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Multiple myeloma

Treatment of Multiple Myeloma (MM) has significantly changed over the last few years. In young patients the use of novel schemes based on Thalidomide, Lenalidomide, or, Bortezomib appear to be superior to VAD as debulky pre-transplant regimens and these schemes do not affect stem cell collection, although some precautions should be taken with Lenalidomide. Interestingly, the initial CR rate obtained with these combinations (particularly with Bortezomib, as shown in two randomized trials) was upgraded following ASCT, which suggests that these novel treatments will not replace ASCT, but will help to enhance its activity, although the EFS and OS of this approach is still unknown. Regarding the role of novel drugs in maintenance therapy after transplant, two randomized trials have shown that Thalidomide maintenance prolongs EFS and OS, particularly in those patients who fail to achieve CR after Transplant. Nevertheless, prolonged treatment may be associated with more resistant relapses to salvage therapy.

In elderly patients Melphalan-Prednisone (MP) has been the gold standard for over 40 years. However, recent data derived from randomized trials demonstrate that, in these patients the combination of Thalidomide, or Bortezomib with MP is superior to the standard MP. An alternative to these MP combinations would be Lenalidomide + Dexamethasone, particularly using low dose Dexamethasone. One important goal in elderly patients will be to achieve the optimal balance between prolongation in survival and quality of life.

The role of novel drugs in relapse MM is well defined, and in fact the overall survival prolongation observed in myeloma patients is mainly due to the efficacy of Thalidomide, Lenalidomide, and Bortezomib, in the relapse-refractory setting.

In spite of this progress, most patients relapse and become eventually refractory to all available treatments. Therefore, drugs with novel mechanism of action are urgently needed in order to improve the outcome of relapsed MM patients.

In this area several targeted oriented drugs are already at early phases of clinical investigation, including: 1. Agents acting against surface receptors present in plasma cells, such as IL6-R, CD56, CS1, or CD40. 2. Agents designed to block RTKs, like, the already mentioned FGFR3, VEGFR; IGF-1R or c-Kit. and 3. Drugs interfering with the activated signalling pathways, including Farnesil Transferase (Tipifarnib), RAF (RAF265), MAPK (SCIO-469), STAT3 (Atiprimod), MTOR

(RAD001) or AKT (Perifosine). Other mechanism which has demonstrated to be critical for MM survival is the unfolded protein response (UPR). Three classes of agents have been designed to target this system: Hsp90 inhibitors, novel proteasome inhibitors (NPI-0052 and Carfilzomib) and inhibitors of aggressome formation (tubacin). Finally, epigenetic is emerging as a relevant player in tumor progression, therefore the use of histone deacetylase (HDAC) inhibitors or demethylating agents seems to be promising for the treatment of MM patients.

Unfortunately, the expectations raised by some of these agents have not been so far confirmed in the clinic. It is probable that these targeted directed drugs will be more effective in science based combinations with other agents which have already shown clear efficacy in MM.