Cardiac toxicity of alemtuzumab in patients with mycosis fungoides/Sézary syndrome

Daniel J. Lenihan, Alvaro J. Alencar, Deborah Yang, Razelle Kurzrock, Michael J. Keating, and Madeleine Duvic

Alemtuzumab is a monoclonal antibody to CD52 that has activity in T-cell leukemia and lymphoma. This study aims to describe the complications and outcomes of a subset of patients with mycosis fungoides/Sézary syndrome who were treated with alemtuzumab. Four of 8 patients, with no prior history of cardiac problems, developed significant cardiac toxicity (congestive heart failure or arrhythmia) that mostly improved after alemtuzumab discontinuation. The role of this agent in potentially inducing important cardiac side effects is suggested and argues for further investigation. (Blood. 2004;104:655-658)

Introduction

Alemtuzumab is a humanized monoclonal antibody that targets the CD52 antigen, which is present on the cell membrane of most T and B lymphocytes.1 The drug was initially approved for treatment of fludarabine-refractory chronic lymphocytic leukemia and has shown promise in the treatment of other lymphoproliferative malignancies, especially Sézary syndrome (SS).2,6

The most common side effects of alemtuzumab are rigors, fever, nausea, vomiting, and rash.1,7 These events, which are infusion related, decrease in frequency after the initial infusions and can be diminished by prophylactic schemes.1 Because most lymphocytes express CD52, immunosuppression is a common adverse consequence of alemtuzumab therapy. Sixty-five percent of patients who receive alemtuzumab therapy experience lymphopenia and opportunistic infections, especially reactivation of cytomegalovirus and herpes viruses.2,7,9

Although less frequent, pulmonary and cardiac events also may occur in patients treated with alemtuzumab2,3,5,7,9 and may necessitate discontinuation of the therapy. In our experience with alemtuzumab, particularly those with mycosis fungoides (MF) or Sézary syndrome (MF/SS), there appeared to be a higher than acceptable risk of cardiac complications. Therefore, we retrospectively reviewed the toxic effects of this agent in patients with MF/SS who had received alemtuzumab therapy at The University of Texas M. D. Anderson Cancer Center.

Study design

We evaluated the medical records of the patients with MF/SS included in a phase 2 trial of alemtuzumab3 and 2 other patients treated off protocol to determine the incidence of cardiac events and outcome after therapy. All patients included in our analysis had given written informed consent to participate.

During the first week of therapy in the trial, alemtuzumab had been administered intravenously on 3 consecutive days at escalating doses of 3, 10, and 30 mg. Beginning with the second week and continuing for up to 12 weeks, patients had received 30-mg infusions 3 times a week. To diminish infusion-related side effects, diphenhydramine (50 mg) and acetaminophen (650 mg), but not steroids, had been administered 30 minutes before alemtuzumab infusion. Patients also received infection prophylaxis until at least 2 months after the end of alemtuzumab therapy.1 Routine laboratory, hematologic, and imaging studies had been performed at baseline. Echocardiography, cardiac enzyme analysis, and electrocardiography had been performed only when necessary.

Results and discussion

A total of 8 patients with MF/SS who had been treated with alemtuzumab were included in our analysis. Table 1 illustrates the characteristics of the 8 patients included, in which 5 had SS and the other 3 had MF, including 1 patient with immunoblastic transformation. The 6 patients who enrolled in the phase 2 study of alemtuzumab had previously received multiple systemic treatments (median, 4 treatments; range, 2-15 treatments), as did the 2 who were treated off protocol. Table 2 indicates the adverse events associated with alemtuzumab therapy.

Patient 1, who was responding to the therapy, developed atrial fibrillation that resolved a few days after discontinuation of alemtuzumab and had no recurrence over the next 4 years with other therapy. His hemoglobin value was 130 g/L (13 g/dL), and no other explanation was identified. Patient 2, who had a clinical response but accompanying neutropenic fever, developed severe congestive heart failure (CHF) and left ventricular (LV) dysfunction (defined as an ejection fraction [EF] < 50%), after the first 30-mg dose of alemtuzumab. There was no evidence of myocardial infarction (MI), and this patient had a previously normal EF prior to alemtuzumab therapy. No active infection was documented. Once appropriate cardiac medications were instituted, her CHF improved. However, her LV dysfunction did not fully resolve, as her...
severe LV dysfunction with an EF of 20% and had no evidence of right-sided chamber sizes by echocardiography but now developed severe CHF. He had a previously normal EF and normal as an outpatient and was asymptomatic several weeks later. He then responded well to alemtuzumab therapy, with elimination of Se cells, decreased skin involvement, and decreased lymphadenopathy, large cell transformation, and marked lymphocytosis resulting in hyperuricemic renal failure and anasarca. He was hemodynamically stable for several days on dialysis and had a normal blood pressure and respiratory status. Her EF at this time was normal. Alemtuzumab was administered at an initial dose of 15 mg intravenously by 24-hour continuous infusion. Within 12 hours of initiation, the patient became hypotensive and unresponsive, and she developed multiorgan failure and probable vascular leak syndrome. A second infusion was given, but the patient died the next day.

