To the editor:

Durable hematologic complete responses can be achieved with lenalidomide in AL amyloidosis

In AL amyloidosis, amyloid fibril deposits, derived from immunoglobulin light chains produced by a clonal plasma cell dyscrasia, accumulate in extracellular tissues and damage vital organs.1 Novel therapies used in multiple myeloma2 can be effective in AL amyloidosis. Separately in the same issue of Blood, our group and the Mayo Clinic described similar results of phase 2 trials of the use of lenalidomide for the treatment of AL amyloidosis.3,4 Here we provide updated information on the durability of complete hematologic response (CR) after treatment with lenalidomide and dexamethasone in AL amyloidosis.

Between 2004 and 2009, 69 patients with AL amyloidosis were treated with lenalidomide and dexamethasone (ClinicalTrials.gov: NCT00091260) at Boston Medical Center. Approval was obtained from the institutional review board of the Boston Medical Center for this study. Informed consent was provided according to the Declaration of Helsinki. The median age was 62 years (range, 42-84 years), and 70% were male. Fifty patients had lambda clonal plasma cell dyscrasia, 36 (52%) had multiorgan involvement, and 31 (45%) had cardiac involvement. Sixty-five patients (94%) had received previous therapy (94% previous melphalan-based therapy, 71% high-dose melphalan/stem cell transplantation, 10% thalidomide, and 7% bortezomib). All patients received lenalidomide and dexamethasone as described in our previous report.3 CR was defined as absence of monoclonal gammopathy in serum and urine by immunofixation electrophoresis, less than 5% clonal plasma cells in the bone marrow biopsy, and normalization of serum-free light chain concentration and ratio.5 Eleven of the 69 patients (16% by intention-to-treat analysis) enrolled on the trial achieved a CR. Fifty-three patients were evaluable after completion of 3 cycles of treatment on the protocol and CR for evaluable patients was 21%. The median dose of lenalidomide at the time of achievement of a CR was 10 mg/d (range, 5-15 mg/d). The median time to achievement of a CR was at 6 cycles. CR occurred by 6 months in 92% of the patients. However, delayed CR occurred in 2 patients at 18 months after initiation of therapy. CR occurred in 2 patients with lenalidomide alone and in 9 patients with lenalidomide plus dexamethasone.

Of the 11 patients with CR, 1 patient died from rejection after orthotopic heart transplantation while on cycle 3 of lenalidomide. Of the 10 surviving patients with CR, 6 (60%) have maintained a CR. Of these 6 patients with continued CR, 2 remain on treatment at 6 and 9 months since initiation and 4 remain off treatment after receiving 9 to 19 cycles. The median duration of CR for patients off treatment is 24 months (range, 9-36 months).

Four of the 10 surviving patients with CR (40%) have relapsed off treatment. All four of these patients are alive and have been treated with combinations of other agents.

Progression on this clinical trial was defined as hematologic relapse after achievement of a CR and/or time to next treatment. The median progression free interval is 49.8 months (Figure 1).

In summary, lenalidomide, alone and in combination with dexamethasone, can induce hematologic complete responses in 16% of previously treated patients with AL amyloidosis. Most CRs occur by 6 months of treatment and 60% of CRs are durable, even off treatment.

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To the editor:

Significantly higher frequencies of alloreactive CD4\(^+\) T cells responding to nonpermissive than to permissive HLA-DPB1 T-cell epitope disparities

Increasing evidence suggests that donor-recipient disparities for human leukocyte antigen (HLA)–DPB1 can be of clinical importance in unrelated hematopoietic stem cell transplantation (HSCT).\(^1\) Two overlapping algorithms for functional T-cell epitope (TCE) matching involving 3 (TCE3) or 4 (TCE4) groups of DPB1 alleles have previously been shown to be significantly predictive of survival after 10/10 and 9/10 matched unrelated HSCT.\(^2,3\) In both TCE3 and TCE4, nonpermissive mismatches are directed against 2 groups of immunogenic antigens encoded by DPB1*09:01, 10:01, 17:01 (TCE3/4 group 1) and DPB1*03:01, 14:01, 45:01 (TCE3/4 group 2), respectively.\(^2,3\) In TCE3, all other frequent DPB1 alleles including DPB1*02:01, 04:01, 04:02 and others are classified as poorly immunogenic TCE3 group 3, and DPB1 mismatches against these alleles are predicted to be permissive.\(^2\) In TCE4, TCE3 group 3 is further subdivided into 2 separate groups comprising DPB1*02 (TCE4 group 3) and the other alleles (TCE4 group 4), with intermediate and poor immunogenicity, respectively.\(^3\)

Rutten and colleagues have recently shown that T-cell responses could be obtained against DP antigens from all 4 groups,\(^4,5\) thereby confirming the observations that led to the discovery of the DP locus by primed lymphocyte testing,\(^6\) as well as those obtained later in mixed lymphocyte reactions (MLRs).\(^7,8\) Interestingly, Rutten and colleagues observed high levels of cytokine production by CD4\(^+\) T cells in response also to autologous DP molecules presumably presenting minor histocompatibility antigens,\(^5\) suggesting that the HeLa cell transfectants expressing DP but not other class II antigens used in their experiments may not quantify physiologic frequencies of alloreactive T helper cells, which increase substantially with the number of mismatched HLA-DP alloantigens in classical in vitro assays.\(^9,10\)

Here, we have quantified the frequency of alloreactive CD4\(^+\) T cells responding to permissive or nonpermissive TCE3 or TCE4 DP mismatches, in classical MLRs between peripheral blood mononuclear cells (PBMCs) of responder (R)–stimulator (S) pairs matched for 10/10 of the non-DPB1 alleles. When S presented both a permissive and a nonpermissive mismatch, the percentage of responding CD4\(^+\) T cells was more than 10-fold higher against the nonpermissive (DPB1*09:01, 10.65%) compared with the permissive mismatch (DPB1*04:02, 0.88%; Figure 1A), and this result was highly reproducible in 3 independent experiments (data not shown). Importantly, in 24 MLRs, we found a consistently higher percentage of CD4\(^+\) T cells responding to nonpermissive DPB1 mismatches according to TCE3 (n = 9; mean 10.13% ± 7.51%; Figure 1B left panel) or TCE4 (n = 14; mean 7.72% ± 6.96%; Figure 1B right panel), compared with permissive mismatches according to TCE3 (n = 15; mean 2.34% ± 2.82%; Figure 1B left panel) or TCE4 (n = 10; mean 1.81% ± 2.82%; Figure 1B right panel). In the Kruskal-Wallis analysis of variance, this difference was significant both for TCE3 (P < .05) and TCE4 (P < .05). Responses against DPB1*02 (TCE4 group 3), classified as permissive for TCE3 but nonpermissive for TCE4, were significantly lower than those against TCE3/4 groups 1 and 2 (10.13% ± 7.51% and 3.39% ± 2.8%, respectively; P = .04, Mann-Whitney test) but higher than those against TCE4 group 4 (1.81% ± 2.82%), resulting in no significant net effect on the predictive value of TCE3 and TCE4.

Our data provide, for the first time, in vitro evidence for differential immunogenicity of DPB1 according to our algorithms. Interestingly, ex vivo evidence was previously reported by Rutten and colleagues\(^4\) who showed that in 2 patients after 10/10 matched HSCT, the number of T cells responding to mismatched DP alloantigens was highest for TCE3/4 group 2 (2.72%), lower for TCE4 group 3 (1.08%), and lowest for TCE4 group 4 (0.41%). Further work is needed to determine the molecular and cellular basis of our algorithms, including the role of the DPx chain.

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References
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