Phase II study of alemtuzumab (anti-CD52 monoclonal antibody, Campath-1H) in patients with advanced mycosis fungoides/Sézary syndrome

Running head: Alemtuzumab in cutaneous T-cell lymphoma

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Abstract

This phase II study evaluated the safety and efficacy of alemtuzumab (Campath-1H) in 22 patients with advanced mycosis fungoides/Sézary syndrome (MF/SS). Most patients had stage III or IV disease, reduced performance status and severe itching. The overall response (OR) rate was 55%, with 32% complete remission (CR) and 23% partial remission (PR). Sézary cells were cleared from blood in 6/7 patients (86%) and CR in lymph nodes was observed in 6/11 patients (55%). The effect was better on erythroderma (OR 69%) than on plaque or skin tumors (OR 40%), and in patients who had received 1–2 previous regimens (OR 80%) than in those who had received ≥3 prior regimens (OR 33%). Itching, self-assessed on a 0–10 visual analog scale, was reduced from a median of eight before treatment to two at end of therapy. Median time to treatment failure was 12 months (range 5–32+). Cytomegalovirus (CMV) reactivation (causing fever without pneumonitis and responding to ganciclovir) occurred in four patients (18%). Six additional patients had suspect or manifest infection (fever of unknown origin, three; generalized herpes simplex, one; and fatal aspergillosis, one). One patient had fatal mycobacterium pneumonia at 10+ months. All serious infectious adverse events (except CMV) occurred in patients who had received ≥3 prior regimens. Progression of squamous cell skin carcinoma was noted in one patient. Alemtuzumab shows promising clinical activity and an acceptable safety profile in patients with advanced MF/SS, particularly in patients with erythroderma and severe itching, and those who were not heavily pretreated.

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Introduction

Mycosis fungoides/Sézary syndrome (MF/SS) are the most common cutaneous T-cell lymphomas (CTCL).\textsuperscript{1} The clinical course of MF/SS is usually indolent with pruritic erythematous areas slowly developing over long periods.\textsuperscript{2} Eventually, however, the erythematous patches become progressively infiltrated, developing into plaques and finally to ulcerating tumors. Some patients may develop progressive, generalized erythema, frequently associated with severe itching. Other tissues and organs, such as peripheral blood, lymph nodes, or viscera, may also be involved. During disease progression, a defect in cell-mediated immunity becomes evident,\textsuperscript{3,4} and septicemia and other infections are common causes of death in patients with advanced MF/SS. Transformation to a high-grade lymphoma may also occur during the course of the disease, and is associated with a poor prognosis.\textsuperscript{5}

The prognosis of MF/SS is based on the extent of disease at presentation.\textsuperscript{2,6} Patients with stage I disease have a median survival of 20 years or more, in comparison with a median survival of around 3–4 years for stage III/IV patients.\textsuperscript{2,7}

The traditional treatment of MF/SS includes both topical and systemic therapies, alone or in combination.\textsuperscript{8} Psoralen and ultraviolet A radiation (PUVA) is effective in early-stage MF/SS, inducing complete remissions (CR) in most patients.\textsuperscript{9–11} PUVA may also be combined with low doses of interferon-\(\alpha\) to treat stage I and II disease.\textsuperscript{12–14} Early aggressive therapy with
radiation and chemotherapy does not improve the prognosis.\textsuperscript{15} Local radiotherapy or total-skin electron-beam irradiation (TSEB) has been used with success to control advanced skin disease.\textsuperscript{16,17} Extracorporeal photopheresis may also be used successfully but is not generally available.\textsuperscript{18,19} Once the disease becomes refractory to topical therapy, interferon-\(\alpha\), bexarotene, single-agent or combination chemotherapy may be given but the duration of response is often < 1 year and ultimately all patients will relapse and become refractory.\textsuperscript{8,20–24} Response rates following combined modality therapy with TSEB and chemotherapy/interferon-\(\alpha\) appear similar to those of other therapies.\textsuperscript{25} Furthermore, the outcome for patients with MF/SS is similar regardless of age.\textsuperscript{26} There is, therefore, a great unmet need for novel treatment modalities for patients with advanced, symptomatic MF/SS.

