Should Carfilzomib or Ixazomib represent the new standard for proteasome inhibitor therapy in myeloma ?

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Multiple myeloma (MM)treatment has undergone considerable improvement with the introduction of novel agents such as Thalidomide, Lenalidomide, Pomalidomide (IMIDs) and proteasome inhibitors (Bortezomib, Carfilzomib, Ixazomib).The backbone of treatment in younger patients with newly diagnosed MM (NDMM) remains single or double high-dose melphalan (HDM) combined with autologous stem cell transplantation (ASCT).[1] With the introduction of Bortezomib containing triple drug induction regimens, such as PAD, VTD and VCD, complete response rates (CR) have increased from less than 25 % to more than 50 %.[2,3]Progression-free survival (PFS) is now approximately 36 months and median survival 96 months.
Other regimens such as bortezomib combined with lenalidomide and dexamethasone (VRD) or carfilzomib combined with lenalidomide and dexamethasone (KRd) may further increase pre-transplant CR rate up to 60 % including stringent CRs.[4,5]Such regimens may also result in prolonged MRD (minimal residual disease)-negativity.[6]These data have raised questions about the necessity of high-dose therapy + ASCT in transplant eligible NDMM.

It should be kept in mind however, that in large randomized trials induction with novel agents followed by HDM and possibly consolidation and/or maintenance therapy not only increases CR but also progression-free survival (PFS) and time to next treatment (TTNT). A large meta-analysis of 4 European trials showed that such an approach is capable of overcoming the poor prognostic impact of unfavorable cytogenetic abnormalities.[7]

Recently Carfilzomib (Kyprolis) and Ixazomib (Ninlaro) have been approved for treatment of relapse/refractory myeloma. The Aspire and Endeavour trials have demonstrated the superiority of KRd over Rd and of Kd over bortezomib/d respectively across different subgroups. The Tourmaline trial showed that oral Ixazomib/Rd is better than Rd for progression-free survival and response. These trials also incorporatedmolecular risk classifications and with longer follow-up will answer which is the benefit in patients with high-risk vs standard risk disease defined by molecular and clinical characteristics. Both proteasome inhibitors will probably move from use in the relapse patient to front-line applications. Because of the oral formulation Ixazomib may be useful for maintenance therapy as well.

The role of these agents at diagnosis and relapse will be discussed.

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Case Male, 58 yr
No prior history of (co)-morbidity

2012: MM IgA-λ 52 g/L, anemia, bone lesions in pelvis and femur
No renal impairment, no hypercalcemia
ISS 3;
Bone Marrow 38 % plasma cells, monoclonal phenotype
FISH gain(1q) (3 copies), del(17p)

1. What is proposed treatment?
    - Vel/Dex induction followed by single HDM/ASCT
    - Len/Dex induction followed by single HDM/ASCT
    - Triple regimen induction followed by single HDM/ASCT
    - Any of these followed by double HDM/ASCT
    - Any of these plus consolidation
    - Any of these plus consolidation plus maintenance
    - No transplant, Len/Dex continuously.

2. Will you give consolidation ?
    - What would be your choice of consolidation ?
    - Depending on achieved response ?
    - How many cycles ?

3. What would be your choice of maintenance
    - Which regimen ?
    - Duration of maintenance ?

4. How will you follow the patient in case of
    - CR
    - PR
5. Is there an indication for allogeneic SCT ?