Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route

Claire E. Dearden, Amit Khot, Monica Else, Mike Hamblin, Effie Grand, Ashok Roy, Saman Hewamana, Estella Matutes, and Daniel Catovsky

Intravenous alemtuzumab is an effective and well-tolerated treatment for T-cell prolymphocytic leukemia (T-PLL). Alemtuzumab given intravenously as first-line treatment in 32 patients resulted in an overall response rate of 91% with 81% complete responses. Studies in B-cell chronic lymphocytic leukemia have shown subcutaneous alemtuzumab to be equally as effective as intravenous alemtuzumab. The UKCLL05 pilot study examined the efficacy and toxicity of this more convenient method of administration in 9 previously untreated patients with T-PLL. Only 3 of 9 patients (33%) responded to treatment. Furthermore, 2 of 9 patients (22%) died while on treatment. Recruitment was terminated because of these poor results. After rescue therapy with intravenous alemtuzumab and/or pentostatin, median progression-free survival and overall survival were similar to the intravenous group. Alemtuzumab delivered intravenously, but not subcutaneously, remains the treatment of choice for previously untreated T-PLL. This study is registered at www.eudract.ema.europa.eu as #2004-004636-31. (Blood. 2011;118(22):5799-5802)

Introduction

T-cell prolymphocytic leukemia (T-PLL) is an aggressive malignancy with a median survival of 7 months in historical series. Intravenous alemtuzumab (Campath), used either alone or in combination with a purine analog, is an effective and well-tolerated treatment, with overall response rates (ORR) ranging between 51% and 95%,2-6 and a median survival of 15 to 19 months in patients achieving a complete response (CR),3,4 increasing to 48 months after consolidation with autologous or allogeneic stem cell transplantation (SCT).7 Studies in chronic lymphocytic leukemia (CLL) have shown subcutaneous alemtuzumab to be as effective as intravenous alemtuzumab.5,6 The UKCLL05 study was designed to examine the efficacy and toxicity of this more convenient method of administration in previously untreated patients with T-PLL. We analyzed the results from our series of patients with T-PLL, who received alemtuzumab intravenously and compared them with those of the subcutaneously treated group.

Methods

UKCLL05 was a prospective nonrandomized pilot study, in which previously untreated patients with T-PLL were given alemtuzumab (Campath) delivered subcutaneously. The primary end point was the ORR, including the CR and partial response (PR) rates. The secondary end points were toxicity, progression-free survival (PFS), and overall survival (OS). The recruitment target was 10 patients over 2 years.

T-PLL was confirmed by a central review of morphology, immunophenotyping and cytogenetics. Patients with World Health Organization performance status > 2 were excluded from the study. The study (EUdraCT no. 2004-004636-31) was approved by the Royal Marsden Hospital/Institute of Cancer Research Committee for Clinical Research (CCR2532) and the Thames Valley Multi-Center Research Ethics Committee (04/MRE12/77). All participants gave written informed consent in accordance with the Declaration of Helsinki.

The dose of subcutaneous alemtuzumab was escalated during the first 3 days (3, 10, and 30 mg) and then given at a dose of 30 mg 3 times a week until maximal response, for a maximum of 18 weeks. A change to the intravenous route was allowed if severe local reactions occurred at injection sites, if there was disease progression, or if only a PR was achieved by week 8. Patients in CR were considered for SCT.

All previously untreated patients with T-PLL referred to the Royal Marsden between October 2005 and July 2007 were recruited to the UKCLL05 trial. We compared the outcomes retrospectively with those of 32 treatment-naive patients with T-PLL who received alemtuzumab by the intravenous route, either before the trial or after it, using the same dose schedule. Apart from the route of administration, the management of these cases was the same as for the UKCLL05 patients.

As per the UKCLL05 protocol, CR was defined as the absence of disease detectable by morphology of blood and bone marrow (including trephine biopsy) and CT scanning; PR was defined as 50% or more reduction in detectable disease, but short of a CR, maintained for 2 months or more. CT scans were not available to confirm CR in 8 patients who received alemtuzumab intravenously.

PFS and OS were estimated using the Kaplan-Meier method. The Fisher exact and Mann-Whitney U tests were used to compare groups. Statistica software by StatSoft was used.

