Intensified alemtuzumab–CHOP therapy for peripheral T-cell lymphoma

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Background: The prognosis of T-cell lymphoma is poor. To explore the addition of the monoclonal antibody alemtuzumab, we studied the efficacy and tolerability of an intensified alemtuzumab–chemotherapy combination for aggressive T-cell lymphoma in a phase II study by Dutch-Belgian Hemato-Oncology Group (HOVON).

Patients and methods: Patients (≤ 65 years) with newly diagnosed T-cell lymphoma received eight CHOP cycles (cyclophosphamide, doxorubicin, vincristine, prednisone) 2-weekly, each cycle with three doses of 30 mg alemtuzumab. Prophylaxis consisted of cotrimoxazole, fluconazole and valaciclovir. Cytomegalovirus (CMV) monitoring took place at least every fortnight.

Results: Twenty patients from 10 centers, median age 50 years, were included. Eighty-five percent received six or more cycles. The overall response was 90% [12 complete remissions (CRs), 1 CR unconfirmed, 5 partial remissions]. Median duration of follow-up of patients still alive was 29 months (range 19–41 months). Median overall survival (OS) and event-free survival (EFS) were 27 and 10 months, with 55%/27% OS/EFS at 2 years. Adverse events consisted of neutropenic fever (n = 8) and CMV reactivation (n = 7), with one CMV disease. Three patients developed secondary Epstein-Barr virus (EBV)-related lymphoma, all after end of treatment.

Conclusions: Although intensified alemtuzumab–CHOP induces high responses, many patients relapse, and the scheme is associated with serious infection-related adverse events. EBV monitoring after end of treatment is required.

Key words: alemtuzumab, EBV, immunochemotherapy, T-cell lymphoma, T-cell non-Hodgkin’s lymphoma

original article

Introduction

The prognosis of patients with mature T-cell lymphoma (T-NHL) treated by classical CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy is extremely poor in most cases, with a median survival varying between 6 and 24 months depending on T-cell subtype, the large majority (>85%) of the patients dying within 2–3 years [1–4]. An exception should be made for the rare patients with ALK-positive anaplastic large cell lymphoma (ALCL) and those cases with a very favorable risk profile [5].

For aggressive B-cell lymphoma (B-NHL), addition of an anti-B-cell monoclonal antibody to classical CHOP chemotherapy has resulted in an impressive improvement of clinical outcomes. Therefore, the exploration of the combination of an anti-T-cell monoclonal antibody with CHOP has been an obvious approach for T-NHL. The anti-CD52-specific antibody alemtuzumab (MabCampath®) appeared to be a suitable monoclonal antibody to evaluate as a therapy for patients with T-cell malignancies. Alemtuzumab has shown activity in T-cell malignancies, especially in a variant of mature T-cell leukemia (T-cell prolymphocytic leukemia) [6–10] and in mycosis fungoides/Sezary syndrome [11].

Because malignant T cells can express high numbers of CD52 cell surface molecules [12–14], mature T-NHLs seem excellent candidates for therapy with alemtuzumab. A pilot study of single-agent alemtuzumab in 14 heavily pretreated patients with relapsed or refractory peripheral T-NHL showed promising results with five responding patients [15]. Tolerability was poor, however, with cytomegalovirus (CMV) reactivation in six patients, pulmonary aspergillosis in two and pancytopenia in four. In another recent study consisting of patients with mature T-cell leukemia or T-cell lymphoma, two out of six patients with mature T-cell lymphoma responded to a combination of alemtuzumab and pentostatin [10].

The dismal prognosis of T-NHL and promising response to alemtuzumab have been the rationale for several groups to initiate phase II studies exploring various combinations of...
alemtuzumab with CHOP chemotherapy despite its potential toxicity. The Dutch–Belgian Hemato-Oncology Group (HOVON) decided in 2005 to initiate a phase II trial (HOVON 69) testing the efficacy and toxicity of a maximally intensive alemtuzumab–CHOP combination, incorporating 90 mg alemtuzumab per 2-weekly CHOP cycle. The 2-weekly CHOP was selected because this scheme had shown better outcome in B-NHL, although specific data regarding CHOP-14 for patients with T-NHL are lacking [16, 17]. We reasoned that we should avoid lack of efficacy due to insufficient dosing of immunotherapy in this phase II trial. Moreover, we were willing to accept toxicity, given the poor outcome of CHOP alone in T-NHL.

