Alemtuzumab Therapy for Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

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Abstract

Purpose: Patients with hypereosinophilic syndrome (HES) or chronic eosinophilic leukemia (CEL) that are refractory to standard therapies are difficult to manage and have significantly shortened life expectancy.

Experimental Design: CD52 is a surface glycoprotein highly expressed on eosinophils. We treated 11 patients with advanced HES/CEL with alemtuzumab, a humanized anti-CD52 monoclonal antibody. Alemtuzumab was administered, in general, first in escalating doses (5, 10, 30 mg i.v. on days 1-3), then at the tolerated dose thrice per week for a total of 12 doses. Patients with complete hematologic response (CHR; normal percent and absolute eosinophil count) were allowed to continue therapy once weekly as maintenance.

Results: Ten patients (91%) achieved CHR after a median of 2 weeks (0.5-5 weeks) of therapy. Bone marrow eosinophilia resolved in four of seven evaluable patients. The median duration of CHR was 3 months (1.5-17+ months). Seven of the 10 CHR patients relapsed, five while off-therapy. Two patients achieved second CHR upon alemtuzumab rechallenge. Three patients experienced mild infusion-related symptoms, two developed cytomegalovirus reactivation requiring therapy, and one developed orbital lymphoma that was successfully treated.

Conclusions: Our limited experience suggests alemtuzumab to be a valuable therapy for advanced HES or CEL, refractory to standard therapies, and supports the clinical evaluation of alemtuzumab in a larger trial.

Hypereosinophilic syndrome (HES) is traditionally defined by the presence of nonreactive blood eosinophilia with an absolute eosinophil count of >1.5 × 10^9/L that persists for over 6 months and is accompanied by some evidence of organ involvement (1). Strict definition of HES, according to the WHO classification system for hematopoietic tumors, requires distinction from molecularly characterized eosinophilic disorders, including platelet-derived growth factor receptor (PDGFR)–rearranged myeloid neoplasm, eosinophilia associated with phenotypically abnormal and/or clonal T lymphocytes, and chronic eosinophilic leukemia that is not otherwise classified (CEL-NOC); the latter diagnosis is assigned in the presence of either a cytogenetic abnormality or >2% peripheral blasts or >5% bone marrow blasts (2). Such distinction is clinically relevant because imatinib mesylate is the treatment drug of choice in the presence of a PDGFR mutation, whereas T-cell clone–associated eosinophilia might progress into overt lymphoma (2, 3). In WHO-defined HES, drug therapy is not always essential and might be postponed in the absence of symptomatic organ involvement. Corticosteroids are the first-line drug of choice in the management of treatment-requiring HES patients. Although most patients initially respond to such therapy, unmaintained remissions are rare, whereas long-term maintenance corticosteroid treatment is associated with substantial side effects (4). Furthermore, corticosteroid-refractory HES is difficult to manage with other drugs and is potentially fatal with a reported 10-year survival of <50% (5, 6). Therefore, novel therapies are being explored, including nilotinib and dasatinib (tyrosine kinase inhibitors), and mepolizumab (anti-interleukin 5 monoclonal antibody; ref. 6).

CD52 is a surface glycoprotein expressed at high levels on B and T lymphocytes and at lower levels on monocytes (7). Interestingly, CD52 is also expressed on the surface of eosinophils but is absent on neutrophils or bone marrow stem cell precursors (8). Alemtuzumab (Campath-1H) is a humanized IgG1k anti-CD52 monoclonal antibody that is currently approved by the U.S. Food and Drug Administration for the
treatment of B-cell chronic lymphocytic leukemia. Two case reports of its use as a therapy for HES has been published thus far (9, 10). We report herein our experience in the therapeutic use of alemtuzumab in 11 patients with advanced HES or CEL-NOC.

Materials and Methods

The current study is an observational study that summarizes clinical observations during compassionate off-label use of alemtuzumab therapy in treatment-requiring patients with either HES or CEL-NOC, treated at the M. D. Anderson Cancer Center (Houston, TX) and the Mayo Clinic (Rochester, MN). Informed consent was obtained before alemtuzumab start in all instances in accordance with the Declaration of Helsinki. Diagnoses of HES and CEL-NOC were according to the WHO criteria (2). Cytogenetic analysis and molecular screening for the presence of T-cell receptor gene rearrangements were done as previously described (3, 11, 12).