Results and discussion

The demographic characteristics of the 32 previously untreated patients given alemtuzumab intravenously were similar to those of...
patients who received it subcutaneously (Table 1). In both groups, the male/female ratio was 2:1 and the median age was just > 60 years. In the intravenously treated group, the immunophenotype was either CD4⁺ (67%) or CD4⁻ and CD8⁺ (33%). A complex karyotype with abnormalities of chromosome 14 [e.g., inv(14)(q11q32)] and/or chromosome 8 (isochromosome 8q) was found in 12 of 17 evaluable patients. Nine patients were recruited to the UKCLL05 trial, of whom 8 had a CD2⁺, CD3⁺, CD5⁺, CD7⁺, and CD4⁺ immunophenotype. Seven had a complex karyotype, and 8 had chromosome 14 abnormalities. The proportion of patients with extramedullary disease was similar between the 2 groups (P = .7).

After intravenous alemtuzumab, the ORR was 91%, with 81% CR. In comparison, only 3 of 9 UKCLL05 patients responded (ORR = 33%, P = .01). All 3 responders qualified as CR (Table 1). Subcutaneous alemtuzumab was well tolerated. Two patients had skin reactions and 2 had asymptomatic cytomegalovirus reactivation. Two had grade 4 hematologic toxicity, considered to be related to the disease itself rather than the treatment. These latter 2 patients died of progressive disease while on treatment. Recruitment was terminated because a review by an independent data monitoring committee concluded that subcutaneous alemtuzumab was not as effective as intravenous alemtuzumab.

Five of the 6 nonresponding UKCLL05 patients were changed to intravenous treatment, resulting in 1 additional CR. Pentostatin, 4 mg/m² weekly, was added for 5 patients, resulting in 2 further CRs (Table 2). Three patients remained alive at 46 to 53 months of follow-up, 2 in continued CR after allogeneic SCT. PFS at 12 months was 67% in both the intravenously and subcutaneously treated groups, and OS at 48 months was 37% and 33%, respectively (Table 1).

As expected, 45 patients who received alemtuzumab intravenously after other previous treatments had lower response rates than those treated de novo (ORR = 74%, not significant; 60% CR: P = .04, Table 1). However, the CR rate was higher, and the ORR rate significantly higher (P = .05), than in the previously untreated patients who received alemtuzumab subcutaneously.

In this series, response rates have been consistently high in previously untreated patients with T-PLL who received intravenous alemtuzumab. The finding of significantly inferior response rates with the use of subcutaneous alemtuzumab as front-line therapy, even when compared with intravenous treatment in relapsed or refractory patients, was unexpected. We are confident that this is a real observation, given that the patients in the UKCLL05 trial had characteristics similar to those treated with intravenous alemtuzumab and also given that the expected response rate was resumed in a subsequent patient cohort after return to first-line treatment via the intravenous route. The difference in response rate between intravenous and subcutaneous alemtuzumab, therefore, could not be attributed to a change in patient population or other management factors.

There are a number of possible explanations for the lower rate of response to subcutaneous alemtuzumab. From pharmacokinetic studies undertaken in CLL, it is apparent that, although the same peak levels of antibody are obtained with both intravenous and subcutaneous administration of alemtuzumab, there is a longer delay in achieving this with the subcutaneous route. This may be particularly critical in this rapidly progressive leukemia, in contrast to CLL. It is also possible that the nonresponding patients developed anti–Campath antibodies, and this could also explain the failure of 4 of 5 patients to respond to a change to intravenous administration. The only recorded evidence of anti–Campath antibodies in CLL occurred when alemtuzumab was administered subcutaneously to previously untreated patients. The subcutaneous route is certainly more immunogenic than the intravenous route, and the nature of T-PLL means that patients are often less immunocompromised than comparable CLL patients.

Although this pilot study was small, the findings are highly relevant to clinical practice. On the evidence presented here, the intravenous, but not the subcutaneous, route of alemtuzumab administration remains the treatment of choice for newly diagnosed patients with T-PLL.

