Editorial

TOURMALINE-MM1: new oral triplet combination for patients with relapsed/refractory multiple myeloma

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The treatment of multiple myeloma (MM) radically changed 11 years ago when the addition of thalidomide to melphalan-prednisone (MPT) was proven to be superior to melphalan-prednisone (MP) alone (1). Various other compounds have been approved since, changing the landscape of MM treatment at diagnosis and in the relapse setting. Despite all these improvements, the vast majority of patients still relapse and the management of this group of patients can be challenging. In particular those patients relapsing after bortezomib and lenalidomide (the backbone of treatment for MM) have a poor outcome with a median event-free survival (EFS) of 5 months and a median overall survival (OS) of 9 months (2).

In the last 2 years novel compounds have become available for the treatment of MM and have been investigated in the relapse/refractory (RR) setting. Results from several clinical trials demonstrated that the addition of a novel agent to the lenalidomide-dexamethasone or bortezomib-dexamethasone increases the quality of the response and translates into a longer progression-free survival (PFS).

A recent publication reported the results of a double-blind, placebo-controlled, phase 3 trial in which 722 patients with MM who had received one to three previous lines of therapy were randomly assigned to receive either ixazomib-lenalidomide-dexamethasone or placebo-lenalidomide-dexamethasone until disease progression or intolerance (3). After a median follow-up of 14.7 months the median PFS was 20.6 months in the ixazomib group and 14.7 months in the placebo group. The advantage in PFS has been observed in different subgroups of patients including those with high risk cytogenetics (PFS 21.4 *vs.* 9.7 months in patients treated with ixazomib or placebo respectively), those previously exposed to immunomodulatory drugs (IMiDs) and those previously exposed to proteasome inhibitors. The quality of the response was better in the ixazomib group with 12% achieving a complete response (*vs.* 7% of the placebo group) and 36% achieving a very good partial response (*vs.* 32%).

The tolerability of the triplet combination including ixazomib has generally not been different from the placebo combination: the percentage of grade ≥3 adverse events was similar (74% ixazomib group *vs.* 69% placebo group), the percentage of serious adverse events was 47% in the ixazomib group and 49% in the placebo group and the rate of treatment discontinuation due to adverse events was 4% in the ixazomib group and 6% in the placebo group. Among the different adverse events, a higher rate of thrombocytopenia grade ≥3 has been observed in the ixazomib group when compared to the placebo group (19% *vs.* 9% respectively) whilst an equal and minimal percentage of peripheral neuropathy grade ≥3 has been reported in both groups (2%). Interestingly no differences were observed between groups, in the reported rates of arrhythmias, heart failure, hypertension,

myocardial infarction and acute renal failure.

The results of this trial confirmed in the RR setting that the triplet combination is able to achieve a deeper response that translate into a longer PFS compared to the double combination. Similar findings have been observed in other trials combining lenalidomide-dexamethasone with alternative novel drugs, such as the ASPIRE trial (carfilzomib-lenalidomide-dexamethasone), the POLLUX trial (daratumumab-lenalidomide-dexamethasone) and the ELOQUENT-2 trial (elotuzumab-lenalidomide-dexamethasone) (4-6). In all these trials the adverse events due to the addition of a third drug have been minimal, confirming the feasibility of a three drug combination regime in the RR setting even for elderly patients or for those with comorbidities.

In the ASPIRE trial the addition of carfilzomib increased the median PFS from 17.6 to 26.3 months, with a similar rate of reported adverse events of grade ≥3 in both groups. Interestingly the addition of carfilzomib did not increase the incidence of grade ≥3 peripheral neuropathy (4). In the POLLUX trial the addition of daratumumab increased the rate of complete response to 43% (from 19% in the lenalidomide-dexamethasone group) with 22% reaching minimal residual disease (MRD) negativity. Almost half of the patients experienced an infusion-related reaction mainly of grade 1–2 during the first infusion of daratumumab and a higher incidence of neutropenia grade ≥3 has been observed in patients receiving the triplet combination (52% *vs.* 37% respectively) (5). The ELOQUENT-2 trial demonstrated that the addition of elotuzumab to lenalidomide-dexamethasone prolongs the median PFS from 14.9 to 19.4 months with an increase in overall response rate from 66% to 79%. Apart from a 10% rate of infusion reactions of grade 1–2 in the elotuzumab arm, there were no differences reported in the percentage of adverse events (6).

All these trials have been designed to have a continuous treatment until progression or intolerance and although the follow-up is still relatively short, the tolerability of the triplet combination is not different from the double combination. In particular, peripheral neuropathy and constipation possibly present from previous treatments appear to be no worse in the group receiving triplet combination. The tolerability as well as the convenience of administration of medications are crucial aspects in a strategy advocating continuous rather than fixed term treatment. No major side effects have been observed in any of these triplet combinations and quality of life assessment has usually been equal or better in patients receiving three drug combinations.

Similarly the route of administration is important for long-term treatment and of the new triple combinations, ixazomib-lenalidomide-dexamethasone is the only exclusively oral treatment, reducing some of the associated burden of injected treatments for both patients and treatment centers. This characteristic can have significant impact in certain patients groups such as the elderly or those with a lack of family support where attending hospital frequently can be challenging and a cause of distress.

Of the 722 patients in the TOURMALINE-MM1 trial, 137 were considered to have a high risk FISH profile. Seventy-five were randomised to the ixazomib group and 62 to the placebo group with a median PFS of 21.4 and 9.7 months respectively. This seems to suggest the addition of ixazomib to lenalidomide-dexamethasone negates the negative impact of carrying a high-risk chromosomal abnormality (3). These results need to be confirmed in a larger population and the cut-off value needs to be calibrated with the other studies however it seems the addition of ixazomib can improve the PFS in patients with high risk FISH.

The limitation of this trial (common to all trials) is the lack of data on particular groups of patients due to the inclusion/exclusion criteria. For instance we have no data on patients with poor renal function (clearance creatinine <30 mL/min/per 1.73 m) and only 15% of patients in this trial were 75 years of age or above. Assessing the efficacy and tolerability of ixazomib-lenalidomide-dexamethasone in patients with these characteristics will help to improve our understanding on how to optimize treatment in these particular challenging patients highly represented in RR patients.

Other triple combinations not including IMiDs have been investigated in RR setting such as bortezomib-panobinostat-dexamethasone and bortezomib-daratumumab-dexamethasone (7,8). Similarly novel combinations using Pomalidomide instead of lenalidomide are under investigation in clinical trials and will hopefully increase the choice of highly effective and well tolerated treatment regimes.

In conclusion it is an exciting time in the world of MM therapy with an excess of newer agents being developed, many showing fairly comparative improvements in PFS; this therefore present a challenge to the physician on selecting the most appropriate combination regimen. The most suitable combination of treatment in the relapsed setting usually depends on efficacy, previous treatment, comorbidities, chronic side effects from previous

treatment and patients' preferences. The results of the TOURMALINE-MM1 trial provide a novel treatment option for patients with MM with its uniqueness in being an exclusively oral regime is likely to be its advantage in respect to the other available combinations.

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Footnote

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