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Real world experience of KPD use in relapsed or refractory myeloma

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INTRODUCTION

- Multiple myeloma (MM) is a haematological malignancy characterised by clonal proliferation of plasma cells.
- Historical studies have estimated median overall survival at 5.7 years from diagnosis.[1]
- Patients with MM have benefitted from a range of new novel treatments in recent years, which has greatly improved prognosis.
- At relapse multi-drug regimens with new agents are preferred, and the choice of treatment often heavily depends on the availability of funding in different European countries for these expensive drugs.
- In Ireland, the VRD regimen (lenalidomide, bortezomib and dexamethasone) can be used in upfront therapy of MM.
- Treatments available at relapse include next-generation proteasome inhibitors (carfilzomib and ixazomib), the next-generation immunomodulatory drug (IMiD) pomalidomide and the CD38 inhibitor daratumumab which is only licensed for use as monotherapy. Therefore, optimal management at first relapse remains challenging.
- After first relapse, remissions tend to be shorter due to the development of resistant plasma cell clones[2]; therefore, early use of regimens which are highly successful at inducing and maintaining remission is preferred.
- Treatment options for patients refractory to lenalidomide and bortezomib are very limited.
- Use of carfilzomib, pomalidomide and dexamethasone (KPD) in bortezomib and lenalidomide-refractory patients has resulted in overall response rates (ORR) of 50% with a median PFS of 7.2 months in a small cohort.[3]
- Treatment with KPD is generally restricted in Ireland due to lack of funding; however, its use has been permitted by our institution.
- In this study we present real-world data on response rates and toxicity of a heavily-pre-treated cohort managed with this combination of therapy.

METHOD

- The present study examined outcomes of patients who have received KPD at a large tertiary referral centre in Limerick, Ireland between May 2017 and June 2020.
- These patients had received lenalidomide and bortezomib and were refractory to or unable to tolerate these treatments.
- The treatment regimen consisted of carfilzomib 20mg/27mg/m2 day 1,2,7,8,14, and 15, dexamethasone 40mg weekly and pomalidomide 4mg 21 of 28 days.
- The primary end-point was response to therapy.
- Secondary outcomes included adverse events as a result of therapy and time to next therapy.
- Response criteria were defined by the International Myeloma Working Group (IMWG) recommendations.[4]

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RESULTS

PATIENT CHARACTERISTICS

- From 2016 through to 2019 14 patients received KPD at our centre.
- The male: female ratio was 7:1.
- The median age at MM diagnosis was 61.2 (46.8-78.5).
- The median time to commencement of KPD from MM diagnosis was 3.8 years (0.5-15.5).
- The median number of prior regimens was 4 (1-11).
- All patients had received bortezomib and lenalidomide prior to starting this regimen.
- Eight patients (57.1%) had an autologous stem cell transplant and 2 patients (14.2%) had a second transplant after a prolonged period of remission.

RESPONSE ASSESSMENT

- The overall response rate (ORR) was 42.8% (6/14) (see figure 1).
- The median number of cycles of KPD in all patients including those still on the regimen was 5 (1-47).
- The median time to next therapy was 12.0 months (3-40.9), excluding 3 patients (21.4%) still undergoing treatment with KPD at time of study closure.
- Refractory myeloma to primary therapy with VRD was seen in two patients and these both achieved an excellent response to second-line therapy with KPD (CR in one patient and VGPR in the other).

TOXICITY

- No grade 4 adverse events (AEs) were recorded.
- Six (42.9%) of patients experienced haematological toxicities necessitating dose reduction, transfusion or growth factor support.
- Five patients (35.7%) developed infections necessitating hospital admission.
- Two patients (14.2%) developed deep venous thrombosis (DVT) despite thromboprophylaxis with low molecular weight heparin (LMWH) and required treatment with a direct oral anticoagulant (DOAC).
- Other AEs of note included avascular necrosis of the hip (grade 2), new onset of atrial flutter (grade 2) and exacerbation of cardiac failure (grade 2).

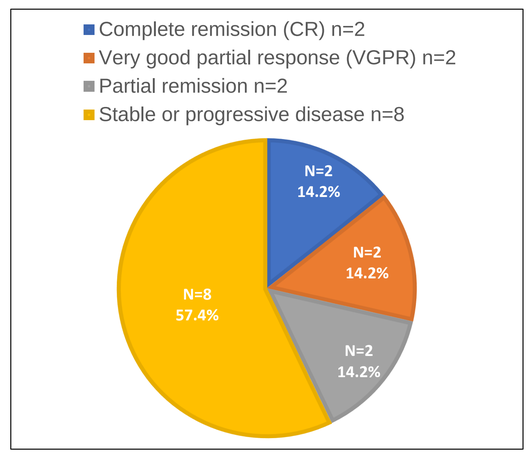

Figure 1: Response to KPD (n=14).

CONCLUSIONS

- Our data show that KPD is a relevant choice in the treatment of multiply relapsed MM.
- It has the capacity to induce remissions even in the 10% of patients who have primary refractory disease to VRD and have had historically very poor outcomes with salvage therapies.
- Haematologic adverse events (AE) predominated.
- There were no grade 4 adverse events recorded.
- It is clear however that venous thromboembolism (VTE) is a significant cause of comorbidity in MM patients treated with combination chemotherapy and can occur despite appropriate use of prophylactic anticoagulation.
- Recent studies have demonstrated the efficacy of low-dose apixaban in prevention of VTE in the setting of IMiD-based therapy, and this may be an important future therapeutic approach.[5,6]
- Peripheral neuropathy is an uncommon event with the novel proteasome inhibitors and no patient in our study suffered from neuropathy as a result of carfilzomib treatment.
- In conclusion, KPD was used successfully at our institution in a group of 14 heavily pre-treated patients with an ORR of 42.8%.
- KPD remains an attractive option for salvage of relapsed and refractory MM in this cohort, and will in future be considered in conjunction with other anti-MM therapies.
- A trial investigating outcomes of KPD in conjunction with daratumumab in the United States is yet to begin recruiting.

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