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CLINICAL TRIALS

Comment on Morgan et al, page 7

M(yeloma)IXing up T maintenance

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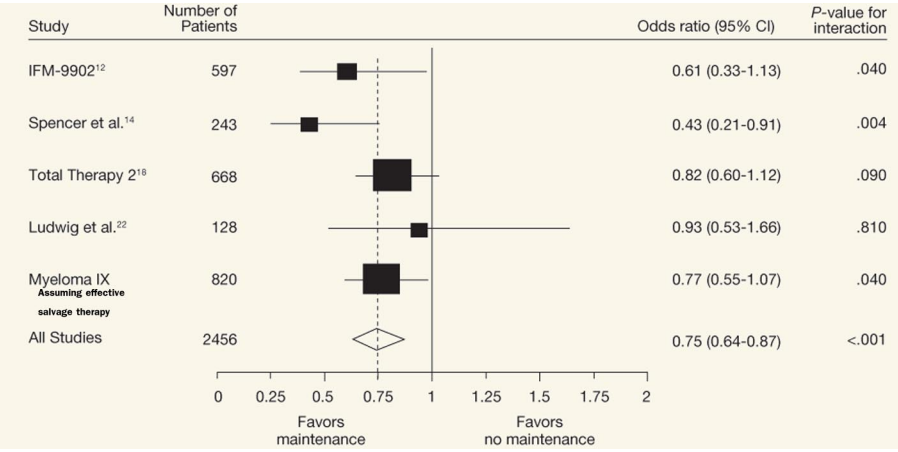
In this issue of *Blood*, Morgan et al clearly show the benefit of thalidomide maintenance in both transplant-eligible and -ineligible patients treated during the MRC Myeloma IX study.[1] This approach adds to the global effort to convert myeloma from an aggressive malignancy with a dismal prognosis to a chronic disease by examining the use of maintenance therapies that should be both efficacious and tolerable in the long term.



Meta-analysis of studies including a thalidomide maintenance regimen. Forest plot demonstrates overall survival (OS) with thalidomide maintenance ($P < .001$). Taken from Morgan et al[1] with permission.

This is the largest randomized study to date to examine the role of thalidomide maintenance, with 820 of an initial cohort of 1970 patients eligible for randomization, and a prolonged median-duration follow-up of 46 months. The data show a significant improvement in progression-free survival across the entire patient cohort (23 vs 15 months) as noted in previous studies[2-5] and help to finally resolve this question. The benefit was most marked in intensively treated patients with a median benefit of 7 months. The results were less impressive in older patients, treated on a nonintensive pathway, where the median improvement in progression-free survival was only 2 months.

An overall survival benefit was not seen in the initial analysis and Morgan and colleagues suggest this is because of the lack of effective salvage therapy available at the time with 48% receiving thalidomide (single agent or in combination) as salvage therapy at the time of progression. This lack in efficacy of salvage thalidomide was most marked in those who received thalidomide during induction and maintenance and there was no detrimental effect in those salvaged with other novel agents, suggesting that maintenance thalidomide does not induce significant cross-resistance. The application of a mathematical model examining the impact of thalidomide maintenance in the context of effective salvage suggested a significant improvement in overall survival across the whole cohort of 5.5% at 3 years (hazard ratio = 0.77, 95% confidence interval 0.60-0.99) and the results of a meta-analysis of this and previously published studies (see figure) seem to confirm this.

The impact of cytogenetics as assessed by interphase fluorescence in situ hybridization (iFISH) is of particular interest. In contrast to the results of the Total Therapy 2 trial, in which the benefits of thalidomide maintenance were greatest in those with adverse metaphase cytogenetics,[3] the favorable subgroup in the Myeloma IX study [defined as the absence of a gain(1q), del(1p32), t(4;14), t(14;16), t(14;20), del(17p)] benefitted from maintenance thalidomide in terms of progression-free survival and an emerging benefit in overall survival; the adverse risk group actually fared worse in terms of overall survival and these observations may help define a group of patients in whom this strategy should be avoided.