Patient 8, who had resistant SS and had multiple prior treatments, had a previously normal EF (59%) prior to receiving alemtuzumab. Within 6 weeks after starting the drug, he developed severe CHF and was found to have profound LV dysfunction (EF 15%) without evidence of MI. Alemtuzumab therapy was discontinued, and the cardiac symptoms improved approximately 10 days later. A repeat EF 2 months later had normalized (EF = 55%).

Patient 7, with rapidly progressing MF/SS, had been admitted with lymphadenopathy, large cell transformation, and marked lymphocytosis resulting in hyperuricemic renal failure and anasarca. She was hemodynamically stable for several days on dialysis and had a normal blood pressure and respiratory status. Her EF at this time was normal. Alemtuzumab was administered at an initial dose of 15 mg intravenously by 24-hour continuous infusion. Within 12 hours of initiation, the patient became hypotensive and unresponsive, and she developed multiorgan failure and probable vascular leak syndrome. A second infusion was given, but the patient died the next day.

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**Table 1. Characteristics of patients with MF/SS treated with alemtuzumab**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y/sex</th>
<th>Disease stage (events)</th>
<th>Previous treatment(s)</th>
<th>No. of alemtuzumab doses/cumulative dose, mg</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/M</td>
<td>IV A (MF)</td>
<td>TSEB, NM, fludarabine + prednisone, bexarotene†</td>
<td>7/223</td>
<td>SD</td>
</tr>
<tr>
<td>2</td>
<td>39/F</td>
<td>IV B (MF/SS)</td>
<td>ABVD/MOPP + XRT, pentostatin, C-MED</td>
<td>1/43</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>74/M</td>
<td>II B (MF)</td>
<td>IFN + isotretinoin, C-MED</td>
<td>9/283</td>
<td>PD</td>
</tr>
<tr>
<td>4</td>
<td>61/F</td>
<td>II B (MF); immunoblastic transformation (LN)</td>
<td>IFN + isotretinoin + TSEB, pentostatin, hyper-CVAD, ESHAP, MINT × 2, TSEB, bexarotene, trimetrexate BCX, gemcitabine HCI, ATRA, liposomal vincristine</td>
<td>15/463</td>
<td>SD</td>
</tr>
<tr>
<td>5</td>
<td>67/F</td>
<td>IV A (MF/SS)</td>
<td>Steroids, cisplatin, PUVA, IFN + isotretinoin + C-MED + TSEB, pentostatin, bexarotene, IL-12, gemcitabine HCI, BCX, L-ATRA</td>
<td>13/403</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>IV A (MF/SS)</td>
<td>Photopheresis, IFN, TMTX, pentostatin, bexarotene, C-MED, ESHAP</td>
<td>18/553</td>
<td>PR</td>
</tr>
<tr>
<td>7*</td>
<td>56/F</td>
<td>IV B (MF/SS)</td>
<td>IFN-isotretinoin + C-MED + TSEB, bexarotene, PUVA, IFN</td>
<td>1/30</td>
<td>PD</td>
</tr>
<tr>
<td>8*</td>
<td>60/M</td>
<td>IV B (SS); angiocentric</td>
<td>PUVA, steroids/denileukin dilitox, SAHA, CHOP</td>
<td>8/183</td>
<td>PR</td>
</tr>
</tbody>
</table>

M indicates male; F, female; SS, Sézary syndrome; MF, mycosis fungoides; LN, lymph node; TSEB, total skin electron beam; NM, nitrogen mustard; ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, DTIC; MOPP, mustard, vincristine, procarbazine, prednisone; C-MED, cyclophosphamide (Cytoxan), methotrexate, etoposide, dexamethasone; IFN, interferon; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; ESHAP, etoposide, methylprednisolone sodium succinate (Solu-Medrol), Ara-C, platinum; MINT, mesna, ifosfamide, mitoxantrone, paclitaxel (Taxold); IL-12, interleukin-12; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; SD, stable disease; PR, partial response; PD, progressive disease; XRT, radiation; ATRA, all transretinoic acid; L-ATRA, liposomal ATRA; PUVA, psoralen plus ultraviolet A; TMTX, trimetrexate; SAHA, suberylanilide hydroxamic acid; and BCX, Biocryst.