Alemtuzumab (Campath-1H) is a humanized IgG\(_1\) monoclonal antibody\textsuperscript{27} directed against CD52, a glycosylated peptide antigen which is expressed on most malignant B- and T-cells\textsuperscript{28} but not on hematopoietic stem cells.\textsuperscript{29} The effector mechanisms of alemtuzumab and other Campath antibodies are not fully understood but may include antibody-dependent cellular cytotoxicity,\textsuperscript{30,31} complement-mediated cell lysis,\textsuperscript{27,32} and apoptosis.\textsuperscript{33} Alemtuzumab has been developed primarily for the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL), in which response rates of 33–81\%, depending on disease stage, have been reported.\textsuperscript{34–36}

Malignant T-cells express particularly high numbers of CD52 cell-surface markers (approximately 500,000 molecules/lymphocyte\textsuperscript{37}), and the intensity of
CD52 expression seems to correlate with the clinical effects.\textsuperscript{38} T-cell malignancies may therefore be particularly responsive to therapy with alemtuzumab. A high CR rate has been reported in patients with T-cell prolymphocytic leukemia (T-PLL) treated with alemtuzumab.\textsuperscript{39} A phase II study\textsuperscript{40} of 50 patients with advanced, heavily pretreated, low-grade, non-Hodgkin’s lymphoma also included eight pilot patients with MF/SS; four of eight patients responded to alemtuzumab therapy, but otherwise no further details were reported. The aims of the present prospective phase II study, in 22 additional patients with advanced symptomatic MF/SS, were to study in detail the response rate, response in relation to tumor site, impact on itching, and infusional toxicity, as well as anti-tumor effects vs infectious complications in relation to disease phase.

**Patients, materials, and methods**

**Design**

This was a phase II, open-label study, conducted in eight European centers in patients with advanced MF/SS who had failed to respond adequately to therapy with at least PUVA and/or radio/chemotherapy. Alemtuzumab was administered using a rapidly-escalating initial dose regimen, followed by 30 mg three times a week for up to 12 weeks. The primary objective was to assess the overall response (OR) rate in these patients. Secondary objectives were to evaluate the safety profile of alemtuzumab and clinical benefit (i.e. relief of severe itching and time to progression in this population). The study was approved by each institution’s ethics committee and written informed consent was obtained from all patients.
Patients

The study was conducted in patients ≥ 18 years of age with a confirmed diagnosis of CD52-positive MF/SS (stage II–IV) who had received ≤ 5 previous systemic treatments, and who had a World Health Organization (WHO) performance status of ≤ 2 and a life expectancy of ≥ 15 weeks. Eligible patients also had creatinine and bilirubin levels no higher than twice the upper limit of normal, and had undergone previous therapy with PUVA and/or local radiotherapy, chemotherapy, or interferon-α, with documented failure to control local and/or generalized MF/SS. Failure was defined as lack of a partial response (PR), or signs of progressive disease (PD) whilst receiving PUVA/radiotherapy, chemotherapy, or interferon-α, or within 3 months after stopping previous treatment. All patients had clinical symptoms or signs (pruritus, skin ulcers, B-symptoms, symptomatic lymphadenopathy, anemia, or thrombocytopenia) needing treatment.

Patients were excluded if they had stage I MF/SS, if they had previously untreated MF/SS with cutaneous involvements, if they needed only local/topical treatment, if their disease had undergone transformation to high-grade lymphoma, if they had CTCL other than MF/SS (the predominant form of CTCL), if they were HIV-positive, or if they had an active ongoing infection not controlled with antibiotics. Other exclusion criteria were: a past history of anaphylaxis following exposure to rat- or mouse-derived monoclonal antibodies; < 4 weeks since previous chemotherapy, PUVA, interferon-α, or radiotherapy; previous therapy with alemtuzumab; and oral corticosteroid
therapy, apart from a maintenance dose of ≤ 10 mg prednisone. Also excluded were pregnant or lactating women, and those of childbearing potential who were not using a reliable method of contraception.

