	Bortezomib, dexamethasone, daratumumab	Documented PD according to IMWG criteria	Unknown
POLLUX[8] (NCT02076009)	Lenalidomide, dexamethasone, daratumumab	PD according to IMWG criteria	Unknown
STRATUS[9] (NCT01712789)	Pomalidomide, low-dose dexamethasone	Refractory or relapsed and refractory disease, and measurable disease*	Unknown
A.R.R.O.W.[10] (NCT02412878)	Once-weekly carfilzomib	RRMM and measurable disease*	Unknown
ICARIA-MM[11] (NCT02990338)	Isatuximab, pomalidomide, low-dose dexamethasone	Refractory to last therapy, intolerance to lenalidomide or bortezomib, or disease progression within 6 mo after ≥PR, and measurable disease*	Unknown
OPTIMISMM[12] (NCT01734928)	Pomalidomide, bortezomib, low-dose dexamethasone	Progression during or after last antimyeloma therapy, and measurable disease*	Unknown
OCEAN[13] (NCT03151811)	Melflufen, dexamethasone	RRMM with measurable disease* and refractory to both lenalidomide and last line of therapy	Unknown (study ongoing)

With the exception of the ASPIRE trial, in which symptomatic multiple myeloma status was required, all studies required measurable disease in their inclusion criteria and followed the International Myeloma Working Group criterion of PD, and therefore could include patients in biochemical relapse.

PR, partial response.

*Measurable disease (ie, increase of 25% from lowest confirmed response value in 1 or more of the following criteria): serum M-protein (absolute increase must be ≥0.5 g/dL) or serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL and/or urine M protein ≥200 mg per 24 h.

phenotype according to cytogenetics and/or positron emission tomography/computed tomography. Furthermore, extending the time until next treatment could enhance the efficacy of retreatment, an important issue in the conventional chemotherapy era when the therapeutic arsenal was limited.

Today, the clinical landscape in MM is substantially different. Progression-free survival (PFS) and OS data are far superior compared with 20 years ago, and there is now a broad range of active drugs to deliver several lines of treatment without potential cross-resistance.[21,22] Our commentary aims to generate discussion about whether, in newly diagnosed MM patients, early detection of treatment failure and a consequent early rescue intervention improves treatment outcomes compared with treating only when clinical manifestations are present. This strategy remains unexplored; therefore, it is important to the debate about timing of treatment initiation to design prospective clinical trials addressing this question. One argument against early treatment at biochemical relapse could be the lack of a proven survival benefit compared with treating at clinical relapse. However, as mentioned, there are already data suggesting that patients treated at biochemical relapse have superior outcomes than those in whom treatment was initiated after clinical relapse.[14] Moreover, it could be envisioned that the efficacy of a new line of therapy may be greater in patients with relapse from MRD⁻ because the tumor would be rechallenged at a time of controlled rather than uncontrolled disease (ie, clinical relapse). Notwithstanding, although the value of MRD as prognostic factor in MM is no longer debated, a proposal of early treatment

intervention based on MRD kinetics may be more complex and requires further investigation because there is yet no evidence that this can improve outcomes. Furthermore, there is a small subset of patients that despite MRD reappearance do not progress in subsequent years and therefore, may not benefit from early intervention.

The efficacy and tolerability of salvage treatments should be better when administered at early/biochemical relapse compared with at symptomatic relapse, when tumor burden is higher.[23-25] Furthermore, it could be hypothesized that in a context of minimal emerging tumor volume, it would be possible to fully rescue patients and to recover their prognosis using alternative therapy embedded within the first-line setting. Preliminary data from the Grupo Español de Mieloma 2012MENOS65 trial support this hypothesis and underpin the potential value of early rescue intervention. In 51 of 53 patients showing early biochemical relapse (increase in serum paraprotein level <0.5 g/dL) in late cycles of induction, subsequent high-dose therapy followed by ASCT was able to disrupt biochemical progression and rescue response. Indeed, the outcome of these patients in terms of PFS and OS was similar to that in patients achieving partial response or better before high-dose therapy/ ASCT (unpublished data). Given these findings, it will be important to design trials to investigate the value of early rescue interventions in patients with early biochemical relapse (ie, paraprotein increases lower than those required by the IMWG criteria definition of PD). These studies should also evaluate the relevance of MRD kinetics, including conversions from negative to positive MRD status and increasing MRD levels in consecutive evaluations. Such trials

should be powered to generate solid evidence of the clinical benefit associated with early rescue intervention; in its absence, it could lead to premature statements of refractoriness in asymptomatic patients with minuscule fluctuations in their disease assessments.

In addition to biochemical relapse, there are other clinical scenarios that could imply early failure of treatment within current standards of MM therapy. These could include obtaining a sub-optimal response (eg, achieving less than a complete remission (CR) or less than MRD$^-$ status, particularly in high-risk patients)[26,27] as the final result of first-line treatment in newly diagnosed MM (transplant-eligible) patients, or a change in the kinetics of response, with response depth ceasing to improve with subsequent cycles of treatment (ie, a stagnant response). Both may represent another model of therapeutic failure that differs from the traditional concept of relapse/progression, and we propose that all 3 models should be considered during scientific discussion preceding future updates of response and progression criteria. Noteworthy, a United Kingdom group has shown that a response-adapted intensification approach improved PFS in patients with initial suboptimal response, though similar PFS2 and OS raises uncertainty on whether intensification at the time of disease progression can balance long-term outcomes.[28] Furthermore, data from a retrospective analysis by the Mayo Clinic uncovered that MM patients who responded more gradually to initial therapy (ie, time to response plateau of ≥120 days) had longer survival than rapid responders reaching a plateau in <120 days.[29]

In summary, the availability of multiple effective drugs beyond first-line treatment should create a framework to evaluate if IMWG criteria for starting treatment in relapsing patients should be expanded to include other adverse clinical conditions that may possibly be detected before symptomatic progression. Early rescue intervention in the settings of early subclinical progression (eg, minimal but consistent increases in paraprotein, progressively increasing MRD levels) and suboptimal or stagnating response kinetics, may offer new opportunities to improve outcomes in MM. Although this may pose challenges in clinical trials with survival outcomes as primary end points, the potential use of MRD as a surrogate marker and primary end point would pave the way for rapid development of future clinical trials, particularly in high-risk MM. For example, to compare optimal standard of care vs a treatment-adapted approach aiming to achieve MRD negativity after transplant, and to make it sustainable with early rescue intervention as soon as MRD converts from negative into positive at a defined threshold (ie, 10^{-4}). Such trials, together with descriptive studies to better define clinical characteristics related to early treatment failure, represent a challenge that clinicians should address if they share the dream of curing MM.

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