Treatment of relapsed multiple myeloma : role of proteasome inhibitors

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Proteasome inhibitors (PI) represent a novel class of antineoplastic agents targeting the ubiquitin-proteasome pathway that interferes with many cellular pathways including protein homeostasis. More than ten years ago two phase II multicenter studies proved the clinical benefit of bortezomib, a boronic acid derivative, for patients with relapsed/refractory multiple myeloma (MM) and started a new era of myeloma treatment. The phase III APEX trial resulted in approval of bortezomib for MM at first or later relapses in many parts of the world. During the ten years that followed, the use of bortezomib was further improved by succesful and safe combinations with other anti-myeloma drugs, and by further optimizing dosing regimens and the route of administration. In contrast with its intial use as single agent, the standard combination became rapidly bortezomib plus dexamethasone. During the years that followed several other anti-myeloma agents that were combined with bortezomib included the immunomodulatory drugs (IMIDs),cytostatic agents like (liposomal) doxorubicin, cyclophosphamide, melphalan and bendamustin, and histone deacetylase inhibitors like vorinostat and panobinostat. The tolerability and safety, and most importantly, the neurotoxicity of bortezomib were further improved by the switch from IV to SC administration, and by once instead of twice weekly administration in more vulnerable patient categories.

The success story of bortezomib in MM stimulated the development of several novel proteasome inhibitors. Carfilzomib is an irreversible proteasome inhibitor from the epoxyketone family, with fewer off-target activities. Recently, two large phase III trials with carfilzomib in relapsed MM were published. In the ASPIRE study, the combination of carfilzomib plus lenalidomide and dexamethasone (KRd) prolonged the median PFS with 9 months compared with Rd in patients that received between 1 and 3 previous treatment lines. In a similar population (ENDEAVOUR), treatment with Kd doubled the median PFS compared with bortezomib-dexa. Although the use of carfilzomib is not associated with significant neurotoxicity, rare cases of cardiac toxicity have been reported. Ixazomib is an oral PI that is structurally more related to bortezomib. A recent phase III study (TOURMALINE-MM1) proved the superiority of Ixazomib plus Rd to Rd alone (median PFS: 20 vs 14 months). Other PI's that are in earlier phases of clinical development include marizomib and oprozomib.

In conclusion, proteasome inhibitors have changed the treatment landscape of MM, and have become an indispensable cornerstone of myeloma treatment throughout the different phases of the disease.