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In this issue of *Blood*, Gertz and colleagues present a retrospective study that analyzes progression-free survival and overall survival in 286 patients comparing those who did not reach a partial response or progressed during induction therapy with a regimen including thalidomide or lenalidomide to those who did achieve at least a partial response.

In multiple myeloma patients, the role of induction treatment before high-dose therapy and stem cell transplantation has been unclear. For many years, the administration of induction therapies with conventional chemotherapy did not improve the outcome of patients receiving high-dose therapy and autologous transplantation. Both progression-free survival and overall survival were not significantly different between patients sensitive or refractory to induction with conventional therapy.[1,2] This treatment paradigm has been changed by the availability of novel agents, such as thalidomide, lenalidomide, and bortezomib. With conventional chemotherapy, the partial response rate after induction therapy was around 50% and complete responses were quite rare. Treatment regimens using these novel agents report partial response rates ranging from 80% to 100%, and complete response from 20% to 40%.[3]

The outcome of the 286 patients studied by Gertz et al compared patients who did achieve a partial response during induction therapy with those who did not. The median overall survival after autologous transplantation was 73.5 months in patients who achieved a partial response and 30.4 months in those who did not ($P < .0005$). Similarly, median progression-free survival was 22.1 months in responders to induction and 13.1 months in nonresponders ($P < .0001$).[4] The authors of this article conclude that the lack of response during induction therapy or the progression, despite a short initial response during induction therapy, predict a poor outcome for patients receiving high-dose therapy and autologous transplantation.

In many studies, the achievement of response, in particular the achievement of complete response or very good partial response, has been considered a strong predictor of outcome, especially for patients undergoing autologous stem cell transplantation. In a recent study, both 5-year event-free survival and 5-year overall survival rates were significantly increased in patients achieving at least very good partial response after autologous transplantation. Unfortunately, this response marker is only available at the end of the entire treatment procedure including both induction and autologous transplantation.[5] The value of the finding of Gertz et al lies in the possibility of using a response marker in the early phases of therapy, allowing a better modulation of treatment choice immediately after the first courses of induction therapy. Other markers equally predict a poor outcome and the need for a more intense treatment approach. The most useful are advanced clinical stage such as the International Staging System 3 or chromosomal abnormalities, such as t(4;14), t(14;16), and del(17). Suboptimal response in the early phases of treatment may represent an advantage over biological markers for the treatment choice of an individual patient.

A suboptimal response might influence physicians' decisions on prolongation of induction therapy from 3 to 6 cycles. It might suggest an increasing of the potency of the induction regimen, moving from a 2-drug combination to a 3-drug combination that includes an additional agent, either novel agents or doxorubicin or cyclophosphamide. The advantage of a tandem, instead of a single, transplantation in patients with suboptimal response after induction therapy or in those with less than complete response after the first transplantation should be considered. Few data are available on the role of consolidation and maintenance

therapy after autologous stem cell transplantation. But similarly, the expectation of poor outcome predicted by suboptimal response after induction therapy might suggest the introduction of a consolidation approach after autologous transplantation, such as bortezomib-cyclophosphamide-dexamethasone, bortezomib-lenalidomide-dexamethasone, or bortezomib-thalidomide-dexamethasone combination.[6] Maintenance therapy is an alternative strategy. Three different phase 3 studies found that thalidomide maintenance improved progression-free and overall survival. Lenalidomide may offer the same advantage with less toxicity[7] and large randomized trials are now addressing its role in the posttransplantation setting. More recently, data on bortezomib maintenance are also showing efficacy in this setting.

Further studies are needed to assess the role of tailored therapies in patients with poor outcome. The study presented by Gertz et al clearly shows that patients who do not reach at least partial response after induction therapy will do considerably worse and different treatment approaches are needed. Whether intensification of induction, use of tandem transplantation, introduction of consolidation, or maintenance therapy are the appropriate choices to overcome poor outcome still remains an open question. Despite this, in newly diagnosed patients, it is reasonable to use all available options to improve suboptimal responses.

On the other hand, we should avoid the risk of undertreating patients with good tumor reduction after induction therapy or autologous transplantation. In a recent analysis, only patients who achieved at least very good partial response after autologous stem cell transplantation received a consolidation with the 3-drug combination, bortezomib-thalidomide-dexamethasone. In these good-prognosis patients, the addition of consolidation after transplantation improved the complete response rate from 15% after transplantation to 50% after consolidation. The absence of a consolidation approach in patients with very good partial response after transplantation may significantly decrease the possibility to achieve a complete response.[8]

In good-prognosis patients, the best treatment option, validated by large phase 3 studies, should be always considered to maximize the chance of a profound tumor reduction and a prolonged remission duration. In patients with poor prognosis, a more intense approach should be offered. The lack of a partial response after induction therapy with novel agents should now be considered another sign of poor prognosis and should suggest an intensification of the reference treatment.

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