Tumor biology should drive classification efforts

We readily acknowledge the many contributions of Professor Daniel Catovsky’s group to the current understanding of T-cell leukemias. However, we fundamentally disagree with the philosophy expressed by them in their present letter and elsewhere. In our opinion, tumor categorization follows understanding and does not precede it. Such classifications are always provisional and subject to improvement based on new knowledge. The current World Health Organization (WHO) scheme is no exception.

Our paper was intended to provide an overview of the types of mature T-cell leukemias encountered at a large referral center and how they relate to the WHO entities. The relative rarity of these tumors means that the unambiguous classification of T-cell tumors remains a difficult task for many hospitals, including our own. We identified helpful parameters for assigning a given T-cell leukemia to a particular WHO category, but also discuss how difficult-to-classify cases and overlap cases point to areas for further study.

A short list of these unresolved issues would include (1) the nature of the 20% to 30% of cases currently classified as T-cell prolymphocytic leukemia (T-PLL) that lack TCL1 expression and their relationship to classical TCL1-expressing T-PLL; (2) the histogenesis and appropriate classification of TdT-negative, high-grade T-cell leukemias with blastoid morphology; (3) heterogeneity in the behavior of large granular lymphocyte proliferations; (4) the pathogenetic relationship of mycosis fungoides to primary Sezary syndrome, which, despite the assertion of the authors above, often lacks epidermotropism on skin biopsy; and (5) the mechanism of action of TCL1, which is the only well-established oncoprotein specifically associated with mature T-cell leukemias, remains a puzzle.

Finally, we believe that future tumor classifications will require more than just diagnostic categorization. Classifications will also incorporate data on risk stratification, pattern of disease progression, and underlying pathogenesis to help guide the optimal selection and timing of therapy. Although the current WHO scheme touches on these areas, we fully expect that future versions will continue the progress in that direction.

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References


To the editor:

Best therapy for primary amyloidosis, a not-yet-solved question

We read with interest the paper from Dispenzieri et al in the May 15, 2004, issue of Blood on a case-match-control study comparing overall survival of 63 primary amyloidosis (AL) patients undergoing transplantation with 63 patients not undergoing transplantation. In contrast, we do not agree with J. Mehta when he wrote, in the accompanying editorial, that “The data from the Mayo Clinic and Boston University are impressive enough to make a prospective, randomised study of high- versus conventional-dose therapy in amyloidosis scientifically unattractive and practically impossible.”

In their paper, Dispenzieri et al compared the survival of amyloidosis patients who received high-dose therapy in the Mayo Clinic in the late 1980s and early 1990s with the survival of matched control patients who were treated by various therapeutic regimens, mainly melphalan and prednisone (MP), but also colchicine and vitamin E, in the early 1980s. From our point of view this study only supports the fact that for selected AL patients, in a center with a great experience, intensive treatment with stem cell support is better that treatments used in the control group. The authors themselves are much more careful than Mehta in their conclusions.

We considered 4 years ago that a prospective randomized comparison of intensive and conventional treatment was needed to solve the issue of the respective merits of both therapeutic strategies in the different risk-groups of AL patients. We thought at this time, as Mehta does, that to compare intensive treatment with MP was unattractive and we choose, as conventional treatment, an association of melphalan and high-dose dexamethasone (M-Dex; melphalan 10 mg/m² and dexamethasone 40 mg for 4 days each month up to 18 months), hypothesizing that this regimen could
provide more frequent and more rapid hematological responses than MP, with subsequent improvement in involved organ function and survival.

The results of a close regimen (same schedule and dose for dexamethasone, melphalan 0.22 mg/kg instead of 10 mg/m² treatment up to 9 months) was recently reported in *Blood* by Palladini et al.³ with a response rate much higher than the one known with MP. 67% of patients achieving a hematological response and 33% a complete remission, versus 28% overall responses for MP.⁴ Functional improvement of the organs involved was observed in 48% of treated patients. This good efficacy seems to have a positive impact on survival and to compare favorably with the one reported after high-dose therapy with stem cell support.⁵

Our experience with M-Dex is similar, with a good response rate, which is probably a little bit lower than with high-dose therapy but with fewer treatment-related deaths, especially in a multicentric setting. Moreover, responses with M-Dex can be very rapid, with a complete response after 1 course for some patients, and most responses occurring before 6 months.

Thus, in contrast to Mehta, we believe that benefit/risk ratios of high-dose versus an effective conventional therapy like M-Dex must be compared in a randomized fashion in patients with primary amyloidosis. In our randomized trial, which is ongoing, M-Dex is compared to a high-dose regimen using melphalan (200 or 140 mg/m², depending on age and clinical status) supported with autologous blood stem cells previously collected after mobilization with granulocyte colony-stimulating factor (G-CSF) alone. More than 80 of the 100 patients planned have been included already in 25 centers, demonstrating that such a study is realizable. We hope that it will be completed at the end of this year and will help to solve the still-persisting issue of dose intensity in AL.

**To the editor:**

**The role of PBSCT in treatment of AL amyloidosis is far from settled**

In contrast to the view proposed by Dr Mehta in the commentary¹ accompanying the case-control study of peripheral blood stem cell transplantation (PBSCT) versus conventional therapy for AL (primary) amyloidosis reported by Dispenzieri et al.² we believe that the role of high-dose therapy with autologous stem-cell rescue for the treatment of AL amyloidosis is far from settled. Neither the commentary, nor the report describing favorable outcomes of patients with AL amyloidosis who laterally underwent PBSCT compared with historical matched controls who were treated “conventionally,” gave sufficient consideration to the generally improved survival of patients with this disease in recent years. Patients in the PBSCT arm were diagnosed from 1992 to 2001 (median, 1999), whereas the matched controls, most of whom were treated with low-dose oral melphalan-prednisone (MP), had been diagnosed from 1983 to 2000 (median, 1992). The Mayo Clinic group has previously reported that patients with AL amyloidosis who were recruited to 1 study between 1982 and 1992 and treated with MP had a median survival of 18 months,³ compared with a median survival of 29 months for another cohort treated identically in a subsequent study performed from 1991 to 1997.⁴ Their inclusion of 7 of 63 control patients who had therapies now recognized to be ineffective (colchicine) or experimental IDOX [4′-iodo-4′-deoxydorubicin] and vitamin E) is also perplexing.

Systemic AL amyloidosis is a highly idiosyncratic disease, and there are many patients in whom treatment with neither PBSCT nor MP is appealing. It is therefore encouraging that numerous other therapeutic options have lately been reported that hold promise of greater and more rapid response rates than MP without the substantial treatment-related mortality and morbidity and high cost associated with PBSCT. Such regimens include dexamethasone with oral or infused melphalan, vincristine-Adriamycin (dorxorubicin hydrochloride)-dexamethasone, and thalidomide-based protocols.⁵ The results of an ongoing randomized French Intergroup study comparing PBSCT with melphalan-dexamethasone are awaited with keen interest throughout the amyloid community.

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**References**

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