A complete hematologic response (CHR) was defined as the reduction of peripheral blood eosinophilia by at least 50% from the baseline value. The schedule for patients treated at the M. D. Anderson Cancer Center was as follows: Alemtuzumab was administered at 5 mg i.v. on day 1; in the absence of grade 3 or 4 toxicity, the dose was increased to 10 mg i.v. on day 2 and to 30 mg i.v. on day 3. Thereafter, alemtuzumab was administered at the tolerated dose level thrice per week, either i.v. or s.c. After a total of 12 doses, patients with CHR continued alemtuzumab at 30 mg i.v. or s.c. once weekly as maintenance. In patients with partial response, alemtuzumab was continued at 30 mg thrice a week for 4 more weeks and then weekly as maintenance. Not all patients received maintenance therapy, however (Table 1). In patients treated at the Mayo Clinic, alemtuzumab was administered s.c. at dose levels ranging from 10 mg weekly to 30 mg thrice a week.

During and for 2 mo after treatment with alemtuzumab, most patients received prophylactic treatment for Pneumocystis jiroveci pneumonia with trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily thrice weekly and for herpes simplex virus infection with valacyclovir 500 mg orally daily. Cytomegalovirus (CMV) antigenemia was routinely assessed, as previously reported (13), in all patients treated at the M. D. Anderson Cancer Center before entering the study and every 12 wk thereafter or up to 2 mo upon alemtuzumab discontinuation. At the Mayo Clinic, CMV antigenemia was assessed only if clinically indicated.

Results

Patient characteristics. Of the 11 patients (Table 1), 9 were treated at the M. D. Anderson Cancer Center and 2 at the Mayo Clinic. All underwent bone marrow examination with cytogenetic studies before alemtuzumab treatment. Nine patients fulfilled the WHO criteria for HES and two those of CEL-NOC. All patients tested negative for JAK2V617F, FIP1L1-PDGFRA, JAK2V617F, and the presence of T-cell receptor gene rearrangements were done as previously described (3, 11, 12).

A complete hematologic response (CHR) was defined as the reduction of the absolute eosinophil count and the percentage of eosinophils in peripheral blood to normal values (<0.4 × 10⁹/L and ≤4%, respectively). A partial response was defined as the reduction of eosinophilic peripheral blood eosinophilia by at least 50% from the baseline value.

We treated 11 patients with advanced HES/CEL. Ten patients (91%) achieved normalization of blood eosinophil percentage and total number (complete hematologic response) at a median of 2 weeks. Resolution of bone marrow eosinophilia was recorded in four of seven evaluable patients. Response was durable in patients receiving maintenance alemtuzumab therapy.

This type of a response has not been described in this patient population even with the use of intensive chemotherapies. Our limited experience suggests alemtuzumab to be a valuable salvage therapy for advanced HES or CEL, and supports the clinical evaluation of alemtuzumab in a larger controlled trial.

Translational Relevance

Patients with hypereosinophilic syndrome (HES) or chronic eosinophilic leukemia (CEL) that are refractory to standard therapies are difficult to manage and have significantly shortened life expectancy. CD52 is a surface glycoprotein highly expressed on lymphocytes and eosinophils. Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved as therapy for chronic lymphocytic leukemia. Its use for HES/CEL has not been investigated.

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leukocyte and eosinophil counts (Fig. 1C) and resolution of both cutaneous lesions and extremity edema (Fig. 1D) that lasted for 10 months. Flow cytometry studies showed the elimination of CD52-positive eosinophils in the patient’s posttreatment bone marrow (Fig. 2A and B). After remaining in CHR for 7 months off alemtuzumab therapy, this patient relapsed with eosinophilic dermatitis and eosinophilia but achieved a second CHR soon after resuming treatment with alemtuzumab (now maintained off therapy for 6 months).

To date, 7 of the 10 patients with CHR have relapsed; five off-therapy and two on-therapy (patient 6 relapsed with myeloproliferative component of the disease: WBC 234 × 10^9/L, only 4% eosinophils and flow cytometry negative for CD52 expression). As was the case in patient 10, patient 8 achieved a second response upon alemtuzumab rechallenge. Five patients have died during follow up: two while in CHR off alemtuzumab therapy (patient 3 died from complications of chronic renal failure, and patient 11 died from complications of therapy of advanced thyroid cancer) and three who had relapsed while off alemtuzumab therapy [patient 1 died from fungal pneumonia after a matched unrelated stem cell transplantation; patient 4 was unwilling to be rechallenged with alemtuzumab due to persistent diarrhea (did not improve on alemtuzumab therapy) and died in the hospice from malabsorption; patient 5 was unwilling to be rechallenged with alemtuzumab due to its schedule (frequent i.v. therapy in the hospital), failed treatment with nilotinib, and died from complications after intensive chemotherapy].

