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/m,[2] 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/m^2, 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.

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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 commentary[1] 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 lately 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′-deoxydoxorubicin] 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 (doxorubicin hydrochloride)-dexamethasone, and thalidomide-based protocols.[5,6] 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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Response:

Determining appropriate treatment options for patients with primary systemic amyloidosis

We would like to thank Dr Jaccard and colleagues and Dr Goodman and colleagues for their cogent comments on our recent paper.[1] We agree that there is no substitute for a sufficiently powered, well-designed, randomized controlled trial to answer questions pertaining to optimal treatment. In a disease as heterogeneous in its manifestations and in its severity as primary systemic amyloidosis (AL), the challenges of making treatment decisions and comparing phase 2 results are further compounded.

We too were impressed by the results of Merlini's group (Palladini et al,[2] from Pavia, Italy) and eagerly await the results of the ongoing randomized controlled trial of Jaccard et al. The Pavia group has recently reported an overall hematologic response rate of 66%, a complete response rate of 33%, and an organ response rate of 48% using oral melphalan and dexamethasone.[2] With a median follow-up of only 20 months, 9 patients (20%) have died, the majority (7 patients) of whom were nonresponders. It will be most interesting to see the long-term progression-free and overall survival rates from the Pavia group study. The Intergroupe Francais du Myelome 94 trial has shown that comparable complete response rates in patients with myeloma do not translate directly into comparable overall survival rates.[3] In that study, despite equivalent complete response rates in the single and tandem transplantation arms, the myeloma patients undergoing tandem transplantation enjoyed a 7-year overall survival, double that of the single transplantation arm.

Drs Goodman and Hawkins suggest that there are other promising therapeutic options that "hold promise of greater and more rapid response rates than melphalan and prednisone without the substantial treatment related mortality and morbidity. . .associated with PBSCT." We remind the authors and the readers that these "promising" alternatives have only been tested in the context of observational and phase 2 trials. Moreover, thalidomide has been shown to be quite toxic in this group of patients.[4,5] Although reported to be associated with hematologic response rates as high as 60%,[6] vincristine-adriamycin-dexamethasone, in theory, could also be quite toxic to patients with AL given the known risk of vincristine and adriamycin in patients with neuropathy and cardiomyopathy, respectively. Lachmann et al's report of cyclical intermediate-dose intravenous melphalan (25 mg/m^2) in 24 patients is also quite encouraging, with more than half of the patients achieving at least a 50% reduction in serum immunoglobulin-free light chain and more than a third demonstrating regression of amyloid load by serum amyloid P component (SAP) scintigraphy.[6] However, only a phase 3 trial will definitively clarify its utility.

The discussion of phase 2 trials brings us to the concept of "response," which is replete with difficulties. What types of responses are most meaningful in AL: hematologic or clinical? In a disease with low tumor burden, like AL, what is a hematologic response? Is it 50% reduction of the M-spike in the serum or in the urine (the latter frequently contaminated by nonspecific proteinuria)? Or is it disappearance of the monoclonal protein and bone marrow plasmacytosis by immunofixation and immunostains? The introduction of the serum immunoglobulin *free* light chain assay (The Binding Site, Birmingham, United Kingdom) has revolutionized our ability to assess hematologic response in patients with a low tumor burden, but there is not yet a consensus on hematologic response criteria using this tool. While only one third of amyloid patients have serum M-spikes of more than 0.1 g/L (1 g/dL) (measurable disease), more than 90% of patients have measurable disease with this new assay.[6,7] Moreover, what is an organ response? How much clinical improvement is required to code a response? There has been an international consensus opinion proposed by the 10th International Symposium on Amyloid and Amyloidosis, which attempts to standardize definitions of organ involvement and treatment response (M.A.G., Ray Comenzo, Rodney H. Falk, Jean Paul Fermand, Bouke P. Hazenberg, Philip N. Hawkins, Giampaolo Merlini, Philippe Moreau, Pierre Ronco, Vaishali Sanchorawala, Orhan Sezer, Alan Solomon, and Giles Grateau, manuscript submitted August 2004).