**Study treatment**

Alemtuzumab (ILEX Pharmaceuticals L.P., San Antonio, TX, USA) was diluted in 100 ml of 0.9% normal saline and administered over 2 hours through an intravenous (iv) infusion line containing a 0.22 micron filter. The first dose was 3 mg, which was increased to 10 mg and then to 30 mg as soon as infusion-related reactions were tolerated. The 30-mg dose was subsequently administered three times a week for up to 12 weeks. Treatment was stopped in the event of patients achieving a CR or fulfilling the criteria for PD. Alemtuzumab therapy was also stopped in patients in whom there was no further tumor reduction or improvement in disease-related symptoms between the Week-4 and Week-8 assessments: these patients were followed without therapy until PD and/or further treatment was needed. Therapy was temporarily discontinued in the event of grade 4 hematological toxicity (platelets < 25 x 10^9/L and absolute neutrophil count [ANC] < 0.5 x 10^9/L) and restarted on recovery of platelets to > 50 x 10^9/L and ANC to > 1.0 x 10^9/L. If treatment was interrupted for > 7 days, the dose was re-initiated at 3 or 10 mg.

**Concomitant treatment**

Patients received paracetamol (1 g orally) and antihistamine (clemastine 2 mg iv) 30 minutes before the infusions. The use of corticosteroids
(betamethasone 8 mg or hydrocortisone 100 mg iv) as secondary prophylaxis during Week 1 in case of flu-like ‘first-dose’ reactions was optional. Once all ‘first-dose’ reactions had disappeared, clemastine and then paracetamol were gradually withdrawn. Patients also received prophylaxis with cotrimoxazole, twice daily, three times weekly, and valaciclovir 500 mg, twice daily, for a minimum of 2 months following discontinuation of alemtuzumab therapy. All patients received oral allopurinol 300 mg per day from Days 1 to 28.

**Disease evaluation**

Disease was evaluated in all patients within 10 days prior to the start of treatment. Patients underwent routine physical and clinical examination, including measurement of lymph nodes, and standard laboratory tests, including blood counts, liver function tests, and serum protein and electrolyte measurements. In addition, they underwent a chest X-ray, a chest and abdominal computed tomography (CT) scan, and bone marrow aspiration/trephine biopsy. Other investigations included assays for tri-iodothyrosine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH), thyroid receptor antibody (TRAK), and thyroid peroxidase antibody (a-TPO). CD52 staining of tumor cells was performed by flow cytometry (FACScan, Becton Dickinson, Stockholm, Sweden) using fluoresceine (FITC)-labeled anti-CD52 monoclonal antibodies (Serotec, Oxford, UK). The tumor cells analyzed were obtained from either blood, bone marrow, or fine-needle aspiration biopsy of an involved lymph node or skin tumor nodule. The size and appearance of skin lesions were documented by physical examination and color photography, and patients self-assessed the severity of their itching.
on a visual analog scale (VAS), from 0 = no itching to 10 = worst possible itching. The tumor nodes and metastases classification system was used for clinical staging as described previously.\textsuperscript{1,41} Fine-needle aspiration biopsy was performed on clinically enlarged lymph nodes to distinguish between stages II/III and IV. Clinical stage IV was determined mainly based on roentgenological and clinical findings; biopsies from visceral organs were not routinely performed.

