of chemotherapy demands. A resourced-stratified list of essential medical devices and drugs is now available,[7] and international commitment to reducing premature mortality from cancer is growing. However, engagement and long-term commitment from all stakeholders remain key to making a step change. Nonetheless, primary prevention should be an essential part of this action and should be a top priority in countries' response to cancer, in close conjunction with early detection, screening, and treatment.

Melina Arnold, Isabelle Soerjomataram
Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon 69008, France
arnoldm@fellows.iarc.fr

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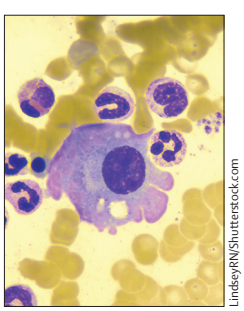
Redefining the treatment paradigm for multiple myeloma



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A shift in the treatment paradigm for multiple myeloma has taken place in recent years. The upfront strategy in transplant-eligible patients with multiple myeloma now typically includes a three-drug induction combining a proteasome inhibitor (eg, bortezomib) and an immunomodulatory drug, followed by autologous stem-cell transplantation and lenalidomide maintenance.[1] In the non-transplant setting, continuous lenalidomide plus dexamethasone is a standard regimen and is the backbone of several three-drug combinations assessed in clinical trials (in combination with bortezomib or daratumumab).[2,3] Lenalidomide is usually administered until progression; thus, newly diagnosed patients with multiple myeloma who are exposed to lenalidomide at first-line will become refractory to the drug at first relapse. To date, no data are available for the efficacy of lenalidomide-based combinations in lenalidomide-refractory patients. The current recommendations for treatment at relapse need to be redefined.

Pomalidomide—a third-generation immunomodulatory drug that is more potent than lenalidomide—has been approved in combination with dexamethasone for patients who relapsed on lenalidomide and a proteasome inhibitor. Based on current data in heavily pretreated patients,[4] only a third of patients receiving pomalidomide and dexamethasone ultimately achieve an objective response. Many attempts to build on the pomalidomide and dexamethasone combination have been made, with several early-phase studies focusing on lenalidomide-exposed or lenalidomide-refractory patients, with promising preliminary activity data.

In *The Lancet Oncology*, Paul Richardson and colleagues report findings of the OPTIMISMM trial,[5] the first randomised phase 3 trial to investigate pomalidomide early in the course of multiple myeloma in lenalidomide-pretreated and lenalidomide-refractory patients. Their findings showed that progression-free survival was significantly improved with a three-drug combination of pomalidomide, bortezomib, and dexamethasone compared with a two-drug regimen of bortezomib and dexamethasone (median 11·20 months [95% CI 9·66–13·73] *vs* 7·10 months [5·88–8·48]; hazard ratio 0·61, 95% CI 0·49–0·77; p<0·0001). Safety of the three-drug combination accorded with known profiles of the individual drugs.

Precocious use of pomalidomide—ideally at first relapse when the disease is more sensitive and the bone marrow microenvironment less compromised—improves progression-free survival compared with use in later treatment. Thus, the combination of pomalidomide, bortezomib, and dexamethasone stands out as an efficacious, safe, and potentially cheap (the bortezomib patent is soon to expire) option at first relapse. Importantly, subgroups analyses suggested that the three-drug combination was effective also in patients with high-risk

cytogenetics—ie, those with abnormalities such as del(17p), t(4;14), or t(14;16)—who currently represent an unmet medical need.

Several compounds have, so far, been combined with pomalidomide in phase 1/2 studies, including alkylators,[6] proteasome inhibitors (eg, carfilzomib and ixazomib),[7,8] and monoclonal antibodies (anti-CS1 and anti-CD38),[9,10] all showing promising overall responses (50–86%) and improved progression-free survival (median 8·2–10·3 months). The advantage of combining pomalidomide with bortezomib rather than another drug still needs to be proven, 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 randomised trial will directly compare the various pomalidomide-based combinations. Therefore, several compounds will emerge as available options, among which clinicians will have to choose the ideal partner for pomalidomide, weighing patient and disease characteristics, previous treatments, and costs.

An exploratory analysis of the OPTIMISMM trial showed an improved time to next treatment of about 14 months, possibly 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 multiple myeloma, the benefit of retreatment with a more potent immunomodulatory drug rather than switching to different drug classes still needs to be assessed. In this regard, the study's 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) lenalidomide or to a lower maintenance dose (10–15 mg) is unknown. It is important to understand whether refractoriness to lenalidomide is dose-dependent and time-exposure-dependent or not, and whether the efficacy of pomalidomide varies according to the definition of lenalidomide-refractoriness. Also, long-term exposure to lenalidomide could suggest sensitivity to immunomodulatory drugs and, thus, justifies subsequent treatment with pomalidomide, whereas early refractoriness to lenalidomide might advocate for a drug class shift.

Pomalidomide, bortezomib, and dexamethasone represents one of the future standards of care in lenalidomide-refractory patients, particularly at first relapse. Alongside this regimen, other drug combinations with or without pomalidomide will emerge as alternatives at first relapse. Without reliable biomarkers predictive of a specific-drug disease sensitivity, a deeper knowledge of the meaning of refractoriness is necessary, which 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.

Francesca Gay, Roberto Mina
Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, 10126 Torino, Italy
fgay.cittadellasalute@gmail.com

FG has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda; and has served on advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Roche, and Takeda. RM has received honoraria from Amgen and Janssen.

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