Certainly several of these issues will be attenuated in the context of a randomized clinical trial. However, only meticulous stratification of patients will allow for interpretable results. Once again, there is no consensus on the best stratification factors in patients with AL, although dominant organ involvement and number of organs involved have been used. Recent data would suggest that using serum levels of cardiac biomarkers may be powerful tools to stratify patients with AL.[8-10]

So what is the best treatment for AL? We agree with Jaccard and colleagues and Goodman and colleagues that for now, the best choice for patients is a well-designed, randomized controlled trial. Until the results are available from such trials, what are hematologists with newly diagnosed AL patients to do? Although not a phase 3 trial, our data suggest that offering high-dose chemotherapy with peripheral blood stem cell transplantation is an appropriate ethical option with potential for improved survival. Referral to an amyloid treatment center for an opinion regarding transplantation is recommended since excellent long-term survival in patients (albeit selected patients) receiving this therapy has been repeatedly demonstrated.[1,11,12]

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Response:

High-dose therapy for amyloidosis

Jaccard et al's caution against high-dose therapy and autologous hematopoietic stem cell transplantation (HSCT) for AL amyloidosis[1] may well prove right if the group's ongoing study, after completion of accrual and adequate follow-up, eventually does show equivalent outcomes with conventional-intensity melphalan-dexamethasone and high-dose melphalan. While their rejoinder implies good outcomes with melphalan-dexamethasone that are comparable to high-dose chemotherapy in the study, exactly what the results are and how they compare with other published data will remain unknown until the study matures and numbers replace descriptions. Methodologic issues may well influence the relevance of the findings. For example, if the dose of melphalan for HSCT in the French cooperative study has been less than 200 mg/m^2 (a point not clarified in Jaccard et al's comments), based on the Boston University data showing superior outcome with the higher dose of melphalan,[2] its findings may well be considered questionable even before the accrual target is met.

There is a well-defined center effect influencing the results of allogeneic HSCT: larger volumes (and correspondingly, experience) being associated with superior outcomes.[3] It is very likely that such an effect exists for autologous HSCT AL amyloidosis too because of the unusual and serious nature of the complications patients with this disease tend to develop after high-dose therapy. If the French experience does suggest higher treatment-related mortality with HSCT than with melphalan-dexamethasone, it is likely to be at least partially attributable to lack of adequate experience since, on an average, each center appears to be recruiting fewer than 1 patient on study per year—and thus autografting 1 patient every 2 years. It is debatable whether such a concern would be applicable to an equal extent to centers with much greater experience in treating patients with amyloidosis.[2,4] If the outcome of autotransplantation in the French study is inferior to that reported by the Boston University and Mayo Clinic groups largely due to higher treatment-related mortality, I would argue that the interests of French patients with amyloidosis would be far better served by receiving high-dose therapy at a small number of specialist centers around France rather than abandoning high-dose therapy altogether.

A number of groups, including ours, have adopted the interesting approach reported by Palladini et al[5] in patients ineligible for HSCT because of the ineffectiveness of other treatment approaches. However, just like the Palladini group,[5] we continue to offer high-dose therapy with autotransplantation to all patients who are eligible for it. If longer follow-up of the data presented by Palladini et al shows that the outcome of melphalan-dexamethasone–treated patients ineligible for HSCT appears similar to that of HSCT recipients treated optimally (200 mg/m^2 melphalan), that would indeed signal a need for a prospective, randomized study comparing melphalan-dexamethasone and high-dose melphalan.

While the retrospective experience of London's National Amyloidosis Centre[6] quoted by Goodman and Hawkins may appear to suggest that the extent of response rather than the type of therapy is important, the paper does not provide adequate information on biologically relevant characteristics to show whether the patient populations were comparable. The study also does not clearly depict event-free and overall survival by the type of therapy provided. Additionally, after initial assessment at the Centre, patients were treated locally by referring physicians, thus bringing up the question of experience influencing outcome just as with the French study.

The Palladini study[7] quoted by Goodman and Hawkins is an evaluation of prognostic indicators rather than specific treatment options or useful alternatives to HSCT. While HSCT may not turn out to be the best approach for AL amyloidosis in the future if newer options evolve, the only substantial peer-reviewed evidence currently available in patients who have been studied in depth and treated relatively homogeneously comes from Boston University and the Mayo Clinic—and favors high-dose melphalan with HSCT.

Following McElwain and Powles's report of the extraordinary activity of high-dose melphalan in plasma cell dyscrasias,[8] it took 15 to 20 years for randomized studies to be published showing that high-dose therapy was indeed beneficial[9,10]—time that Barlogie et al[11,12] spent studying important second-generation dose-intensity questions. The Jaccard study evaluating HSCT in amyloidosis should of course continue. However, should we be initiating additional comparative studies without learning from the French study and the Mayo and Boston experience? I think not.