Total and differential white blood cell counts were repeated once weekly during treatment. Serum electrolyte, uric acid, and liver function tests were repeated every 4 weeks. Physical examination and assessment of skin lesions and lymph nodes were repeated after 4 and 8 weeks of therapy, and again at the end of treatment, at 2-months post-treatment, and then every third month until the development of PD or for a maximum of 2 years. The patient’s self-assessment of itching was repeated after 4 and 8 weeks of therapy, at the end of treatment, and then every second month during follow-up until the development of PD or for a maximum of 2 years. T3, T4, TSH, TRAK, and a-TPO measurements were repeated at the end of alemtuzumab therapy, and at 3, 6, 9, 12, and 18 months after completion. If initially abnormal, bone marrow aspiration, trephine biopsy, and chest and abdominal CT scans were repeated after 4 and 8 weeks, at the end of treatment, and thereafter every 6 months during follow-up until PD or for a maximum of 2 years. Patients achieving a clinical CR underwent a skin biopsy on completion of alemtuzumab therapy.
Outcomes

The primary outcome measure was the OR rate (CR plus PR, according to the criteria detailed below). Secondary outcome measures were adverse events and clinical benefit (i.e. the reduction of severe itching and time to treatment failure).

Response rate

Response was evaluated after 4, 8, and 12 weeks of treatment, mainly according to the criteria described previously. These were:

Complete remission (CR): Complete disappearance of all previously detectable disease parameters and no new lesions. No palpable lymph nodes > 1 cm or nodes on CT scan > 1.5 cm. Bone marrow negative if initially positive. Absence of neoplastic, circulating lymphocytes. Normal skin. CR confirmed by skin biopsy. CR must be maintained for ≥ 1 month.

Partial remission (PR): Decrease of ≥ 50% from baseline in the sum of the products of the two largest perpendicular diameters in all measurable and evaluable lymph nodes and five pre-defined, representative skin lesions, respectively. No new lesions.

Stable disease (SD): < 50% decrease from baseline in the sum of the products of the two largest perpendicular diameters in all measurable and evaluable lesions. < 50% increase from baseline/nadir in the sum of the products of the two largest perpendicular diameters in all measurable and evaluable lymph nodes and five pre-defined, representative skin lesions, respectively. No new lesions.
Progressive disease (PD): > 50% increase from nadir in the sum of the products of the two largest perpendicular parameters of measurable lymph nodes or the five pre-defined, representative skin lesions, respectively. Appearance of new lesions.

Time to response was measured from the day of the initial treatment until the first objective documentation of OR. Time to treatment failure was measured in responding patients from the day of the initial treatment to objective documentation of PD and/or requirement for additional therapy for MF/SS, death or last follow-up.

Results

Patient population

A total of 22 patients, median age 61 years (range 38–77), who had received a median of three prior therapies (range 1–5) were enrolled. Patient characteristics are shown in Table 1. All patients had strong CD52 expression (arbitrary grading using flow cytometry) on the tumor cells. The majority of the patients had advanced disease (stage II, 14%; stage III, 45%; stage IV, 41%). B-symptoms (fever, night sweats, weight loss) were present in 36% of the patients. Seven patients (32%) had Sézary cells in the blood. Seventeen patients had itching, with a median VAS score of 8 (range 1–10). All patients were evaluable for safety and efficacy.
Table 1. Patient characteristics ($n = 22$)

<table>
<thead>
<tr>
<th>Clinical stage, %</th>
<th>IA</th>
<th>IB</th>
<th>IIA</th>
<th>IIB</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IVA</th>
<th>IVB</th>
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<td></td>
<td></td>
<td>5</td>
<td>9</td>
<td>27</td>
<td>18</td>
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<td>IB</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td>9</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
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<td>18</td>
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<td></td>
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<tr>
<td>IVA</td>
<td></td>
<td>32</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IVB</td>
<td></td>
<td>9</td>
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<th>WHO performance status, %</th>
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<th>2</th>
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<tr>
<td>0</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>55</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B-symptoms, %</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36</td>
<td></td>
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<tr>
<td>No</td>
<td>64</td>
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<th>Number of previous regimens</th>
<th>Median (range)</th>
<th>Median (range)</th>
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<tr>
<td>Number of previous regimens</td>
<td>Median (range)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>3</td>
<td>1–5</td>
<td>1–10</td>
</tr>
</tbody>
</table>

Dosing

The alemtuzumab dose was rapidly escalated to the target dose of 30 mg per infusion after a median time of 5 days (range 4–13). The median treatment time was 10 weeks. Eleven patients (50%) completed all 12 weeks of treatment. The reasons for withdrawal were: non-response or PD (five
patients, at Weeks 4, 7, 7, 8, and 8, respectively); infectious complications (five patients, at Weeks 4, 5, 5, 6, and 8, respectively); and fatigue grade 3 (one patient, at Week 6).

