To the editor

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High-Dose Melphalan versus Melphalan plus Dexamethasone for AL Amyloidosis

TO THE EDITOR: Jaccard et al. (Sept. 13 issue)[1] report on a difficult trial comparing high-dose melphalan with melphalan plus dexamethasone in patients with immunoglobulin-light-chain (AL) amyloidosis, but their results must be interpreted with caution. The treatment-related mortality rate (24%) in the group that received high-dose melphalan is more than twice the rate in centers performing transplantations for AL amyloidosis.[2] The study by Jaccard et al. enrolled many patients with involvement of three or more organs (36%) and poor cardiac status, thereby introducing a bias in favor of melphalan plus dexamethasone.[2] Moreover, 10 of 37 patients in the group treated with high-dose melphalan received an inadequate dose of melphalan (140 mg per square meter of body-surface area).[3] The results underscore the lack of benefit of high-dose melphalan in high-risk patients but do not address the role of high-dose melphalan in lower-risk patients.

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TO THE EDITOR: The French multicenter study reported by Jaccard et al. showed no difference between high-dose melphalan and melphalan plus dexamethasone in AL amyloidosis. This finding raises questions concerning the management of life-threatening diseases. Should patients with rare diseases such as amyloidosis be treated anywhere (the average center enrolled <1 patient annually) or only at experienced referral centers?[1] Does the need for simple treatment options that can be delivered anywhere and to everyone negate the need to develop intensive (and potentially toxic) options that may provide additional therapeutic benefit for selected patients? Transplant-related mortality is substantially higher at low-volume, inexperienced centers[1] — very likely a concern with most of the study centers.

It is unclear whether the groups in the French study were truly comparable, since no information was provided on levels of the N-terminal fragment of B-type natriuretic peptide and troponin T, biomarkers shown to be of critical prognostic significance in amyloidosis.[2]

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TO THE EDITOR: Despite the absence of comparative trials, stem-cell transplantation has been adopted widely in the treatment of AL amyloidosis, particularly in North America, but it has been associated with procedural mortality of more than 13%, even in specialist centers. In contrast, chemotherapy without transplantation has been favored in the United Kingdom, where the median survival exceeded 60 months and treatment-related mortality was less than 7% among 448 patients with AL amyloidosis who received such regimens.[1] Furthermore, a complete clonal response is not always necessary for long-term survival, since one third of patients with AL amyloidosis at our center who survived for longer than 10 years had only a partial hematologic response. The findings of our open but relatively large studies thus accord with those of the study by Jaccard et al. and, outside the context of much-needed larger clinical trials, support cyclic chemotherapy guided by frequent assessments of serum free immunoglobulin light chains and organ function, weighed cycle by cycle against treatment-related toxicity.[2]

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TO THE EDITOR: The inferior survival (median, 22 months) of patients treated with high-dose melphalan for AL amyloidosis, as reported by Jaccard et al., is probably due to the design of the study. Intensive treatment of AL amyloidosis is a challenge; in the French trial, there were 50 intended transplantations during 5 years in 29 centers, and treatment delay may have contributed to the high treatment-related mortality in the high-dose melphalan group.

In the prospective multicenter trial conducted by the Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON), 70 previously untreated patients with AL amyloidosis (World Health Organization performance-status score, 0 to 2), 47% of whom had cardiac involvement and more than 55% of whom had high-risk disease,[1] received vincristine, doxorubicin, and dexamethasone (VAD), followed in 47 patients by high-dose melphalan (140 to 200 mg per square meter). The transplantations were performed in tertiary referral centers. Nine patients died from treatment-related causes (13%): seven during treatment with VAD and two after treatment with high-dose melphalan. The 4-year overall survival rate among all the patients was 62%, while the 4-year survival rate after transplantation was 78%.

We believe that there is still insufficient evidence that intensive therapy for AL amyloidosis should be abandoned.

