Relapsed/refractory patients

Safety and efficacy of pomalidomide, dexamethasone and pegylated liposomal doxorubicin in patients with RRMM

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Relapsed and Refractory Multiple Myeloma (RRMM) patients are commonly treated with triplet regimens that combine a steroid such as dexamethasone (DEX), an immunomodulatory drug, and a proteasome inhibitor, and more recently, combinations include the use of monoclonal antibodies. Studies have shown that the efficacy of immunomodulatory drugs (IMiDs), such as thalidomide and lenalidomide, plus DEX, can be enhanced by the use of pegylated doxorubicin (PLD). However, drug resistance can be circumvented by switching to a third generation IMiD such as pomalidomide (POM).

In a recent study, the first clinical trial to examine the use of POM plus DEX and PLD was established. Alexa Cohen, from Oncotherapeutics, West Hollywood, US, conducted a multi-center, non-randomized and open-label study, in which they investigated the optimal dose of POM for RRMM patients in phase I followed by a Phase II portion for LEN-refractory MM patients only. This study was published in the British Journal of Hematology in November 2017.

Phase I of this study consisted of three cohorts: patients who received POM at 2 mg (Cohort 1), 3 mg (Cohort 2) or 4 mg (Cohort 3), and received POM once daily starting on day 1 for 21 consecutive days of a 28-day cycle. Patients also received DEX at 40 mg and PLD at 5 mg/m², both given IV on days 1, 4, 8, and 11 of a 28-day cycle. LEN-refractory MM patients in phase II were given an initial dose of 4 mg of POM. However, due to adverse effects (AEs), such as recurrent neutropenia, the dose was adjusted and the remainder of the patients received 3 mg of POM. The primary endpoint for phase I of the trial was to identify the Maximum Tolerated Dose (MTD) of POM in combination with DEX and PLD for patients with RRMM. The objective for phase II was to determine the efficacy of this combination among patients refractory to LEN, and to establish the safety, tolerability, PFS, time to first response and duration of response (DOR).

Key Findings:

Patient demographics:

- N = 68 patients (pts)
- Median age = 66 yrs
- Median number of prior treatments = 4 (range 1–22)
- Median number of cycles completed for all patients treated in phase I and II of the trial = 3 (range 1–8 cycles)
- Median follow up in this trial = 6.7 months
- Four pts in phase II displayed dose-limiting toxicities (DLTs) resulting in 40 pts receiving POM at the 3 mg dose (instead of 4 mg)

Table 1. Efficacy endpoints were compared between pts receiving 4 mg of POM and those receiving 3 mg of POM:
Clinical Benefit rate (CBR) in combined phase I and II (pts receiving 3 mg vs 4 mg) = 42% vs 40%

CBR in phase II (pts receiving 3 mg vs 4 mg) = 51% vs 44%

Slightly worse outcomes for pts with prior LEN- and BORT- containing regimens when compared to the overall population

Pts enrolled in phase II (4 mg of POM vs 3 mg of POM):
- Median PFS: 5.4 vs 8 months
- Median DOR: 4.8 vs 9 months

Safety:
- Most common haematological AEs (all grades, any cause): neutropenia (69%), leucopenia (54%), lymphopenia (51%), hypokalemia (38%), thrombocytopenia (34%), high blood urea nitrogen (32%) and hyperglycaemia (29%)
- Most common non-haematological AEs: hyponatraemia (41%), fatigue (32%), constipation (16%), fever (16%) and upper respiratory infection (16%)
- Eight pts experienced ≥ Grade 4 AEs: hypoglycaemia (n = 1), lymphopenia (n = 1) and neutropenia (n = 6)

Overall, this study demonstrated the efficacy and durability of responses to POM in combination with PLD and DEX for treating MM patients who are refractory to LEN. It was also observed that patients who received 3 mg of POM with PLD+DEX, as part of either phase I and II (combined) or phase II, showed an improvement in ORR and PFS, as well as safety. Overall patients receiving 3 mg of POM experienced less toxicity than those receiving POM at 4 mg. Therefore, it can be concluded that this novel combination of POM at 3 mg with a modified 28-day dosing cycle of IV PLD and DEX, is well tolerated and results in clinically important efficacy offering a valuable option to RRMM patients.

References


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