**Efficacy**

Examples of clinical responses in two patients with severe, generalized erythroderma and plaque stage, respectively, are shown in Figures 1 and 2. The OR rate was 55%. Seven patients (32%) achieved CR (one after 4 weeks, three after 8 weeks, and three after 12 weeks of therapy). PR was observed in five patients (23%). Three patients (13%) had SD and seven patients (32%) had PD. The OR rate in patients who had received 1–2 previous regimens was 80% (8/10), compared with 33% (4/12) in those who had received ≥3 prior regimens. Responses in relation to disease site are shown in Table 2. Tumor cells were cleared from blood (as assessed by morphological examination and verified by a negative flow cytometry analysis) in 6/7 patients (86%), and CR with regard to lymphadenopathy was observed in 6/11 patients (55%); all six patients had tumor-involved lymph nodes rather than dermatopathic lymphadenopathy. The OR rate in the skin was 55%, including 32% CR. Erythroderma responded in 69% of the patients, 38% of whom achieved CR. The corresponding number for plaque/tumors in the skin was 40% OR, with 30% CR.
Table 2. Response by disease site

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>OR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Blood</td>
<td>7</td>
<td>6 (86)</td>
<td>6 (86)</td>
<td>0 (0)</td>
<td>1 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>11</td>
<td>6 (55)</td>
<td>6 (55)</td>
<td>0 (0)</td>
<td>3 (27)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Skin</td>
<td>22</td>
<td>12 (55)</td>
<td>7 (31)</td>
<td>5 (23)</td>
<td>5 (23)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>16*</td>
<td>11 (69)</td>
<td>6 (38)</td>
<td>5 (31)</td>
<td>4 (25)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Plaque/tumors</td>
<td>10*</td>
<td>4 (40)</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>

N indicates total number of patients assessed (denominator for %).

*Some patients had erythroderma and plaque/tumors simultaneously.

Self-assessment (VAS) of itching/pruritus before and after alemtuzumab treatment is shown in Table 3. Itching was reduced from a median of eight (at baseline) to two (at the end of the treatment period). Itching was also improved by ≥ 10 mm (VAS) in three of six patients who did not fulfill the criteria for PR.

The median time to treatment failure in responding patients was 12 months (range 5–32+ months; Figure 3). PD following a previous response to alemtuzumab was, in most patients, characterized by worsening of erythema and/or progression of plaque or tumors.
Table 3. Self-assessment of itching/pruritus using a visual analog scale* (VAS) before and after alemtuzumab treatment

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>Baseline VAS</th>
<th>End-of-treatment VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (range)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>All patients</td>
<td>17</td>
<td>8 (1–10)</td>
<td>2 (0–9)</td>
</tr>
<tr>
<td>Responders</td>
<td>11</td>
<td>8 (6–10)</td>
<td>1 (0–6)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>6</td>
<td>6 (1–9)</td>
<td>5 (0–10)</td>
</tr>
</tbody>
</table>

*VAS: 0 = no itching; 10 = worst possible itching.
Adverse events

Infusion-related adverse events

Infusion-related adverse events included fever, rigors, nausea, hypotension, rash/urticaria, bronchospasm, and fatigue. These were confined to the first infusion(s) and were largely mild to moderate in severity. Thirteen patients (59%) received iv corticosteroids as secondary prophylaxis during Week 1. There were no National Cancer Institute (NCI) grade 4 reactions (Table 4), and no patient was withdrawn from the study due to ‘first-dose’ reactions. After the first week, almost all side-effects had disappeared.