**Acknowledgments**

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**Authorship**

Contribution: C.E.D. was the principal investigator and cowrote the paper; A.K. and M.E. analyzed the data and cowrote the paper; D.C., M.H., E.G., A.R., and E.M. entered patients into the study; E.M. reviewed the diagnostic material; S.H. critically reviewed the data; and all authors had access to the primary clinical trial data, reviewed the paper, and approved the final draft.

Conflict-of-interest disclosure: C.E.D. received honoraria and research funding from Schering Health Care (United Kingdom). The remaining authors declare no competing financial interests.

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**Table 1. Alemtuzumab treatment for T-cell prolymphocytic leukemia at the Royal Marsden Hospital: patient characteristics and treatment outcomes**

<table>
<thead>
<tr>
<th>Alemtuzumab treatment</th>
<th>No. of cases</th>
<th>Sex, male/female</th>
<th>Median age (range)</th>
<th>No. (%) with extramedullary disease</th>
<th>ORR, no. (%)</th>
<th>CR rate, no. (%)</th>
<th>PFS at 12 mo, %</th>
<th>Given SCT, %</th>
<th>OS at 48 mo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous at first-line</td>
<td>32</td>
<td>22:10</td>
<td>62 (36-85)</td>
<td>10/24 (42)</td>
<td>29/32 (91)</td>
<td>26/32 (81)</td>
<td>67</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>Subcutaneous at first-line</td>
<td>9</td>
<td>6:3</td>
<td>61 (36-79)</td>
<td>4/9 (44)</td>
<td>3/9 (33)</td>
<td>3/9 (33)</td>
<td>67</td>
<td>55</td>
<td>33</td>
</tr>
<tr>
<td>Intravenous as subsequent therapy†</td>
<td>45</td>
<td>34:11</td>
<td>59 (35-81)</td>
<td>15/26 (58)</td>
<td>31/42 (74)</td>
<td>25/42 (60)</td>
<td>26</td>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

*Including skin, liver, central nervous system, ascites, tonsils, larynx, and pleural effusions.
†Including SCT where applicable.
‡After prior pentostatin (n = 32) or other treatment, including cladribine, fludarabine, cyclophosphamide, chlorambucil, and CHOP (n = 13).
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>WBC, × 10^9/L</th>
<th>Alemtuzumab, wk</th>
<th>Response after subcutaneous alemtuzumab</th>
<th>Intravenous alemtuzumab given</th>
<th>Response after intravenous alemtuzumab</th>
<th>Pentostatin added</th>
<th>Response after pentostatin</th>
<th>Stem cell transplant</th>
<th>Disease progression</th>
<th>PFS from start alemtuzumab, mo</th>
<th>Vital status</th>
<th>OS from start alemtuzumab, mo</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>79</td>
<td>217</td>
<td>7</td>
<td>CR</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>No</td>
<td>—</td>
<td>Yes</td>
<td>34</td>
<td>Alive</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>66</td>
<td>118</td>
<td>11</td>
<td>CR</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Autograft</td>
<td>21*</td>
<td>Died</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>61</td>
<td>96</td>
<td>14</td>
<td>CR</td>
<td>No</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>Allograft</td>
<td>No</td>
<td>46</td>
<td>Alive</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>78</td>
<td>115</td>
<td>9</td>
<td>NR</td>
<td>Yes</td>
<td>CR</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>13*</td>
<td>Died</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>41</td>
<td>206</td>
<td>15</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>CR</td>
<td>Allograft</td>
<td>No</td>
<td>51</td>
<td>Alive</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>60</td>
<td>183</td>
<td>12</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>CR</td>
<td>Allograft</td>
<td>Yes</td>
<td>11</td>
<td>Died</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>50</td>
<td>203</td>
<td>13</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>NR†</td>
<td>Allograft</td>
<td>Yes</td>
<td>0</td>
<td>Died</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>76</td>
<td>73</td>
<td>4</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
<td>Died</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>76</td>
<td>205</td>
<td>8</td>
<td>NR</td>
<td>No</td>
<td>—</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>0</td>
<td>Died</td>
<td>2</td>
</tr>
</tbody>
</table>

WBC indicates white blood cell; —, not applicable; and NR, nonresponse.

*Re-treated with alemtuzumab (intravenously) achieving second response.
†Achieved good PR after DexaBEAM before allograft.
References


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