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Management of Induction Failures in Newly Diagnosed Transplant-Eligible Multiple Myeloma

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In this issue of *Leukemia & Lymphoma*, Blocka et al. report a retrospective case series of newly diagnosed transplant-eligible myeloma patients. They focus on a population of patients that failed to achieve a response after first-line induction therapy. A direct comparison is made between salvage therapy prior to transplant and compare this to outcomes in patients that go directly to stem cell transplantation with refractory disease [1]. The authors found that deepening of response with second-line induction therapy prior to stem cell transplantation did not improve progression-free or overall survival and concluded that primary non-responders could go directly to high-dose therapy and stem cell transplantation without compromising their progression free survival.

These conclusions must be taken with a caution. Despite a cohort of 1559 patients that were stem cell transplant-eligible, the group that received salvage therapy for induction failure prior to transplant numbered only 23 and would be underpowered to detect differences in outcomes. In addition, only 12 of these 23 received novel agents as part of their induction therapy, and the remaining 11 did not receive novel agent induction therapy, which could have a profound effect on the ability to achieve a salvage response. Even so, the question is clinically relevant. In the era of novel agent induction, response rates to triplet therapy are 86% [2]. This response rate is up from 50% to 60% in the era when induction was doxorubicin-vincristine-dexamethasone. The question of whether the 14% of patients failing to achieve a PR to induction would benefit from deepening the response pre-transplant is regularly asked.

There is no doubt that patients who fail to achieve a partial response to novel agent-based induction therapy have an inherently poorer outcome. These individuals have biologically declared themselves as being resistant to induction, usually with an immunomodulatory drug and proteasome inhibitor, usually bortezomib-thalidomide-dexamethasone or bortezomib-lenalidomide-dexamethasone. These patients, without regard to transplantation status, have an inherently poorer outcome. We previously have reported that progression-free survival was 22.1 months versus 13.1 months if there was an induction failure with immunomodulatory agents. Absence of a response to induction therapy predicts a poorer outcome after high-dose therapy [3]. The same conclusion can be drawn in patients who fail to respond to bortezomib-based induction. The three-year overall survival rates in bortezomib-responsive and bortezomib-non-responsive induction were 76% and 53%, respectively. Moreover, patients who were failures to induction with bortezomib-based

therapy were older, had lower hemoglobin, and had a higher incidence of ≥ 17 p and international stage 3 disease. In this analysis, bortezomib-based induction failure, seen in 25% of patients, was the strongest independent factor predicting survival [4]. Another group compared induction failure with patients that received both novel agent induction as well as non-novel agent induction. Patients who had not seen novel agents as part of induction and failed to respond that subsequently had stem cell transplantation had similar survival to those patients that responded to non-novel agent induction. However, if induction was novel agent-based and a response was not achieved, the four-year overall survival was 60.5%, highly significant, reaffirming that patients that fail novel agent induction therapy have adverse biology and are destined to do poorly with or without stem cell transplantation [5]. A confirmatory trial was published, demonstrating that in patients treated with bortezomib-dexamethasone, failure in attaining a very good partial response prior to stem cell transplant was associated with a shorter progression-free survival [6].

A retrospective analysis of patients whose data was submitted to the American Society for Bone Marrow Transplantation was reviewed; 539 patients with multiple myeloma were identified that went on to stem cell transplantation after having achieved less than a partial response to first-line induction therapy. Unfortunately, the dates were 1995 to 2010 and, presumably, the majority of these patients never had exposure to novel agents. Nonetheless, in this non-novel agent-based cohort, using second-line therapy before stem cell transplantation did not improve therapy-related mortality, relapse risk, progression-free or overall survival and concluded that if a patient failed to achieve a response to induction; immediate stem cell transplantation was fully justified without the use of a second-line salvage regimen [7].

There is a powerful association between response depth and survival outcomes in multiple myeloma, but this was largely limited to novel agent induction because achievement of very deep responses in the pre-novel agent era was infrequent [8].

One important trial that supports the use of second-line salvage prior to stem cell transplantation is the MRC myeloma XI trial [9]. In this trial 136 transplantation eligible patients received cyclophosphamide, thalidomide, dexamethasone (CTD) and 260 transplant eligible patients received cyclophosphamide, lenalidomide, dexamethasone (CRD). Patients achieving a very good partial response or better went directly to stem cell transplantation. Patients achieving less than a partial response received a proteasome inhibitor based triplet second-line. Patients achieving a minor response or a partial response (N=583) underwent randomization to further induction therapy with a proteasome inhibitor based triplet (cyclophosphamide bortezomib dexamethasone, CVD) or immediate transplantation. Overall 38% of patients improved their response following CVD. This translated into an improvement in progression free survival from 28 months to 48 months with a hazard ratio of 0.5 in the transplant eligible population. Post-transplant responses remained deeper for those randomized to receive cyclophosphamide bortezomib dexamethasone. This suggests that patients failing primary induction with an ImiD be considered for second-line therapy prior to stem cell transplantation.

One limitation of all of these comparative studies is few had carfilzomib, ixazomib, daratumumab, or pomalidomide included in induction. As induction regimens continue to improve, the answer to the question of second-line salvage therapy or immediate transplant may change. However, based on the available data we have at this time for the 14% of patients that fail to achieve a partial response or better after induction, immediate stem cell transplantation appears to provide similar outcomes to those patients receiving second-line salvage induction followed by autologous stem cell transplantation. As combinations of induction therapy evolve, this conclusion may change. But for the time being, one could not criticize a transplant center for immediately moving forward with autologous stem cell transplantation in the setting of primary refractory disease.

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