To the editor:

Increases in B-type natriuretic peptide (BNP) during treatment with lenalidomide in AL amyloidosis

The combination of lenalidomide and dexamethasone can produce hematologic responses in previously treated patients with AL amyloidosis. Since this prospective study (ClinicalTrials.gov: NCT00091260) was initiated, NT-proBNP and BNP have been found to be useful biomarkers for cardiac involvement, prognosis, and response to therapy in patients with AL amyloidosis. Here we report on the retrospective analysis of the prospectively collected data on changes in BNP during lenalidomide therapy on this trial.

Sixty-eight patients with AL amyloidosis were treated with lenalidomide and dexamethasone at Boston Medical Center. Approval for this study was obtained from the Institutional Review Board of the Boston Medical Center. Informed consent was provided according to the Declaration of Helsinki. The median age was 64 years (range, 42 to 85 years); and 69% were male. Fifty-one patients (75%) had clonal plasma cell dyscrasia, and 38 (56%) had cardiac involvement. All patients received lenalidomide and dexamethasone as described in our previous report. Twenty-four of the 68 total patients enrolled did not meet the eligibility to be included in this analysis due to either BNP levels of < 100 pg/mL at baseline and at 1 and 3 months after treatment or unavailability of BNP measurement after 1 or 3 cycles of lenalidomide. Therefore, 44 patients are included in this analysis. An increase in BNP was defined as > 30% increase from baseline value at enrollment on the trial after cycles 1 or 3.

Thirty-eight patients (86%) had > 30% increase in BNP level from baseline, 30 (68%) had an increase after 1 cycle and an additional 8 (18%) patients after 3 cycles of lenalidomide (Figure 1). The mean dose of lenalidomide for patients with an increase in BNP after 1 cycle was 15 mg (range, 5-25 mg) and after 3 cycles was 10 mg (range, 5-15 mg). Of the patients with increase in BNP, only 5 patients (13%) had worsening of renal function by > 50% from baseline. The increase in BNP after 1 and 3 cycles occurred in 23 of 29 patients (79%) with cardiac involvement and 15 of 15 patients (100%) without cardiac involvement. Cardiac troponin I levels were not measured after 1 and 3 cycles of lenalidomide. All the patients with an increase in BNP were asymptomatic without association of modification in NYHA class congestive heart failure.

The median survival of these 44 patients is 53 months since initiation of lenalidomide therapy. At these early time points of 1 and 3 months, 20% (n = 9/44) of patients had > 50% improvement in serum free light chain levels, and 2% (n = 1/44) of patients had improvement in BNP of 30% or more.

In conclusion, BNP increased by > 30% in a substantial proportion of patients with AL amyloidosis during treatment with lenalidomide. The mechanism for asymptomatic rise in BNP is not clear; however, the temporal relationship with lenalidomide initiation, the relatively rapid increase, and the absence of other identifiable precipitants for most of the patients suggest that lenalidomide may be playing a role. Moreover, patients with AL amyloidosis receiving lenalidomide whose BNP rises should not be assumed to be failing therapy without other signs of disease progression, but should be monitored closely and treated as necessary.
needed for signs or symptoms of congestive heart failure should they occur.

J.B.Z. designed research and edited the manuscript; and V.S. designed and performed research, analyzed data, and wrote the manuscript. U.T. designed and performed research, analyzed data, and wrote the manuscript; D.C.S. edited the manuscript; K.T.F. designed research and collected and analyzed data; S.F. and A.S. collected and analyzed data; and V.S. designed and performed research, analyzed data, and wrote the manuscript.

Conflict-of-interest disclosure: J.B.Z. is employed by Celgene Corp, whose product (lenalidomide) was studied in the present work. The remaining authors declare no competing financial interests.

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References


To the editor:

Double-negative T cells are non–ALPS-specific markers of immune dysregulation found in patients with aplastic anemia

We read with interest the recent article by Dowdell and colleagues exploring somatic FAS gene mutations among patients with autoimmune lymphoproliferative syndrome (ALPS),1 a syndrome characterized by defective CD95 (Fas) cell surface–mediated apoptosis. In assigning the diagnosis of ALPS, demonstration of a population of peripherally expanded CD4-CD8- double-negative T lymphocytes (DNTs; >1.5% of normal lymphocytes) that express αβ T-cell receptors (αβ-TCRs), is widely considered a key laboratory criteria.2,3 As indicated by the authors, the pathogenic nature of DNT cells remains a matter of debate. Indeed, patients with rare autoimmune diseases, including systemic lupus erythematosus (SLE) and immune thrombocytopenic purpura (ITP), have demonstrated mild elevations, suggesting that DNTs may perhaps be more common among immune disorders.4,5

Aplastic anemia (AA) is characterized by an acquired, progressive loss of hematopoietic function thought to result from an immune-mediated reaction that targets the hematopoietic stem cell.6 We undertook a retrospective study of 22 pediatric patients with idiopathic AA of varying disease severity, consecutively diagnosed at our institution between 2007 and 2010. Study approval was obtained by the Oregon Health & Science University Institutional Review Board. In the 11 patients evaluated most recently we performed a detailed immunophenotypic analysis of lymphocyte subsets as part of the diagnostic workup. Remarkably, our study showed an elevated proportion of double-negative T cells (range, 4.3%-9.1% of CD3+ lymphocytes) in 9 patients (Table 1). Further subfractionation revealed that 10 of our 11 patients (including 2 with DNT just below the upper limit of normal) demonstrated a predominant elevation of γδ TCR—rather than the more common αβ TCR—expressing DNTs. Peripherally expanded DNTs are considered pathogenic in the peripheral cytopenias of patients with ALPS. However, our findings suggest that their occurrence may not be limited to this syndrome and their role might be more complex than the destruction of mature cells in

Table 1. Immunophenotypic analysis of T-cell subpopulations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age at diagnosis, y</th>
<th>Sex</th>
<th>αβ TCR (0%-1.5%)‡</th>
<th>γδ TCR (0%-2%)</th>
<th>CD4+CD8- (0%-4%)</th>
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<tr>
<td>MAA</td>
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<td>4.5</td>
<td>7</td>
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<td>F</td>
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<td>6.4</td>
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<tr>
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<td>M</td>
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<td>1.6</td>
<td>4.6</td>
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<tr>
<td>SAA</td>
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<td>1</td>
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<tr>
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<td>10</td>
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<tr>
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<tr>
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<tr>
<td>SAA*</td>
<td>16</td>
<td>F</td>
<td>1.3</td>
<td>3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

MAA indicates moderately severe aplastic anemia; SAA, severe aplastic anemia.

*Repeat bone marrow evaluation revealed monosomy 7, consistent with the diagnosis of MDS.

‡Normal range for test.
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