Morgan et al have attempted to determine whether the benefit of maintenance thalidomide was because of a true maintenance or consolidation effect. There was no difference in the number of patients who improved their response between the maintenance versus no maintenance arms. Although there was no discernable effect of thalidomide maintenance on progression-free survival in patients with favorable iFISH achieving a complete response, those patients who did not achieve a complete response at the time of randomization benefitted from a significantly improved progression-free survival and an emergent effect on overall survival. The authors suggest that these observations are consistent with a true maintenance effect and seem to be in keeping with the results of other studies that suggest there is no benefit in thalidomide maintenance in those who have already achieved a deep response.[2,4]

Thalidomide maintenance therapy has previously been used at doses ranging from 50 to 400 mg. The Myeloma IX study shows that smaller doses of 50 to 100 mg are sufficient to provide clinical benefit but it also emphasizes the fact that long-term tolerability remains an issue with this agent, as shown by median duration of treatment of 7 months with 50% of subjects discontinuing treatment before progression and one-quarter stopping because of peripheral sensory neuropathy.

There is now little doubt that a low-dose thalidomide maintenance strategy is beneficial in some patients, whether treated intensively or not. However, close monitoring for toxicity, especially neuropathy, is mandatory to prevent compromising further treatment options such as bortezomib. In the future, maintenance treatment with agents that are better tolerated is likely to become the standard of care for all myeloma patients. In this regard both lenalidomide and bortezomib have proven to be effective and safe.[6-8] Lenalidomide appears to be an attractive oral agent with a low toxicity profile, which may overcome many of the issues noted with thalidomide including neuropathy, but bone marrow suppression with prolonged exposure remains a potential concern. Other options for maintenance therapy include histone deacetylase inhibitors, such as romidepsin[9] and panobinostat; antibodies such as elotozumab (anti-CS1) are also being investigated. For the foreseeable future, thalidomide will remain the standard of care for maintenance therapy for selected patients with newly diagnosed myeloma because it is the most widely investigated and accessible agent in this setting.

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Comment on Karp et al, page 55

Two genes, tipifarnib, and AML

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Karp and colleagues' study of tipifarnib plus etoposide for elderly adults with newly diagnosed AML in this issue of *Blood* can be divided into two sections: (1) evaluating two dosage schemes of the combined therapy and (2) the use of a two-gene ratio of high *RASGRP1* and low *APTX* expression to predict which patients are most likely to benefit from tipifarnib based therapies.[1]

The outcome of AML in elderly patients continues to be dismal, particularly for those patients who are not candidates for conventional high-dose therapy. These cases are often complex, with multiple comorbidities, less tolerance and less responsiveness to conventional chemotherapy, and possession of adverse prognostic features such as unfavorable cytogenetics and antecedent myelodysplastic syndrome at diagnosis; all predicting for a gloomy future.[2] Elderly AML patients are in dire need of new and better therapeutic options.

Farnesyltransferase inhibitors (FTIs) are one of the alternative therapeutic options being explored for elderly AML. FTIs function by competitively inhibiting the addition of a farnesyl moiety to several important signaling molecules[3] and thus target multiple pathways, including the RAS pathway implicated in the pathogenesis of solid and hematologic malignancies.[4,5]

Ras, a small farnesylated GTPase, is critical for many receptor-mediated pathways leading to MEK/ERK activation.[2] The *RAS* family of genes is involved in the regulation of proliferation, differentiation, cell adhesion, and apoptosis of cells. The farnesyl group on *RAS* is essential for activation. Activation of RAS genes with or without activating mutations is frequent in MDS and AML.[2] Targeted disruption of farnesyltransferase by FTIs leads to the inactivation of *RAS* function. Yet to be understood is the lack of correlation between *RAS* mutations and response to FTIs in clinical studies. Possibly this reflects *RAS* activation by alternative pathways.

Tipifarnib is an oral, very potent, and highly selective FTI with a relatively low toxicity profile.[6] Single-agent tipifarnib has shown antileukemic activity in patients with MDS and refractory/poor risk AML[7] However, a phase 3 study comparing single-agent tipifarnib to best supportive care including hydroxyurea in patients 70 years of age or older with untreated AML failed to demonstrate a survival advantage of tipifarnib.[5,8] Subsequently, based on evidence of in vitro synergy for tipifarnib with etoposide, a phase 1 trial combining these two agents in elderly poor-risk AML patients led to an improved CR rate of 25% across multiple dose levels of both drugs compared with 14% for single-agent tipifarnib.[9] Disappointingly similar results were attained in the present phase 2 study of tipifarnib and etoposide at two dose schedules.[1]

The most compelling portion of this study is the use of high *RASGRP1* and low *APTX*