Redefining the treatment paradigm for multiple myeloma

Continuous immunomodulation: Redefining the treatment paradigm of multiple myeloma?

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In recent years, we witnessed a dramatic shift in the treatment paradigm of multiple myeloma (MM). The upfront strategy in transplant-eligible MM patients now often includes a 3-drug induction combining a proteasome inhibitor (PI; mainly bortezomib) and immunomodulatory-drug (IMiD), followed by autologous stem-cell transplant (ASCT) and lenalidomide maintenance.[1] In the non-transplant setting, continuous lenalidomide-dexamethasone (Rd) is a standard regimen, and currently the backbone of several 3-drug combinations evaluated in clinical trials (in combination with bortezomib or daratumumab).[2] Newly diagnosed MM patients exposed to lenalidomide at first-line will increase in the near future. Consequently, because lenalidomide is usually administered until progression, most of these patients become refractory to the drug at first relapse.

Nevertheless, Rd is the backbone of several 3-drug regimens at first relapse, combined with either a PI or a monoclonal antibody (MoAb).[3] To date, no data are available on the efficacy of lenalidomide-based combinations in lenalidomide-refractory patients. Thus, with the constant increase of lenalidomide-refractory patients at first relapse, the current recommendations for treatment at relapse need to be re-defined.

Pomalidomide, a third-generation IMiD more potent than lenalidomide, has been approved in combination with dexamethasone (Pd) in patients who had failed prior lenalidomide and a PI. Based on current data in heavily pretreated patients, only one-third of patients receiving Pd ultimately reach an objective response (ORR).[4] Many attempts to build upon Pd have been made, with several early-phase (I/II) studies focusing on lenalidomide-exposed and/or refractory patients, with promising preliminary efficacy data.

OPTIMISMM[5] is the first randomized, phase 3 study to investigate pomalidomide early in the course of the disease, showing that a 3-drug combination including an IMiD and a PI is better than a 2-drug regimen. Of note this advantage does not come at the cost of increased toxicity; also, using pomalidomide precociously, ideally at first relapse, when the disease is more sensitive and the bone marrow microenvironment less compromised, prolongs progression-free survival (PFS; median, 21 months) compared to its use in later lines. Thus, PVd stands out as an effective, safe and potentially cheap option (due to the expiration of bortezomib patent in the next future) at first relapse. Importantly, the combination was effective also in high-risk patients, who currently represent an unmet medical need.

Still, some open questions remain. Several compounds have been so far combined with pomalidomide in phase I/II studies, including alkylators,[6] PIs (carfilzomib and ixazomib)[7,8] and MoAbs (anti-CS1 and anti CD38),[9,10] all showing promising ORR (50-86%) and prolonged PFS (median, 8·2-10·3 months). The advantage of combining pomalidomide with bortezomib rather than another drug still needs to be proved, particularly considering that bortezomib is already a backbone of frontline regimens. In fact, patients refractory to full dose bortezomib were excluded from the OPTIMISMM trial.

It is unlikely that a randomized trial will directly compare the various pomalidomide-based combinations; therefore, a bucket of compounds will emerge as available options, among which clinicians will have to choose the ideal partner for pomalidomide, weighing patient and disease characteristics, prior therapies and costs.
An exploratory analysis of the OPTIMISMM trial showed an improved time-to-next-therapy of about 14 months, attributable to the immune-enhancing effects associated with pomalidomide, and supporting a continuous immunomodulatory treatment. Nevertheless, in the context of the clonal disease evolution of MM, the benefit of re-treatment with a more potent IMiD rather than switching to different drug classes still needs to be evaluated. In this regard, the current definition of lenalidomide-refractoriness does not consider the dose and the treatment-duration of lenalidomide at which refractoriness develops. In the present study, 70% of patients were refractory to lenalidomide; however, the proportion of those refractory to full-dose (25 mg) or to a lower, maintenance-dose (10-15 mg) is unknown. It is important to understand whether refractoriness to lenalidomide is dose and time-exposure dependent or not and whether the efficacy of pomalidomide varies according to lenalidomide-refractoriness definition. Also, a longterm exposure to lenalidomide may suggest sensitivity to IMiDs and thus justifies a subsequent treatment with pomalidomide; whereas an early refractoriness to lenalidomide might advocate for a drug-class shift.
PVd represents one of the future standards of care in lenalidomide-refractory patients, particularly at first relapse. Alongside PVd, other regimens with or without pomalidomide will emerge as alternatives at first relapse. Lacking reliable biomarkers predictive of a specific-drug disease sensitivity, a deeper knowledge of the meaning of refractoriness is necessary. This will allow clinicians to tailor treatment not only according to prognostic baseline parameters, but also based on dynamic predictive markers of disease sensitivity to a specific drug or class, ultimately improving treatment efficacy.

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