Scientific & Clinical

INDUCTION THERAPY PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION

Myeloma Today in conversation with Prof. Antonio Palumbo

Antonio Palumbo, MD
University of Torino and Italian Multiple Myeloma Study Group (GISMM)
Torino, Italy

Your response to a study performed by investigators at the Mayo Clinic was recently published in Blood. Would you please explain the complex issues involved to our readers?

This retrospective study looked at the impact of response failure with thalidomide or lenalidomide regimen as induction therapy prior to autologous stem cell transplantation (ASCT) in multiple myeloma. The study analyzed progression-free survival (PFS) and overall survival (OS) in 286 patients, comparing patients who achieved a partial response (PR) to those who did not achieve at least a PR or progressed during therapy after induction with a regimen that contains thalidomide or lenalidomide.

The Mayo investigators conclude that an absence of a response to induction therapy with thalidomide or lenalidomide predicts a poorer outcome receiving high-dose therapy and ASCT. Study patients who did not achieve PR during induction therapy, or those who progressed despite a short initial response during induction therapy, had a significantly shorter OS from transplantation and a shorter PFS.

How do you assess the value of those results?

In many clinical studies, the achievement of response, in particular the achievement of complete response (CR) or very good partial response (VGPR) has been considered a strong predictor of outcome, especially for myeloma patients undergoing ASCT. In a recent study, both 5-year PFS and 5-year OS rates were significantly increased in patients achieving at least VGPR after ASCT. Unfortunately, this outcome can only be measured at the end of the entire treatment procedure including both induction and transplantation.

The value of the finding of The Mayo Clinic study is in the possibility of predicting response early in the therapy, thus allowing for a better assessment of treatment choices available to the patient after the initial courses of induction therapy.

Cytogenetic markers can predict a poor outcome and the need for a more intense treatment approach but suboptimal response in the early phases of treatment may represent an advantage over biological markers for the treatment choice of an individual patient.

What is your opinion about the therapy options for patients who do not respond to induction therapy?

If a patient has a suboptimal response to the initial treatment regimen – if the patient does not achieve PR on a two-drug combination therapy – from a practical point of view, an intensification of treatment should be considered to attempt to increase the patient's chances of reaching CR:

• Increasing the potency of the two-drug induction regimen by moving to a three-drug combination that includes an additional agent, then possibly a four-drug combination.

• Prolongation of induction therapy from three to six cycles.

• Consider the advantage of a tandem instead of a single ASCT.

• Decide on consolidation or no consolidation, although few data are available on the role of consolidation and maintenance therapy after ASCT. Three different phase 3 studies found that thalidomide maintenance improved PFS and OS. Large

randomized trials are now investigating the role of lenalidomide maintenance, which might offer the same benefits as thalidomide but with less toxicity. Data on bortezomib maintenance are also showing benefits in this setting.
Which 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.

What is your opinion about the therapy options for good-prognosis patients?
In good-prognosis patients, the best treatment option should be considered upfront to maximize the chance of a significant reduction of disease and a prolonged duration of remission. Clinicians should avoid the risk of under-treating patients who respond to induction therapy or ASCT. A recent study showed that in patients who have a good prognosis, the addition of consolidation after ASCT improved the CR rate from 15% after transplantation to 50% after consolidation.

Any closing comments?
It is difficult to give patients a clear message. Further studies are needed to assess the role of tailored therapy in myeloma. But physicians and patients should not underestimate the difference between the outcome of a phase 3 trial with 600 patients and the outcome of a phase 2 trial with 30 patients. It is risky to base standard of care regimens on small Phase 2 clinical trials. Evidence-based prospective phase 3 randomized clinical trials are essential to validate the standard of care treatment regimens for myeloma. MT
Editor's Note: The Continuing Medical Education (CME) article "Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction" by Drs. Gertz, Kumar, Lacy, Dispenzieri, Dingli, Hayman, Buadi, and Hogan (Division of Hematology, Mayo Clinic, Rochester, MN) was published in Blood on March 25, 2010.