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Sommario	The outcome of patients affected by Multiple Myeloma (MM) has markedly improved over the past decade, both in young and elderly patients. In the past years, conventional therapy, such as melphalan plus prednisone (MP), was the only active treatment against MM. Since the 1980s, high doses of chemotherapy plus autologous stem cell transplantation (ASCT) proved to be the most suitable option for young newly diagnosed multiple myeloma (YNDMM) patients. More recently, new active classes of drugs, such as proteasome inhibitors-PIs (e.g., bortezomib) and immunomodulatory drugs-IMiDs (e.g., thalidomide and lenalidomide) became the standard of care, alone or in association with the old agents, either for f?rst-line therapy in the transplant and non-transplant settings, or for the treatment of relapsed disease. Actually, three-drugs combinations, including at least bortezomib or lenalidomide in combination with dexamethasone, followed by ASCT is considered the optimal choice for all YNDMM. Patients and Methods: we retrospectively analyzed our Centre experience in the last 25 years comparing the results obtained with old drugs- that is conventional chemotherapy- versus novel agents –such as lenalidomide and bortezomib- in YNDMM. We also performed an additional analysis on the effect of a single versus

tandem ASCT either with old agents or with novel agents. Results: Between August 1989 and May 2014, 258 YNDMM patients underwent ASCT. The median age was 54 years (range, 18-69), 137 were men. As induction treatment, between October 1988 and October 2008, 173/258 patients received old drugs, i.e. vincristine, doxorubicin and dexamethasone (VAD; n=167) or MP (n=6), while 85/258 patients, between February 2005 and November 2013, were treated with novel agents, i.e. velcade-based (n=67) or IMiD-based regimens (n=18). All 258 patients received high doses of melphalan and single (n=153) or tandem (n=105) ASCT. Overall, after induction, 67 patients (25.9%) achieved complete response (CR), near CR (nCR) or very good partial response (VGPR). More in detail, among patients treated with new drugs, a CR/nCR/VGPR was observed in 36/85 patients (42.3%) after induction, in 36/85 patients (42.3%) after single ASCT and in 27/50 patients (54%) after tandem ASCT. No differences were observed in terms of response and survival between IMiDs or bortezomib-based regimens. For patients treated with old drugs, a CR/nCR/VGPR was recorded in 31/173 (17.9%) after induction, in 50/173 patients (28.9%) after single ASCT and in 19/55 patients (34.5%) after tandem ASCT. Overall survival (OS) and progression-free survival (PFS) at 10 years, for all 258 patients, was 44.4% and 22.5%, respectively. OS and PFS were better for patients in CR/nCR/VGPR after induction compared to those in partial response or stable disease (OS: 62.1% vs 40.7%, p=0.06 and PFS: 36.2% vs 17.2%, p=0.06). In addition, OS was slightly better for patients treated with new drugs than those treated with old drugs. In fact, OS at 8 years was 66.1% (IC 95%:53.5-81.7) for the first group vs 51.5% for the second group, respectively (p = 0.26 n.s.). PFS was significantly improved for patients treated with new drugs than those treated with old drugs. In fact, PFS at 8 years was 55% for the first group vs 25.3% for the second group, respectively (p = 0.0047). Supposing that the impact on OS was influenced by the salvage treatments used after the progression of disease, we further analyzed patients that relapsed. Among our 258 patients, 144 presented a first relapse. Our cohort of relapsed patients was divided in 4 different groups: 1) 51 patients treated with old agents as first and second line therapy (35.4%); 2) 79 patients treated with old agents for first line therapy and novel agents for second line therapy (54.8%); 3) 2 patients treated with novel agents in induction therapy and subsequent old agents in second line therapy for worsening clinical condition (1.4%); 4) 12 patients treated with novel agents both in first and second line treatment (8.3%). Our analysis was focused on group 1 and 2. The group 3 was not considered for the small number of patients and because the choice of treatment was based exclusive on clinical worsening condition; the group 4 was not included for the small number of patients and because follow up is too short. OS at 10 years for patients of group 2 was significantly higher than patients of group 1 (20.4 vs 2.4%; p < 0.0001). Also PFS at 10 years showed better results for patients of group 2 (10% vs 2.3%; p = 0.02). The PFS2 at 10 years, considered as the interval from the start of the first line treatment to progression after second-line therapy or death from any cause, showed better results for patients of group 2 than patients of group 1 (25.7% vs 9.2%; p = 0.0002). Conclusions: Our experience confirmed that novel agents provide better outcome and deeper responses as induction treatment for YNDMM patients and tandem ASCT still improve the responses in these patients. Moreover, novel agents have also a significant impact in the subsequent lines of treatments, showing

	better results in terms of PFS2. In the light of the newer IMiDs and PIs, the challenge is to assess the exact role of ASCT in the modern setting; our next effort will be the evaluation of YNDMM patients treated with the new-generation agents (carfilzomib and others) in terms of outcome and safety, and the role of ASCT even in this setting, in a larger cohort of patients and with a appropriate follow up.
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