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TO THE EDITOR: The French phase 3 trial of stem-cell transplantation for systemic AL amyloidosis shows the morbidity that results when the treatment of patients with multiorgan dysfunction is based on criteria for transplantation that are "not as stringent as those used in large North American centers."[1,2] We have completed a phase 2 trial testing risk-adapted stem-cell transplantation and adjuvant chemotherapy in 45 patients with newly diagnosed, untreated AL amyloidosis (NCT00089167). Aggressive supportive measures minimized the morbidity associated with granulocyte colony-stimulating factor and gastrointestinal bleeding, and there was a stopping rule for a rate of treatment-related morbidity exceeding 10%. The rate of treatment-related morbidity was 4%; the rates of overall and complete hematologic responses were 79% and 38%, respectively; and the rate of organ responses was 48%.[3] Median survival is undefined and for patients with cardiac involvement exceeds 3 years.

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THE AUTHORS REPLY: The comments about our report mainly concern patient selection and the multicenter nature of our study. We addressed the critical issue of patient selection by means of a subgroup analysis using the Mayo Clinic criteria.[1] For patients with high-risk disease, the results confirmed the lack of benefit of high-dose melphalan, as already suggested by others.[2] For patients with low-risk disease (59 patients, including 27 with only one involved organ, who received mainly 200 mg of melphalan per square meter when treated in the high-dose group), the survival curves showed a nonsignificant difference in favor of oral melphalan plus high-dose oral dexamethasone, challenging the use of high-dose melphalan in this group of patients. For patients

treated with oral melphalan plus high-dose oral dexamethasone, the 3-year overall survival rate was 80%, showing that they were actually "good risk" patients. With censoring of data for patients who died early and patients who could not receive their assigned treatment, the results of the landmark analysis strongly argued against the superiority of high-dose melphalan, even in groups with 0% treatment-related mortality and 100% treatment feasibility. This probably resulted from the very similar hematologic response rates in the two treatment groups, in a disease in which a clonal response is mandatory for improved survival.

Our 24% rate of treatment-related mortality with high-dose melphalan is in keeping with the results of several other multicenter studies and can be considered as representative of the results with high-dose melphalan when used outside some tertiary referral centers. The better results obtained in these referral centers probably reflect not only better management of the disease but also better selection of candidates for high-dose melphalan. Both were likely factors in the impressive results reported by Comenzo et al. Studies comparing new standard-dose regimens with (optimized) high-dose treatments should now be performed in tertiary referral centers. In our opinion, further improvements in the survival of patients with AL amyloidosis are likely to result from the use of new drugs and innovative therapeutic approaches.

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Early Thimerosal Exposure and Neuropsychological Outcomes

TO THE EDITOR: Thompson et al. (Sept. 27 issue)[1] report the results of a study investigating the neuropsychological outcomes of early exposure to thimerosal. As a dissenting member of the panel of external consultants for this study, I object to the authors' conclusion that there is no causal association between thimerosal and children's brain function. The sample comprised children who were least likely to exhibit neuropsychological impairments. Specifically, children with congenital problems, those from multiple births, those of low birth weight, and those not living with their biological mother were excluded. The sample was skewed toward higher socioeconomic status and maternal education — factors that are associated with lower rates of neurobehavioral problems and higher intervention rates and that were not measured. The sampling frame included only children enrolled from birth in the health maintenance organization (HMO) and still enrolled after 7 to 10 years, excluding children in higher-mobility families, who tend to have lower academic and behavioral function.[2] Children with neurobehavioral problems may have been less likely to remain with the HMO. Only 30% of families selected for recruitment participated, a low rate for scientific research. Among the families selected for recruitment, 26% refused to participate. Another 28% "could not be located," which included families that did not respond to multiple recruitment attempts (internal documentation from the study contractor, Abt Associates) — another form of refusal.

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TO THE EDITOR: Recently, I summarized several nutritional factors that are likely to play a large