18

Novel agents for the treatment of multiple myeloma

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The availability of the novel agents, such as thalidomide, bortezomib and lenalidomide, has expanded treatment options and has improved outcomes for multiple myeloma (MM) patients. A preliminary distinction between MM patients is needed: patients younger than 65 years are considered eligible for autologous stem cell transplantation (ASCT), whereas those older than 65 are usually not considered ASCT candidates. Despite ASCT with melphalan 200 mg/m^2 being the standard conditioning regimen, in case of co-morbidities, a gentler approach with reduced-dose melphalan (100 mg/m^2) can be a valid alternative option [1].

In the transplant setting, the traditional induction treatment before ASCT has been the combination vincristine-adriamycin-dexamethasone (VAD) for many years. However, in the era of novel agents, new induction treatments have now become available, showing higher efficacy than VAD in terms of survival and response rate. Several studies showed that the use of thalidomide plus dexamethasone (TD) resulted in a significant higher at least partial response (PR), ranging from 48% to 80%, with complete response (CR) rates of 4% to 16% [2], and, in particular, it proved to be superior to VAD (at least PR of 76% vs 52%, respectively; $P < .001$) [3]. Induction with lenalidomide has also been investigated in various trials. Two large randomized trials [4,5], have shown that a high proportion of patients responded to induction with lenalidomide plus dexamethasone (RD). In these two studies, responders to RD induction were 82% and 85%, with a CR rate of 4% and 22%, respectively. Various trials have assessed the efficacy of bortezomib plus dexamethasone (VD) as induction before ASCT. In the French IFM phase III randomized study comparing VT with VAD [6], after 4 cycles of treatment, the proportion of responders with VD was higher than with VAD (82% vs 65%, including 15% vs 7% CR/near CR, respectively). Response rate with VD remained higher also after ASCT (40% vs 22% CR/near CR). Moreover, VD led to a prolonged progression-free survival (PFS) than did VAD (69% vs 60% at 2 years, respectively; $P < .01$), but no considerable differences in overall survival (OS) were observed [6]. Recently, the Italian group has explored the efficacy of the 3-drug combination bortezomib-thalidomide-dexamethasone (VTD) as compared to TD. This phase III trial showed that the first option is far superior both before ASCT (response rates: 94% vs 79%, with 32% vs 12% CR/near CR) and after ASCT (55% vs 32% CR/near CR; $P < .001$) [7]. This also translated into a longer PFS (90% vs 80% at 2 years for VTD vs TD, respectively; $P < 009$) but no significant differences in OS were reported.

Novel agents have also contributed to change treatment options in the non-transplant setting. For many years, the oral combination melphalan-prednisone (MP) has been regarded as the standard approach for patients ineligible for ASCT. Five randomized trials have now demonstrated the superiority of the 3-drug combination, melphalan-prednisone-thalidomide (MPT), to MP [8–12]. In all of them, MPT resulted in higher PR (42–76% vs 28–48%), higher at least very good partial response (VGPR) or near CR rate (15–47% vs 6–8%) and longer PFS (14–27.5 vs 10–19 months) than did MP. In two studies, the PFS advantage observed with MPT also translated into a significant OS advantage (45.3–51.6 vs 27.7–32.2 months) [9,10]. The combination MP has also been compared to melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R) in a phase III trial [13]. Responses with MPR-R were significantly higher than in the MP group (at least PR in 49% of patients, at least VGPR in 11% and CR in 5%; $P < .001$). PFS was significantly improved in patients who received MPR-R compared with those who received MP (22.5 months vs 15 months), and no differences were found in the 1 year OS (92% in both arms). A randomized trial comparing MP with the 3-drug combination bortezomib-melphalan-prednisone (VMP) reported a significant improvement in PR (71% vs 35%), CR (30% vs 4%; $P < .001$), and OS at 3 years (72% vs 59%; $P = .0032$) with the VMP regimen. Thus, VMP confirmed as a new standard of care for ASCT ineligible patients [14].

In the light of the trials mentioned above, standard induction regimens are being challenged and replaced by novel agent combinations. In the transplant setting, a number of newer induction regimens are now available, and they proved to be superior to VAD. Similarly, in the front-line treatment of patients not eligible for transplantation, regimens incorporating novel agents have been found to be superior to the traditional MP regimen.

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