With a mature median follow-up of 29 months (range 19–41 months) for patients still alive, we herein present the final outcome of the HOVON 69 study.

design and methods

patient selection

Patients with newly diagnosed T-NHL according to the World Health Organization (WHO) 2001 classification of the following types were eligible: extranodal natural killer/T-cell lymphoma, nasal type, enteropathy-type T-cell lymphoma, if measurable disease, subcutaneous panniculitis-like T-NHL (of note, the difference between the alpha-beta and gamma-delta subtypes as provisionally outlined [18] and later on defined in the WHO 2008 was not recognized yet), angioimmunoblastic T-cell lymphoma (AILT) and peripheral T-cell lymphoma, unspecified (T-NHL NOS). Patients with ALCCL were excluded. Similarly, patients with hepatosplenic type T-NHL were excluded due to a lack of measurable disease. Other reasons for exclusion were intolerance of exogenous protein administration, severe cardiac dysfunction (NYHA classification II–IV) or left ventricular ejection fraction <45%, significant renal dysfunction (serum creatinine ≥1.69 mg/dl) unless related to NHL, significant hepatic dysfunction (total bilirubin ≥1.75 mg/dl) or transaminases ≥2.5 times normal level unless related to NHL, suspected or documented central nervous system involvement by NHL, known HIV positivity, active uncontrolled infections, uncontrolled asthma or allergy requiring steroid treatment, prior treatment with chemotherapy, radiotherapy or immunotherapy for the underlying lymphoma, except local radiotherapy in case of (potential) organ dysfunction by localized lymphoma mass or infiltration and finally a history of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma. Patients had to be 18–65 years inclusive with a WHO performance status of 0, 1 or 2. Stage of the disease should be II or more. Disease parameters had to be measurable. All patients had to give written informed consent. Patients had to be registered by phone, fax or via Internet at the HOVON data center, before the start of the chemotherapy. The institutional review board of each participating center approved the study and written informed consent was obtained from all patients before entry in the study. The study was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonization and Guidelines for Good Clinical Practice. Pathology specimens were centrally reviewed (JO). This trial was registered at ISRCTN, number: ISRCTN5226529.

treatment regimen, supportive care and CMV monitoring

Eight cycles of CHOP chemotherapy in combination with alemtuzumab were given at 14 days intervals. On day 1, the following three drugs were given i.v.: cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and vincristine 1.4 mg/m² with a maximum of 2 mg. Oral prednisolone or prednisolone was given at a dose of 100 mg daily on days 1, 2, 3, 4 and 5. At day 2, before bedtime, granulocyte-colony-stimulating factor (G-CSF, Pegfilgrastim) was given at a dose of 6 mg subcutaneously. Alemtuzumab (MabCampath®) was given in three doses of 30 mg (total 90 mg) per CHOP cycle subcutaneously per injection, at days 1, 5 and 10. During the first cycle, the first alemtuzumab dose consisted of 3 mg and the second dose 10 mg. During the first injection of 3 mg, the patient was observed with an intravenous line for 2 h. Premedication with paracetamol (1000 mg) and an antihistaminic (e.g. clemastine 2 mg) was mandatory; this could be tapered during the next 2 weeks. In the absence of reactions such as rigors, mucosal congestion or edema and/or drop in systolic blood pressure >30 mm Hg, the third and subsequent doses consisted of 30 mg, which were subsequently given at home by self-injection. Otherwise, the lower doses were continued under ambulatory observation.

Prophylaxis against tumor lysis consisted of allopurinol, 300 mg, during the first weeks. Prophylaxis against infections associated with T-cell lymphocytopenia such as pneumocystis jiroveci and herpes infections consisted of cotrimoxazole 480 mg twice a day, three times a week; during granulocytopenia, the dose was increased to 960 mg, twice daily; fluconazole 100–150 mg once a day and valaciclovir 500 mg twice a day. All three drugs were continued until 2 months after the last alemtuzumab dose.

CMV (re) activation had to be monitored with an appropriate antigen or virus DNA detection technique according to the methods of the participating hospital at least every fortnight or more frequently if necessary based on prior results or clinical outcome. In case of active CMV disease and/or laboratory signs of reactivation (positive antigenemia or rising PCR results) prompt (preemptive) treatment should be instigated with oral valgancyclovir or intravenous gancyclovir according to the rules of the local hospital. In case of CMV disease, alemtuzumab had to be permanently discontinued and the patient went off protocol treatment. Subsequently, patients were advised to continue therapy with CHOP alone.