*Patient was treated off protocol. The other patients were enrolled in a phase 2 study of alemtuzumab.
†Bexarotene.
‡Isotretinoin.
§Gemcitabine HCI.
|†Denileukin dilitox.

EF weeks later was 39%. Patients 3 and 4 both died during alemtuzumab therapy of infectious complications, and during their infectious illness there was no documented evidence of LV dysfunction.

Patient 5 received 13 doses of alemtuzumab but noted increasing fatigue, fever, and shortness of breath beginning after the initial dose. She required hospitalization for 10 weeks for aggressive intravascular treatment of symptomatic CHF, pulmonary edema, as well as *Legionella pneumonia*, but she did not have LV dysfunction.

Patient 6 had SS, with a baseline white blood cell count greater than 80 × 10⁹/L (80 000 cells/mL) and 80% Sézary cells. He responded well to alemtuzumab therapy, with elimination of Sézary cells, decreased skin involvement, and decreased lymphadenopathy, but he developed a deep venous thrombosis with a subsequent pulmonary embolism. He was undergoing anticoagulation therapy as an outpatient and was asymptomatic several weeks later. He then developed severe CHF. He had a previously normal EF and normal right-sided chamber sizes by echocardiography but now developed severe LV dysfunction with an EF of 20% and had no evidence of MI. Alemtuzumab therapy was discontinued, and the cardiac symptoms improved approximately 10 days later. A repeat EF 2 months later had normalized (EF = 55%).

**Table 2. Adverse events in patients with MF/SS treated with alemtuzumab**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cardiac risks</th>
<th>Adverse event(s)</th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>Atrial fibrillation</td>
<td>—</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>CHF/LV dysfunction, ventricular tachycardia</td>
<td>60</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>CAD</td>
<td>Anasarca/infection</td>
<td>—</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>HTN</td>
<td>Infection</td>
<td>—</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>CHF/infection</td>
<td>—</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>CHF/LV dysfunction</td>
<td>60</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>7*</td>
<td>HTN</td>
<td>Prolonged hypotension</td>
<td>60</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8*</td>
<td>HTN/DM</td>
<td>CHF/LV dysfunction</td>
<td>59</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; ANTH, anthracyclines; —, not done; CHF, congestive heart failure; LV, left ventricular; CAD, coronary artery disease; HTN, hypertension; and DM, diabetes mellitus.
He then required maximal CHF therapy, including 10 days of inotropic support to sustain his blood pressure. A myocardial biopsy failed to reveal any myocarditis or myocytolysis, and he had no coronary artery disease (CAD) by angiogram. Furthermore, cytomegalovirus (CMV) antigenemia remained essentially undetectable. He has since recovered symptomatically, but his EF (30%) is still reduced.

Although alemtuzumab therapy may have shown promise in the treatment of SS, our patient group had an overall modest response. Partial responses to alemtuzumab occurred in only 3 of the 8 patients. None of the 8 patients achieved complete response. In contrast, Lundin et al reported an overall response in 4 of 8 patients with MF, with complete remission in 2 patients. Another phase 2 study, which included 22 patients with MF/SS, showed an overall response rate of 55% and a complete remission rate of 32%. A third study, involving 39 patients, included 3 patients with SS; 2 of these patients achieved a complete response and the other achieved a partial response. A higher number of previous treatments would be a possible explanation for the lower overall response in the patients in our analysis in comparison to these other studies.

Although 7 of the 8 patients in our analysis had no preexisting cardiac problems, 3 experienced CHF and 2 experienced arrhythmias temporally associated with alemtuzumab. In addition, 3 of the 8 had documented LV dysfunction during therapy that had not been present previously. Two of these patients had received doxorubicin during previous therapy (Table 2) for their disease, but one did not. No other explanation for the LV dysfunction in these patients was discovered, including CAD or MI. One patient underwent a myocardial biopsy to exclude myocarditis, which indicated no evidence of infection, inflammation, or direct cytotoxicity of the myocardial cells. It is interesting to note that the patient with prior CAD had no apparent cardiac complications. Among the 6 patients in the trial, cardiac adverse events developed after a median of 10 full doses of alemtuzumab (range, 1-18 doses), corresponding to approximately 4 weeks of therapy and a median cumulative dose of 223 mg (range, 43-553 mg). The 2 patients treated off protocol developed toxicity at generally lower doses than in the trial.

