in the protein’s DNA contact regions that weaken the binding of the protein to its targeted DNA but retain a similar protein structure. It is this second class that both gives rise to the adverse prognosis of DLBCL and often demonstrates allele-specific “gain-of-function mutations” that confers new properties on a mutant p53 protein. These mutant proteins apparently bind to other transcription factors (like p73) and alter their functions, making the cell more resistant to apoptosis and chemotherapy. These “gain-of-function” phenotypes have been demonstrated in cell cultures and in transgenic mice. The observations made in these papers suggest the possibility that allele-specific “gain-of-function” mutations can act in humans to contribute to poor overall survival. Unlike many tumor suppressor gene mutations, most of the p53 mutations found in tumors are missense mutations (92 in the DLBCL study), rather than deletions or insertions (10 in that study) that destroy the structure of the protein. That observation suggests that tumors may select for a p53 missense mutation that provides a helpful “gain-of-function” for tumor growth and survival before and during treatments. This idea will clearly need additional studies examining the possible altered transcriptional patterns brought about in a p53 mutant allele-specific fashion in DLBCL and FL. There ought to be a transcriptional “signature of genes” of that mutant p53 protein, disrupting the function of other transcription factors. The concept that tumor suppressor genes contribute to the origins and development of cancers by their loss of a function will now have to be modified to include the oncogene-like activity of a mutant p53 protein that has a “gain-of-function.”

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

Comment on Palumbo et al, page 3107

Crossover confusion: MPT still best

Brian G. M. Durie CEDARS-SINAI COMPREHENSIVE CANCER INSTITUTE

In this issue of Blood, Palumbo and colleagues describe the long-term results of adding thalidomide to MP as treatment for myeloma in elderly patients. Primary induction with MPT versus MP improves response and PFS, but not overall survival, in this study.

How best to use thalidomide and other novel agents like lenalidomide and bortezomib is the key question in myeloma clinical research today. Introduction of these agents has improved overall survival for myeloma patients, as illustrated by a recent Mayo Clinic analysis. However, which is the best combination and/or sequencing of agents? The trial by Palumbo and colleagues that led the way in evaluating modifications to the melphalan and prednisone (MP) regimen involved 331 patients: 167 patients received melphalan, prednisone, and thalidomide (MPT) for six 4-week cycles followed by ongoing thalidomide (100 mg) as maintenance versus MP alone in 164 patients for 6 cycles. Both response (partial response [PR], 68.9% vs 47.6%; 95% CI very good partial response [VGPR] 44.9% vs 14.7%); and progression-free survival (PFS) are substantially better (21.8 months vs 14.5 months) with MPT versus MP. However, overall survival is roughly equivalent at 45 months versus 47.6 months.

So how do we explain this and what can be recommended to patients? In the 2 French trials, MPT produced an improved response, PFS, and overall survival. The Facon et al trial included patients aged 65 to 75 years; the Hulin et al trial, patients age 75 or more years, as summarized and compared in the table. Collectively, these data led to the approval of MPT in the frontline nontransplant setting in Europe. The MPT PFS data at 24.1 to 27.5 months are very consistent: the major difference between the trials is the remarkably good overall survival in the MP arm of the Palumbo study, which results in no comparative survival benefit for the MPT arm. This is most likely because of the short MP induction of 6 months followed by rapid crossover, with relapse treatment incorporating novel agents including thalidomide. There is, in addition, the sense that the now-recommended longer frontline 12-cycle (18 months’) MPT induction regimen in the Intergroupe Francophone du Myelome (IFM) trials is more effective as a synergistic combination versus the 6-cycle MPT regimen followed by thalidomide maintenance. However, it is known that thalidomide maintenance does improve survival for patients with at least 10% residual disease (ie, < VGPR), which is a confounding factor in the Palumbo et al trial. Further clarification is also awaited with regard to 2 MPT versus MP studies that show prolongation of PFS but no overall survival benefit.

Right now, the final analysis is that MPT is a very effective new standard of care for patients in the nontransplant setting. Increasingly, crossover therapy can be expected to confuse the interpretation of frontline trials. Recently, Morgan et al have used a new statistical approach assessing “life-years” in an effort to compensate for the impact of crossover. The duration of induction therapy is also a crucial variable deserving more attention, particularly since magnetic resonance imaging data indicate slow evolution of remissions over 12 to 18 months.