Table 4. Infusion-related adverse events*† following iv administration of alemtuzumab in 22 patients with MF/SS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NCI grade 1–2 Patients, %</th>
<th>NCI grade 3‡ Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>68</td>
<td>5</td>
</tr>
<tr>
<td>Rigors</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Rash/urticaria</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

*Most side-effects disappeared after 1 week during continued alemtuzumab treatment.

†Thirteen patients (59%) received iv corticosteroids as secondary prophylaxis during Week 1.

‡No grade 4 reactions occurred.
**Hematological toxicity**

Hematological toxicity is shown in Table 5. Transient grade 4 neutropenia was recorded in four patients (18%) after a median time of 11 weeks (range 8–12). One patient (5%) developed transient grade 4 thrombocytopenia. The grade 4 cytopenias recovered spontaneously (without granulocyte-colony stimulating factor usage) during continued alemtuzumab treatment or after the end of the treatment period (in patients with late-occurring neutropenia) after a median time of 2 weeks (range 1–5).

**Table 5. Hematological side-effects (n = 22)**

<table>
<thead>
<tr>
<th>NCI grade</th>
<th>0–1 n (%)</th>
<th>2–3 n (%)</th>
<th>4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>21 (95)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17 (77)</td>
<td>1 (5)</td>
<td>4 (18)*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (82)</td>
<td>3 (13)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*After 8–12 weeks of treatment.

**Infectious complications**

Eleven of 22 evaluable patients (50%) had no infectious complications during or after alemtuzumab treatment. One patient developed fatal pulmonary aspergillosis 2.5 months after the end of alemtuzumab treatment. This patient had chemotherapy-refractory disease, clinical stage IIIB, and rapid PD prior to and during treatment. One patient developed fatal mycobacterium pneumonia.
10 months after the end of treatment. The patient had chemotherapy-refractory disease and PD at this timepoint, as well as a history of recurrent bronchitis prior to alemtuzumab therapy. The causal relationship between study drug and the fatality was regarded as probable by the physician. Four patients (18%) had reactivation of cytomegalovirus (CMV) infection, presenting as fever without pneumonitis; all four responded to iv ganciclovir. Two patients developed fever of unknown origin (without neutropenia), which resolved following iv antibiotics. Another patient developed febrile neutropenia 2 months after the last dose; fever resolved following iv antibiotics and the neutrophil count normalized. One patient developed a generalized herpes simplex virus (HSV) reactivation, which resolved following foscarnet treatment. Another patient (with PD during alemtuzumab treatment) had long-lasting fever after the end of therapy, which did not respond to antibiotics. No causative agent could be identified and lymphoma-related fever was suspected.

All serious infectious adverse events occurred in the patients who had received $\geq 3$ previous treatment regimens for MF/SS, except for CMV which was equally distributed between less heavily pretreated patients (1–2 previous regimens) and those who had very advanced MF/SS.

*Other side-effects*

Progression of a pre-existing squamous cell carcinoma was observed in one patient during alemtuzumab therapy.
Discussion