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To the editor:

IL-1 gene cluster polymorphisms and development of primary gastric B-cell lymphoma in *Helicobacter pylori* infection

In addition to bacterial virulence factors, host immune response plays a pivotal role in the outcome of chronic *Helicobacter pylori* infection. The capacity of the host to mount an interleukin-1β (IL-1β)–driven response is influenced by sequence variants in the IL-1/IL-1RN cluster.[1]

El-Omar et al[2] were the first to report an association between IL-1B -31 and IL-1RN 2/2 of IL-1RN 86 variable number of tandem repeats (VNTRs) and the development of chronic hypochlorhydric response to *H pylori* and the risk of gastric cancer. In contrast, very little is known about germ-line mutations predisposing patients with chronic *H pylori* infection to develop gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Therefore, we read with great interest the report by Rollison et al[3] in Blood about an association between the proinflammatory genotype IL-1RN 2/2 with gastric marginal zone lymphoma in a retrospective series of 66 cases from northern England.

We investigated the functional variants in the IL-1 cluster and their influence on the development of primary gastric B-cell lymphoma in 153 patients participating in an intention-to-treat prospective multicenter study of the German-Austrian-Lymphoma Study Group.[4] Included as controls were 344 patients with *H pylori* infection undergoing upper gastrointestinal (GI) endoscopy when histology of 2 biopsies taken from the antrum and the corpus of the stomach excluded gastric lymphoma.

Table 1. Characteristics of 153 patients with primary gastric B-cell lymphoma

Disease stage	No.	Low grade	High grade	Sex, no. male/ no. female	Median age, y
E I	39	28	11	22/17	64
E I1	51	40	11	23/28	60
E I2	27	9	18	17/10	59
E II	4	1	3	3/1	67
E II1	26	7	19	17/9	66
E III	2	1	1	2/0	63
E IV	4	2	2	2/2	57

Stages of disease, histological grade, and median age of 153 patients with primary gastric B-cell lymphoma. The stage was defined according to the Ann Arbor staging system[6] with modification by Musshoff[7] and Radaszkiewicz.[8]

Of 153 patients with primary gastric B-cell lymphoma, 88 presented with low-grade (MALT) and 65 patients with high-grade lymphoma (Table 1). The allele frequencies in the control group match well with those previously reported in the literature.[2] There were no significant associations found with the histological grade or stage of disease in single marker analysis. Of patients with

Table 2. Single-marker analysis

Locus and genotype	Low grade, range, %	High grade, range, %	All, range, %	Controls, range, %	E I, range, %	E II-IV, range, %
IL-1β -31						
C/C	8-13.1	10-12.1	18-12.5	45-13.1	11-10.2	7-20.6
C/T	30-49.2	35-42.2	65-45.1	146-42.4	52-48.2	13-38.2
T/T	23-37.7	38-45.8	61-42.4	153-44.8	45-41.7	14-41.2
IL-1β + 3954						
C/C	4-6.7	3-3.7	7-5.0	24-7.2	3-2.8	3-9.4
C/T	20-33.3	26-32.1	46-32.6	121-36.3	37-34.6	9-28.1
T/T	36-60.0	52-64.2	88-62.4	188-56.5	67-62.6	20-62.5
IL-1RN 86VNTR						
1/1	30-46.9	46-52.9	76-50.3	185-53.8	58-51.3	17-47.2
1/2	27-42.2	31-35.6	58-38.4	118-34.3	43-38.1	14-38.9
1/3	2-3.1	4-4.6	6-4.0	11-3.2	5-4.4	1-2.8
2/2	4-6.3	5-5.8	9-6.0	27-7.9	6-5.3	3-8.3
2/3	1-1.6	1-1.1	2-1.3	2-0.6	1-0.9	1-2.8

Single-marker analysis of the proinflammatory haplotype IL-1β -31/IL-1 RN 86 VNTR. SNPs at IL-1β -31 and + 3954 were genotyped by allelic discrimination (TaqMan technology, ABI 7700, Aplera, Foster City, CA). IL-1RN 86 VNTR was genotyped by Southern blot after amplification. Alleles were sized relative to a 100-bp ladder (allele 1 = 4 repeats, allele 2 = 2 repeats, allele 3 = 5 repeats, allele 4 = 3 repeats, allele 5 = 6 repeats). Haplotype case-control analysis was performed using HAPMAX.[9] Hardy-Weinberg equilibrium was confirmed for all polymorphisms tested in gastric lymphoma group and controls. Three types of analysis were performed: (1) all patients with primary gastric B-cell lymphoma were compared against controls, (2) patients separated in low-grade and high-grade lymphoma were compared against controls, and (3) patients with disease stage E I were compared against patients with disease stages E II to E IV. Statistical analysis was performed using SISA Binominal program (Uitenbroek, Daan G, Binomial, SISA, http://home.clara.net/sisa/binomial.htm).