Toxicity. Three patients experienced fever and rigors during alemtuzumab infusion. Two of these patients also experienced infusion-related shortness of breath and hypotension, requiring transient dose reductions and supportive care with hydrocortisone, acetaminophen, and diphenhydramine. In

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Prior therapy</th>
<th>Rx/symptoms at study entry</th>
<th>Absolute baseline PB eosinophils (×10^9/L)/percent</th>
<th>Baseline BM eosinophil percent</th>
<th>Cytogenetic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/m</td>
<td>Steroids, imatinib, 2CdA, PEG-IFNα</td>
<td>None/bone pain, profound fatigue</td>
<td>1.7/24%</td>
<td>14%</td>
<td>46,XY</td>
</tr>
<tr>
<td>2</td>
<td>24/m</td>
<td>Steroids, imatinib, cromolyn, PEG-IFNα, nilotinib, dasatinib</td>
<td>PRD 30 mg daily/diarrhea, nausea, vomiting</td>
<td>1.8/21%</td>
<td>38%</td>
<td>46,XY</td>
</tr>
<tr>
<td>3</td>
<td>45/f</td>
<td>Steroids, MTX, imatinib</td>
<td>PRD 15 mg daily/renal insufficiency, diarrhea</td>
<td>1.2/10%</td>
<td>35%</td>
<td>Monosomy Y, trisomy 8</td>
</tr>
<tr>
<td>4</td>
<td>69/m</td>
<td>Steroids, dasatinib</td>
<td>PRD 30 mg daily/nausea, vomiting, diarrhea</td>
<td>10.1/23%</td>
<td>14%</td>
<td>46,XY</td>
</tr>
<tr>
<td>5</td>
<td>53/m</td>
<td>CsA, steroids, ATG, cytarabine, imatinib</td>
<td>HU 3 g daily/rash, progressive splenomegaly</td>
<td>25.2/49%</td>
<td>10%</td>
<td>t(5;6)(q22;q21)</td>
</tr>
<tr>
<td>6</td>
<td>31/f</td>
<td>Imatinib, splenectomy, HU, steroids</td>
<td>HU 2 g daily/pleural effusion, chest pain, dyspnea, fever</td>
<td>29.7/9%</td>
<td>32%</td>
<td>46X,Y</td>
</tr>
<tr>
<td>7</td>
<td>62/m</td>
<td>Steroids, imatinib, dasatinib</td>
<td>PRD 80 mg daily + Furosemide 120 mg twice daily/extensive edema</td>
<td>14.3/70%</td>
<td>68%</td>
<td>46X,Y</td>
</tr>
<tr>
<td>8</td>
<td>70/f</td>
<td>PEG-IFNα + steroids, HU</td>
<td>PRD 40 mg daily/heart failure (EF 33%), fever, bone pain</td>
<td>0.7/14%</td>
<td>10%</td>
<td>46,XX</td>
</tr>
<tr>
<td>9</td>
<td>50/f</td>
<td>Steroids + MTX, imatinib</td>
<td>High-dose steroids/ cerebritis, thalamic infarcts, panniculitis</td>
<td>15.0/50%</td>
<td>60%</td>
<td>46,XX</td>
</tr>
<tr>
<td>10</td>
<td>82/m</td>
<td>None</td>
<td>None/severe peripheral edema with skin blistering, severe fatigue</td>
<td>28.7/82%</td>
<td>68%</td>
<td>46,XY</td>
</tr>
<tr>
<td>11</td>
<td>61/m</td>
<td>None</td>
<td>None/dyspnea at rest, profound fatigue</td>
<td>36.3/49%</td>
<td>28%</td>
<td>46,XY</td>
</tr>
</tbody>
</table>

Abbreviations: PB, peripheral blood; BM, bone marrow; m, male; f, female; PEG-IFNα, pegylated IFNα; HU, hydroxyurea; 2CdA, cladribine; ATG, antithymocyte globulin; MTX, methotrexate; CsA, cyclosporine A; ND: not done; tiw, thrice a week; allo-SCT, allogeneic stem cell transplantation; PR, partial response; PRD, prednisone.