As far as comparative efficacy is concerned, it is important to note a recent randomized trial indicating equivalent, but not better, PFS with thalidomide and dexamethasone versus MP. Conversely, a large randomized trial comparing 12.5 months of bortezomib plus MP (VMP) versus MP showed striking response and PFS superiority of VMP versus MP. However, the PFS of 21.7 months is similar to MPT, and greater neurotoxicity with bortezomib is a concern. There is excitement about what can become the next new standard in the nontransplant setting. Strong candidates are MP plus lenalidomide (MPR)
and lenalidomide plus low-dose dexamethasone. Early data indicate excellent PFS and overall survival results with both. The 82% 2-year survival seen with ongoing lenalidomide/low-dose dexamethasone therapy (for patients ≥ 65 years) is particularly promising. This ECOG trial also brings into focus the need to assess best response and survival over time. The results of direct comparative trials are awaited with great anticipation.

For now, the current standard is MPT, which is a well-tolerated oral regimen with a manageable side effect/toxicity profile. A personalized approach to treatment selection is recommended, and can allow use of MP alone for very elderly or frail patients and stronger consideration of VMP in the setting of high-risk cytogenic features and/or renal impairment and/or if deep vein thrombosis risk is a particular concern. Neurotoxicity can be proactively managed for both MPT and VMP with appropriate dose modifications as necessary. It is wonderful to finally have effective new options available for tailored use.

**Conflict-of-interest disclosure:** The author is on the advisory boards of both Celgene and Millennium Pharmaceuticals.

**REFERENCES**


**MPT comparisons: treatment durations and crossover therapy**

<table>
<thead>
<tr>
<th>Trial (ages ≥ 65 and &gt; 75)</th>
<th>Response at 6 to 18 mo, %</th>
<th>PFS median, mo</th>
<th>Duration of induction MP and MPT, mo</th>
<th>Thalidomide maintenance</th>
<th>Thalidomide at relapse for MP</th>
<th>Median overall survival for MPT, mo</th>
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<tr>
<td>Italian</td>
<td></td>
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*Thalidomide and bortezomib combinations used.

**CLINICAL OBSERVATIONS**

Comment on Barlogie et al, page 3115

**Biology, treatment, and time**

Angela Dispenzieri  MAYO CLINIC

Barlogie and colleagues report that patients with abnormal baseline metaphase cytogenetics and enrolled on TT2 had better overall survival (OS) rates when randomized to thalidomide.

**T**otal therapy 2 (TT2) was a randomized prospective treatment trial composed of a complex regimen (induction, 2 autologous peripheral blood stem cell transplantations [ASCT’s], consolidative chemotherapy, and maintenance) given with or without thalidomide during all phases of treatment. In their original report with 42 months’ follow-up, the higher complete response and event-free survival rates enjoyed by patients on the thalidomide arm had not translated into superior OS. However, in the current paper at 72 months’ follow-up, a distinct survival advantage was seen for the 30% of patients with abnormal cytogenetics.

This paper carries 3 important messages. The first but simplest is a reminder that early reports of OS may be misleading. The second is that with novel agents and transplantation, in selected patient populations, unprecedented OS rates can be achieved; for TT2, the median OS was 8 years!

The third concept is that thalidomide administration as part of the initial treatment strategy for patients with myeloma has an important impact on long-term OS for the subgroup of patients with abnormal cytogenetics. Given the potential for toxicity using this drug (grade 3–4 peripheral neuropathy in 27% for TT2 with thalidomide vs 17% without) and 80% 5 year OS in other less complex tandem transplant strategies for low-risk patients (low β2 microglobulin and no deletion 17, deletion 13, or t[4;14]) by fluorescence in situ hybridization (FISH), it is a critical observation that the 70% of patients with normal cytogenetics do not benefit from thalidomide incorporated into TT2.

There are 7 other randomized trials that address the role of thalidomide in association with alkylator-based therapy; however, none focuses on the heterogeneity of myeloma biology and its interaction with thalidomide. The Intergroupe Francophone du Myelome (IFM)
Crossover confusion: MPT still best

Brian G. M. Durie