Cardiac adverse events are infrequently mentioned in studies of patients receiving alemtuzumab. Of interest, all such reported incidents have occurred in patients with T-cell malignancies (Table 3). In 3 studies of patients with T-cell malignancies, no cardiac side effects were reported. In the M. D. Anderson study, the patient with MF (listed in Table 1), as well as 1 patient with T-cell prolymphocytic leukemia, developed cardiac adverse events.

The association between cardiac adverse events, alemtuzumab, and T-cell malignancies may be explained by a cytokine-release syndrome, defined as an increased level of serum tumor necrosis factor-α, interferon-γ, and interleukin-6 after alemtuzumab infusion. The drug may activate or kill T cells that secrete these cytokines, leading to coronary vasospasm, potentially CMV-related myocarditis, or even toxic “stunning” of the myocardium. Myocardial stunning, typically described in ischemic heart disease, is defined as transient myocardial dysfunction without infarction. In general, the LV dysfunction or stunning is mostly reversible but may be recalcitrant if the damage is severe enough. The toxic stunning hypothesis is supported by the findings in each of our patients who developed LV dysfunction. All 3 patients developed myocardial dysfunction during alemtuzumab therapy, which at least partially resolved and recovered. CMV antigenemia was not significantly elevated in these patients, suggesting myocarditis was unlikely, and significant CAD, MI, or vasospasm were not seen. This cytokine release would explain why cardiac side effects of alemtuzumab have been reported only in patients with T-cell malignancies. Additionally, the previous treatment with doxorubicin in certain patients probably resulted in subclinical myocardial damage that was unmasked by alemtuzumab therapy. The concept of sequential stressors resulting in myocardial dysfunction, at least transiently, may explain cardiotoxicity rarely seen with newer monoclonal antibody therapy. Of interest, patients with multiple sclerosis treated with alemtuzumab have experienced exacerbation of their neurologic symptoms secondary to cytokine release. However, these effects of the drug can be successfully blocked by using prophylactic steroids in those patients.

Another possible mechanism of cardiac toxicity is that alemtuzumab targets the heart directly. There is no evidence that CD52 is expressed on cardiac myocytes. However, alemtuzumab could kill T cells that infiltrate the heart, causing myocyte dysfunction or electrical disturbances as an unwanted secondary effect. Although cardiac involvement of lymphoma is rare, autopsy studies of subjects with MF revealed a 15% to 30% incidence of cardiac involvement. A study reported gross cardiac involvement in 7 of 12 subjects. Therefore, the potential direct effect of alemtuzumab on T cells residing in the myocardium remains a possibility.

In summary, we found that alemtuzumab therapy was associated with adverse cardiac events, including congestive heart failure and LV dysfunction, in a substantial proportion of patients with MF/SS who did not have a history of cardiac problems. All 3 patients who clearly developed left ventricular dysfunction and congestive heart failure during alemtuzumab therapy had been previously treated with doxorubicin, suggesting this population of patients may be at particularly high risk for untoward effects. Although the pathogenesis of the cardiac effects of alemtuzumab is unknown, the toxicity may be the result of cytokine release and, thus, could be potentially attenuated. Furthermore, these effects are serious, and treatment of MF/SS with alemtuzumab was terminated as a result. Investigation is warranted into the potential mechanisms.

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**Table 3. Previously reported cardiac events in patients treated with alemtuzumab**

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease (n)</th>
<th>No. of patients with cardiac events</th>
<th>Cardiac event(s)</th>
<th>Cumulative dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keating et al, 2002¹</td>
<td>T-cell prolymphocytic leukemia (75)</td>
<td>1</td>
<td>Atrial fibrillation</td>
<td>Unspecified (acute reaction)</td>
</tr>
<tr>
<td>Damaj et al, 2002¹</td>
<td>PTCL-nodal (1)</td>
<td>1</td>
<td>MI</td>
<td>10</td>
</tr>
<tr>
<td>Lundin et al, 199²</td>
<td>B-cell lymphoma or MF (50)</td>
<td>1</td>
<td>MI</td>
<td>About 300*</td>
</tr>
</tbody>
</table>

PTCL indicates peripheral T-cell lymphoma; MI, myocardial infarction; and MF, mycosis fungoides.

¹Patient received 10 doses of 30 mg after an initial dose of either 3 mg or 10 mg (not specified).
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