* Patients were given alemtuzumab initially at the dose of 5 mg i.v. on day 1, then 10 mg i.v. on day 2, and 30 mg i.v on day 3, if tolerated.
† After a bolus of high dose methylprednisolone at 1 mg/kg/d × 1.
all instances, infusion-related reactions were first noted during the loading doses of alemtuzumab on days 1 to 3 and subsided over the course of subsequent doses. However, in patient 4, alemtuzumab therapy was ultimately abandoned because of persistent infusion-related fever even after dose reductions.

As expected, all patients developed lymphopenia during treatment with alemtuzumab. Two (18%) patients developed CMV reactivation: patient 1 while in CHR off-alemtuzumab therapy and patient 7 after 3 weeks of therapy. Both cases presented with CMV antigenemia and fever of unknown origin with no associated organ disease. Both episodes resolved after the administration of short courses of gancyclovir or valgancyclovir. Patient 8 developed EBV-positive orbital/maxillary sinus diffuse large B-cell lymphoma while being rechallenged with alemtuzumab for relapsed HES. Alemtuzumab therapy was stopped and the patient underwent surgical debulking and involved field radiotherapy. The patient is currently in complete remission from both her lymphoma and HES. Patient 3 developed periorbital cellulitis while in CHR and off-alemtuzumab therapy, requiring a course of i.v. antibiotics.

**Table 3. Individual clinical characteristics and response to alemtuzumab in 11 patients with HES or CEL (Cont’d)**

<table>
<thead>
<tr>
<th>Alemtuzumab therapy</th>
<th>Best hematologic response/time to response</th>
<th>Overall duration of response/duration off therapy</th>
<th>BM CR while in CHR (BM with normal %Eo)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg tiw × 12 doses</td>
<td>CHR/0.5 wk</td>
<td>6 wk/3 wk</td>
<td>Yes</td>
<td>Relapsed off therapy and died after allo-SCT</td>
</tr>
<tr>
<td>30 mg s.c. tiw × 12 doses, then 30 mg tiw × 3 doses every 1-2 mo for 10 mo*</td>
<td>CHR/3 wk</td>
<td>68+ wk/28+ wk</td>
<td>No (BM Eo 7%)</td>
<td>CHR off alemtuzumab</td>
</tr>
<tr>
<td>30 mg s.c. tiw × 12 doses, then weekly × 2 doses*</td>
<td>CHR/0.5 wk</td>
<td>32 wk/31 wk</td>
<td>Yes</td>
<td>Died of unrelated medical reasons while in CHR off therapy</td>
</tr>
<tr>
<td>30 mg s.c. tiw × 12 doses*</td>
<td>CHR/0.5 wk</td>
<td>7 wk/4 wk</td>
<td>No</td>
<td>Relapsed off therapy and died in the hospice</td>
</tr>
<tr>
<td>30 mg i.v. tiw × 24 doses*</td>
<td>CHR/1.5 wk</td>
<td>9 wk/2 wk</td>
<td>ND</td>
<td>Died after not responding to nilotinib, and 2CdA + cytarabine</td>
</tr>
<tr>
<td>30 mg i.v. tiw × 3 doses, then s.c. tiw*</td>
<td>CHR/1 wk</td>
<td>6 wk/0 wk</td>
<td>ND</td>
<td>Relapsed on therapy; in CR post allo-SCT</td>
</tr>
<tr>
<td>30 mg s.c. tiw × 9 doses. Therapy stopped 4 wk due to CMV reactivation; then resumed at 30 mg s.c. tiw × 15 doses, then weekly*</td>
<td>PR/12 wk</td>
<td>2+ wk/0 wk</td>
<td>No (BM Eo 28%)</td>
<td>PR on weekly alemtuzumab</td>
</tr>
<tr>
<td>30 mg s.c./wk × 8 des</td>
<td>CHR/4 wk</td>
<td>12 wk/8 wk</td>
<td>ND</td>
<td>Relapsed off therapy. Rechallenged with 30 mg s.c. every week × 8 then every other week × 4, then every 3 wk × 4. Currently in CHR off therapy for 5 mo</td>
</tr>
<tr>
<td>30 mg s.c. once or twice a week</td>
<td>CHR/5 wk</td>
<td>24 wks/0 wk</td>
<td>ND</td>
<td>Relapsed on therapy; receiving dasatinib</td>
</tr>
<tr>
<td>30 mg i.v. × 1 caused hypotension. Reduction to 10 mg × 1, then 5 mg tiw × 6, followed by 10 mg tiw × 6. Then, 10 mg s.c. twice weekly × 28*</td>
<td>CHR/5 wk</td>
<td>40 wk/28 wk</td>
<td>Yes</td>
<td>Relapsed off therapy. Rechallenged with 30 mg s.c. every week × 8 then every other week × 2. Currently in CHR off therapy for 6 mo</td>
</tr>
</tbody>
</table>

