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FOREWORD

Pomalidomide: when expectations are understated

"The treatment with pomalidomide plus low-dose dexamethasone and the latest advances of therapies in relapsed-refractory multiple myeloma are analyzed in the field of practice setting, in order to provide insights into possible approaches to the treatment of relapsed-refractory multiple myeloma."

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Multiple myeloma (MM) largely remains an incurable disease. Progressively acquired drug resistance is a major reason for the limited benefit of most MM therapies. In 2004, Kumar *et al.* [1] conducted a study on outcomes in relapsed MM. The study revealed decreasing response duration with increasing number of salvage regimens, likely reflecting acquired drug resistance. More recently, the International Myeloma Working Group [2] investigated outcomes in patients with relapsed-refractory MM (RRMM). The median overall survival and event-free survival from T0 were 9 and 5 months, respectively. The study has confirmed the poor outcome, once patients become refractory to current treatments. Although MM remains a complex and challenging disease, in recent years the management of this disease has benefited substantially from the introduction of new drugs such as proteasome inhibitors and immunomodulatory drugs (IMiDs). These agents exert their effects through several mechanisms including direct cytotoxicity, antiangiogenic effects, inhibition of bone resorption and activation of antitumor immunity.

Among IMiDs, pomalidomide seems to have a more potent antimyeloma activity in RRMM patients, and a similar favorable safety profile compared with thalidomide and lenalidomide [3].

In Phase I–II studies, pomalidomide plus low-dose dexamethasone (Poma + LoDEX) demonstrated activity in MM patients refractory to both bortezomib and other IMiDs [4–6]. The pivotal, multicenter, open-label, randomized Phase III trial (MM-003) [7] compared Poma + LoDEX with high-dose dexamethasone in previously treated adult patients with RRMM who had received at least two prior treatment regimens, including both lenalidomide and bortezomib, and had demonstrated disease progression on the last therapy. In this study on overtreated patients, overall survival – possibly underestimated because of the crossover from high-dose dexamethasone to Poma + LoDEX arm – was 12.7 months, whereas progression-free survival was 4 months, with a median follow-up of 10 months. Based on the results of this Phase III trial, EMA granted accelerated approval of pomalidomide, which is now considered a new effective strategy for RRMM patients [8].

KEYWORDS
• drug resistance
• immunomodulatory drugs
• multiple myeloma • pomalidomide

"Progressively acquired drug resistance is a major reason for the limited benefit of most multiple myeloma therapies."

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Interestingly, in these clinical trials time to progression achieved with Poma + LoDEX in responding patients was superior to time to progression achieved with the immediately prior treatment: this finding suggests that pomalidomide is able to change the natural course of disease.

Recently, more evidence has been accumulated on the efficacy of pomalidomide in patients that have relapsed after lenalidomide or proteasome inhibitors treatments [9,10]. However, 'field-practice' information is necessary for a more grounded evaluation of the benefits of pomalidomide. Indeed, field-practice experiences, including case reports, are important since they complement evidence derived from clinical trials in unselected patients often presenting multiple comorbidities or challenging management [11,12].

In this supplement, we present two cases of MM patients refractory to previous treatments including bortezomib and lenalidomide. The treatment with Poma + LoDEX and the latest advances of therapies in RRMM are analyzed in the field of practice setting, in order to provide insights into possible approaches to the treatment of RRMM.

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