Finally, all blood products had to be irradiated until 6 months after the last alemtuzumab injection to avoid transfusion-related graft-versus-host disease.

response monitoring and definitions

All patients underwent complete staging procedures including laboratory tests, a computed tomography (CT) scan of neck, thorax and abdomen, bone marrow biopsy and preferably positron emission tomography (PET) scan. Extranolad sites had to be monitored and documented if indicated. After the third and eighth alemtuzumab–CHOP cycle, patients had to be restaged aiming at all initial involved sites (including CT scans, preferably PET scans and bone marrow biopsies if initially positive; extranolad sites had to be restaged accordingly), and response had to be assessed according to the International Workshop Guidelines from 1999 [19].

Primary end point consisted of overall response, i.e. partial response (PR) or complete remission (CR) including CR undefined (CRu) on protocol. Secondary end points consisted of 1) event-free survival (EFS) [i.e. time from registration to induction failure (i.e. no CR, CRu or PR on induction treatment), death or relapse whichever occurred first]; 2) overall survival (OS) measured from the time of registration; 3) toxicity CTCAE (Common Terminology Criteria for Adverse Events) grade 3–4, except nausea, vomiting, alopecia and hematological toxicity.

statistical considerations

This phase II trial followed an optimal two-stage Bryant–Day design [20] to evaluate whether the treatment would be worth further study. Sample size calculation was based on the response and safety end points. The following assumptions were made: an overall response rate >50% was considered acceptable; <20% was unacceptable. A toxicity rate >50% CTCAE grade 3–4 (except nausea, vomiting, alopecia and hematological toxicity) was unacceptable; <20% CTCAE grade 3–4 was acceptable. The probability of
accepting a treatment as worth further study, while its response rate was unacceptable, was limited to 10% (\(\alpha = 0.10\)). The probability of accepting a treatment as worth further study, while its toxicity rate was unacceptable, was limited to 15% (\(\alpha = 0.15\)). The probability of rejecting a treatment for further study, while it was acceptable with respect to both response and toxicity, was limited to 20% (\(\beta = 0.20\)). These assumptions implied a sample size of 18 patients. To account for an unexpected loss of 10%, the total number of patients to be included was planned to be 20 patients. All primary efficacy analyses were done according to the intention-to-treat principle. Survival estimates were calculated with the Kaplan–Meier method.

**Results**

Between November 2005 and October 2007, 20 patients with a median age of 50 years were included by 10 different centers. The majority (55%) of the patients had an unfavorable International Prognostic Index (IPI) risk profile (Table 1). Eighty-five percent of the patients received six or more cycles of therapy. Thirteen patients completed all eight cycles of alemtuzumab–CHOP, 1 patient, seven cycles; 3 patients, six cycles; 1 patient, five cycles; 1 patient, three cycles; 1 patient, only 1 treatment cycle. Twelve patients (60%) obtained CR on protocol, 1 patient CRu and 5 patients (25%) PR for an overall response rate of 90%. Only two patients failed to respond. With a median follow-up of 29 months (range 19–41 months) for those alive, the median OS was 27 months, with 70% of the patients alive at 1 year, and 55% alive at 2 years (Figure 1). The median EFS was 10 months, with 45% of the patients remaining event free at 1 year and 27% event free at 2 years (Figure 1). An analysis per T-cell lymphoma subset is given in Table 2. No relationship between age, sex, stage and outcome was seen. Only a favorable IPI risk profile predicted a better outcome (\(P = 0.025\)). Eleven patients died: 6 patients because of lymphoma, 1 nonresponding patient with progressive disease due to cardiotoxicity after salvage treatment, 3 patients because of infections (1 patient developed pneumonia during the seventh cycle, while suffering from progressive lymphoma; 2 patients died because of infections, both while in CR, 7 and 9 months after the end of the chemotherapy) and 1 patient died because of secondary Epstein–Barr virus (EBV)-related B-cell lymphoma (see below).