**Discussion**

The present study shows the value of alemtuzumab as therapy for advanced HES or CEL. The rationale for such therapy is based on the constitutive expression of CD52 by eosinophils but not neutrophils (8). Despite the refractory and/or advanced nature of their disease, >90% of our patients achieved alemtuzumab-induced normalization of their blood eosinophil count that was accompanied in most instances with complete resolution of signs and symptoms of disease. Of note, the majority of these patients had failed therapy with corticosteroids, cytoreductive agents, and one of several tyrosine kinase inhibitors, including imatinib, nilotinib, and dasatinib. This patient group has poor outcome; even therapeutic attempts with the use of intensive chemotherapy resulted in only 50% complete remission rate of short duration (14).

Median duration of a response was relatively short, which was primarily the result of patients relapsing while off alemtuzumab therapy. Therefore, continued therapy with alemtuzumab seems to be necessary for maintaining remission status. Although the occurrence of acute infusion-related
Fig. 1. Effect of alemtuzumab therapy. A, bone marrow specimen from patient 3 showing extensive dense interstitial infiltration by eosinophils before alemtuzumab therapy. B, a H&E-stained bone marrow specimen obtained from the same patient within 3 mo from alemtuzumab therapy shows remarkable reduction in the percentage of eosinophils with respect to the total bone marrow cellularity. C, alemtuzumab therapy normalized WBC and eosinophil counts in peripheral blood of patient 10. Note the “rebound” in the eosinophil levels after alemtuzumab dose reduction (5 mg) secondary to infusion-related side effects before achieving a durable CHR on 10 mg twice weekly that was maintained for several months even after alemtuzumab discontinuation. D, top panels show extensive erythematous dermatitis in patient 10 before alemtuzumab therapy characterized by significant interstitial eosinophilic infiltration of the dermis and subcutis (inset) with remarkable blistering and hemorrhage of the hands. Bottom panels show complete resolution of all the cutaneous changes during alemtuzumab therapy. Original magnifications, ×100 (A) and ×200 (B and inset D).

Fig. 2. Effect of alemtuzumab therapy on blood eosinophils. Bone marrow cells obtained from patient 10 were labeled with fluorescent anti-CD52 and anti-CD123 monoclonal antibodies (to highlight eosinophils) and subjected to flow immunophenotypic analysis. A, strong positivity (82%, right top quadrant) in pretherapy sample. B, absence of eosinophils in posttherapy sample.
reactions was expected and effectively managed by supportive care measures, chronic complications of immunosuppression (e.g., CMV reactivation and lymphoma) were documented and warrant critical assessment of risk-benefit balance before considering alemtuzumab therapy for patients with HES or CEL-NOC. Two patients in this report were given alemtuzumab as an initial therapy for their disease, judged by their treating physician to be most suitable for rapid elimination of disease-related debilitating symptoms. However, we would not advocate the use of alemtuzumab in therapy naïve patients due to the above-mentioned risks, but it can be used in advanced cases refractory to standard therapies.

The development of CMV reactivation in 2 (18%) of our patients is in keeping with prior reports (13). Fortunately, there is now evidence for successful prevention of this particular alemtuzumab-associated complication with prophylactic treatment with valgancyclovir (450 mg orally twice daily; ref. 15). Therefore, we recommend that patients should receive valgancyclovir in addition to the standard prophylactic therapy during treatment with alemtuzumab. Unfortunately, there are no similarly effective preventive measures against the development of treatment-associated lymphoma, which is believed to be related to impaired immune surveillance due to alemtuzumab-induced T-cell depletion (7). Therefore, the best one can do at present is close monitoring for early recognition and treatment. Incidentally, such monitoring is also required to detect other complications of alemtuzumab therapy, including autoimmune cytopenia (7).

Prospective clinical trials are needed to carefully assess the value of alemtuzumab as therapy for HES/CEL, most appropriately in a salvage setting for patients with refractory disease. We recommend that maintenance therapy be included in further studies to optimize the benefit derived. This is especially important in the context of other novel therapies, including mepolizumab, an anti–interleukin-5 monoclonal antibody that has been shown, in a randomized study, to facilitate corticosteroid tapering in patients with controlled HES (16) and may have a role as a therapy for patients with an uncontrolled disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References
