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## The road to cure in multiple myeloma: incorporation of novel agents into autologous stem cell transplantation

Because of its potential of significantly increasing the rate of complete response (CR) up to the 30% range and prolonging the duration of event-free survival (EFS) and overall survival (OS) by approximately one year when compared with conventional chemotherapy, since the mid 1990s autologous stem-cell transplantation (ASCT) has been considered the standard of care for younger patients with newly diagnosed multiple myeloma (MM). More recently, introduction into the clinical practice of novel agents targeting the myeloma clone in its bone marrow microenvironment has changed the treatment paradigm for patients who are candidates for ASCT. In particular, recognition that thalidomide and bortezomib exhibit remarkable activity in advanced refractory MM has stimulated their testing in different clinical scenarios, such as induction therapy in preparation for ASCT. Studies of thalidomide-dexamethasone (TD), eventually combined with a third drug such as doxorubicin (TAD) or cyclophosphamide (CTD), provided demonstration of increased rates of at least very good partial response (VGPR) with thalidomide-based regimens in comparison with traditional therapy given before ASCT. Since most of these studies were intended to explore

pre-transplantation induction therapy, EFS and OS comparisons were frequently hampered. A large trial addressed this issue by randomizing patients to receive or not thalidomide up-front incorporated into melphalan-based double ASCT. In comparison with the no thalidomide arm of the study, addition of thalidomide to double ASCT significantly increased the CR rate, up to 62%, and prolonged EFS, whose 5-year estimate was 56%. After a median follow-up of 8 years, a survival advantage has recently become apparent among the one third of patients with metaphase cytogenetic abnormalities, a finding initially not reported. Similarly to thalidomide, also bortezomib has been incorporated into newer induction regimens in an attempt to increase the CR rate before ASCT and to ultimately improve post-autotransplantation outcome. Two large phase III studies conducted in France and Italy have explored the role of bortezomib-dexamethasone (VD) and VD combined with thalidomide (VTD) in comparison with VAD and TD, respectively, as induction therapy for younger patients who are candidates to receive ASCT. In both of them, VD and VTD were superior to the control group in terms of CR and  $\geq$ VGPR, a finding confirmed also

in high-risk patients carrying chromosome abnormalities. Importantly, high-quality responses effected by bortezomib-based regimens were furtherly increased following the first ASCT and resulted in significantly longer progression-free survival.

Although data so far available suggest that

novel agents and ASCT are complementary, a key issue is whether treatment with novel agents delays or eliminates the need for auto-transplantation. Randomized clinical trials comparing these two approaches will definitely answer this unresolved question within the next few years.