**Adverse events during and after the intensified alemtuzumab–CHOP scheme**

All nonhematological adverse events were scored according to the CTC criteria and are listed in Table 3. Because several severe adverse events occurred after the end of therapy, these have been outlined as such. The majority of grade 3 and 4 adverse events occurred after the end of therapy and died 7 months later. The EBV+ T-cell lymphoma was clonally different from the first T-cell lymphoma. The second patient developed CD20+ intracerebral lymphoma 5 months after cycle 8 followed by an EBV+ pharyngeal B-cell lymphoma. She died of relapse with presence of both the panniculitis-like T-cell lymphoma and EBV+ B-cell lymphoproliferative disease. The third patient developed relapse of his AILT-cell lymphoma 1 year after the end of therapy.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Sex</th>
<th>11 males/9 females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (range)</td>
<td>50 (20–65)</td>
</tr>
<tr>
<td>T-NHL WHO category</td>
<td></td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma (NOS)</td>
<td>10</td>
</tr>
</tbody>
</table>

Stage: 
<table>
<thead>
<tr>
<th>III/IV</th>
<th>9/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI risk profile</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
</tr>
<tr>
<td>Low–intermediate</td>
<td>7</td>
</tr>
<tr>
<td>Intermediate–high</td>
<td>9</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
</tr>
</tbody>
</table>

*All lymphomas were classified according to the World Health Organization (WHO) 2001 classification. Also when applying the WHO 2008 classification, the diagnosis of subcutaneous panniculitis-like T-NHL was confirmed in all three cases. In one case with DNA available for clonality analysis, rearrangement of the alfa–beta T-cell receptor was found, excluding a primary cutaneous gamma–delta T-cell lymphoma. Both other cases lacked lymphoma involvement of dermal and epidermal layers making a primary cutaneous gamma–delta T-cell lymphomas unlikely.

**Figure 1.** Kaplan–Meier estimate of overall survival (thick lines) and event-free survival (thin lines) of all 20 patients with aggressive T-cell lymphoma, treated with alemtuzumab–CHOP therapy.
Infections 2 (10%) 11 (55%) 1 (5%) a
Adverse events after intensified alemtuzumab–CHOP therapy

Table 3. Adverse events during and after intensified alemtuzumab–CHOP therapy

During intensified alemtuzumab–CHOP therapy

- Infections
- Constitutional symptoms
- Gastrointestinal
- Neurological
- Dermatological
- Pulmonary
- Allergy
- Pain
- Cardiac
- Urogenital
- Endocrine/metabolic
- Hemorrhage
- CMV reactivation

At the end of intensified alemtuzumab–CHOP therapy

- CMV disease
- EBV lymphoproliferative disease

aThis patient subsequently developed also secondary EBV lymphoma.

Discussion

This phase II trial with an intensified alemtuzumab–CHOP regimen for primary aggressive T-cell lymphoma showed a high response rate, but this was followed by many relapses and impressive infection-related adverse events. Our trial ran in parallel with several other phase II trials applying alemtuzumab–CHOP. Two of these have been published in 2007 [22, 23]. In both studies, alemtuzumab as well as CHOP were given at much lower doses, i.e. alemtuzumab at 30 mg per cycle and eight cycles of CHOP at a 21-day [23] or even 28-day [22] schedule in anticipation of toxicity. CRs ranged from 65% to 71%, OS at 1 year ranged from 44% [23] to 70% [22], with EFS percentages of 43% [23] to 54% [22]. The most frequent side-effects were grade 4 neutropenia and CMV reactivation. Major infections were J-C virus reactivation, pulmonary invasive aspergillosis, Staphylococcus sepsis and pneumonia [22]. Two treatment-related deaths were encountered [23]. Kim et al. [23] closed their study prematurely because of the toxicity observed.

The overall response rate of 90% in our study fulfilled the criteria for justification of a future phase III trial. However, many patients showed a relapse, which demonstrates that induction therapy with alemtuzumab–CHOP is effective but not durable. One solution might be the use of additional etoposide with CHOP (CHOEP) for patients with T-cell lymphoma below the age of 60 years, as was presented by the German High-Grade Lymphoma Study Group [5]. Another improvement could consist of intensification therapy after induction therapy by adding autologous stem-cell transplantation [24–29]. Thus far, all data from upfront transplantation studies were obtained without the use of alemtuzumab. Often, early progression precluded progress to transplant. In this regard, the suggestion by Reimer et al. [28] that pretransplant therapy should be intensified in order to improve the final outcome after transplantation is important. The recently launched European Intergroup phase III trials (ACT-1 and ACT-2) for primary T-NHL will therefore incorporate both concepts, comparing classical CHOP with alemtuzumab–CHOP, both arms followed by upfront autologous stem-cell transplantation for patients younger than 60 years.