In this study, a clinical response following alemtuzumab treatment was recorded in > 50% of patients with advanced MF/SS. Responses were obtained in all disease sites associated with MF/SS, with a preference for erythrodermic vs the plaque/tumor stage of the disease, and for less heavily pretreated patients vs those with refractory disease. Furthermore, of 11 patients with lymphadenopathy at baseline, six (all of which had tumor-involved lymph nodes) achieved CR in the nodes, a site considered less responsive to alemtuzumab therapy in patients with B-cell lymphomas or advanced B-CLL. Dermatopathic lymphadenopathy did not respond to alemtuzumab treatment in any of our patients. Itching, which was severe in many patients prior to therapy, improved markedly or disappeared during alemtuzumab treatment in most patients. Long lasting (> 12 months) remissions were observed in half of the responding patients. These results seem to compare favorably with those of other targeted therapeutics that have been tested in patients with CTCL, such as chimeric anti-CD4 (OR, 7/8 patients; median response duration, 5 months) and denileukin diftitox (toxin-coupled anti-CD25), which attained an OR rate of 30% in 71 patients with CTCL for a median duration of 7 months. The clinical responses obtained in the present study were similar to those obtained with modern agents, such as 2-chlorodeoxyadenosine (2-CdA), pentostatin, and bexarotene; however, the median response duration with these agents is reportedly less than the median response duration achieved in the patients treated in the present study.
Alemtuzumab therapy resulted in moderate ‘first-dose’ infusion-related side-effects. In thirteen of our patients (59%), corticosteroids were given iv as secondary prophylaxis during Week 1; flu-like symptoms, particularly rigors, were frequently reduced. Therefore, iv corticosteroid prophylaxis may be recommended in most patients during the first week of alemtuzumab treatment.

The treatment therapy was associated with acceptable hematological toxicity; 18% of patients experienced transient grade 4 neutropenia, which occurred late (Weeks 8–12) during therapy. This is in contrast to other recent reports in patients with B-CLL, who developed transient neutropenia after 2–4 weeks of therapy. This may be explained by the absence or low degree of bone marrow infiltration in MF/SS compared with B-CLL. Growth factor support may be recommended in patients with prolonged or recurrent episodes of neutropenia whilst receiving alemtuzumab treatment.

Given the T-cell suppressive effects of alemtuzumab and the suppression of T-cell-mediated immunity that accompanies CTCL with advancing stage, an increased risk of opportunistic and other severe infections was expected during this trial in the mainly advanced, heavily pretreated MF/SS patients. Even though half of our patients completed therapy without any immediate or late-occurring major infectious complications, an increased risk was detected. This was considered to be attributable to alemtuzumab treatment in combination with the advanced disease stage of our patients. Notably, except for CMV, all serious infectious adverse events occurred in patients who had
received ≥ 3 previous regimens for MF/SS. Reactivation of CMV, as well as other viruses, must always be excluded in the event of fever of unknown origin in alemtuzumab-treated patients. The risk of opportunistic infections, such as *Pneumocystis carinii* pneumonia (not observed in this study), tuberculosis, and fungal infections, also needs to be taken into account. The introduction of antiviral and cotrimoxazole prophylaxis has reduced, but not eliminated, the risk of infectious complications during alemtuzumab treatment.34–36,40

In conclusion, this study indicates that alemtuzumab has clinically significant activity in patients with advanced MF/SS. The side-effects reported in this study are acceptable in relation to the severity of the disease in our patients. The findings of this phase II, multicenter study therefore support the role of alemtuzumab as treatment for patients with advanced MF/SS, provided that antibiotic and antiviral prophylaxis are used, and that patients are kept under close observation during and after treatment. These results indicate that there is scope for investigation of combination therapies with other modern drugs in the treatment of advanced CTCL. Our data indicate that early treatment with alemtuzumab may result in a higher efficacy, which also appears to be associated with a lower incidence of infections. Alemtuzumab should also be evaluated in patients with other types of T-cell lymphoma.

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References


Figure legends

Figure 1. Skin appearance before (A) and after (B) 12 weeks of alemtuzumab treatment in patients with advanced erythrodermic MF/SS. The erythroderma, which is present all over the body causing severe itching and repeated infections, responded gradually to alemtuzumab therapy and the patient went into an unmaintained CR, which lasted for 18 months.

Figure 2. Plaque related to MF/SS on the lower left leg before (A) and after (B) 12 weeks of alemtuzumab treatment.

Figure 3. Time to treatment failure in patients (n = 12) with advanced MF/SS who responded to alemtuzumab therapy.
Phase II study of alemtuzumab (anti-CD52 monoclonal antibody, Campath-1H) in patients with advanced mycosis fungoides/Sezary syndrome

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