It is hardly possible to compare our results with those of other studies, given the extreme heterogeneity of patients with peripheral T-cell lymphoma. Moreover, most published studies are small or consist of a mixture of patients with cutaneous T-cell lymphoma, T-cell leukemia or peripheral T-cell lymphoma, largely because of the rarity of the disease. Phase III trials that carefully stratify for histology and other patient characteristics are needed to prove that immunochemotherapy is better than chemotherapy alone.

The role of histology, e.g. subtype of T-cell lymphoma might also be important, given the presumably heterogeneous CD52 expression on these tumors. Whereas studies published between 2006 and 2007 [13, 30, 31] still assume that CD52 expression varies around 50% on most mature T-cell lymphomas, more recent studies applying flow cytometry [32] or immunofluorescence [33] suggest that the large majority (>90%) of peripheral T-cell lymphoma NOS is CD52-positive. Using the same techniques, it seems that ALCCL cases lack CD52 expression.

The dose of alemtuzumab selected in the HOVON 69 trial could not be based on available pharmacokinetic data [34]. In fact, the alemtuzumab schedule applied in the study was somewhat resembling the one known from the CLL setting, a disease with rather different features than T-cell lymphoma in terms of tumor cell distribution, number of circulating tumor cells and thereby soluble CD52 levels. The similar outcome from both other studies that incorporated much lower doses of alemtuzumab (30 mg per 21 or 28 days) [22, 23] suggests that...
lower doses might be as effective as the high dose used by us. If at all possible, future studies should aim at more pharmacokinetics related to tumor bulk and—specifically—CD52 expression on the malignant T cells.

In our study, the percentages of patients with severe nonhematological side-effects (CTCAE grade 3–4) were below the upfront considered unacceptable level of 50%. This analysis of stopping rules took place halfway the trial. Many of the adverse events (see below) took place after the end of the study. However, adverse events were noteworthy, primarily neutropenic fever episodes and CMV reactivation in 7 out of 20 patients. Moreover, three patients developed an EBV-related secondary lymphoproliferative disease.

EBV-lymphoproliferative disease is a familiar complication after solid-organ transplantation and related to the severity of immunosuppression [35, 36]. Presumably, the markedly immunosuppressive combination of the intensified alemtuzumab–CHOP regimen may have contributed to the development of EBV-lymphoproliferative disease after the end of therapy. Remarkably, EBV-lymphoproliferative disease was also observed after a combination of alemtuzumab (70 mg per cycle, 10 mg day 1 and 30 mg on days 2 and 3) and fludarabine/cyclophosphamide/doxorubicin for T-cell lymphoma [37]. Here, fludarabine might have contributed to the alemtuzumab-associated T-cell immunosuppression. Alemtuzumab kills different cell types expressing CD52 such as T cells and B cells. Therefore, during treatment with alemtuzumab combinations, EBV+ B cells will be eliminated. However, after the end of therapy, the imbalance between lack of immune surveillance by the T cells and recovering EBV+ B cells obviously can result in an outbreak of EBV-lymphoproliferative disease. Alemtuzumab has been given as monotherapy to thousands of patients with chronic lymphocytic leukemia or T-cell prolymphocytic leukemia with only rare observations of EBV disease [38, 39]. This suggests that either the combination of high doses of alemtuzumab with CHOP chemotherapy or an as yet unknown intrinsic patient factor related to T-cell lymphoma may be responsible for this adverse event. The latter is supported by the fact that other adverse events such as neutropenic fever, CMV reactivation, but also other fungal or viral infections were found both in the ‘low-dosed’ alemtuzumab–CHOP studies and in ours, again suggesting that an intrinsic patient-related susceptibility for infections might also be very important.

For many years, a relationship between EBV+ B-cell lymphoma and T-cell lymphoma has been observed, not only in AILT but also in peripheral T-cell lymphoma [40]. In a study by Zettl et al. in 2002, out of 600 cases with nodal T-cell lymphoma, 17 cases with secondary EBV-associated B-cell lymphoma were reported; 13 with AILT, 1 peripheral T-cell lymphoma and 3 cases with co-existing EBV-related B-NHL as part of a composite lymphoma. Notably, these published cases were all treated before alemtuzumab became part of the therapy.

In all, the clinical effects resulting from the degree of T-cell immunosuppression observed in our study suggests a lower alemtuzumab dose to be applied in combination with chemotherapy in future studies. Moreover, it is now strongly recommended that in addition to monitoring of CMV reactivation during therapy, also EBV is monitored, starting after the end of alemtuzumab–CHOP.

Aggressive T-cell lymphoma has long been an outcast among the malignant lymphomas because of its rarity, the often poor performance status of patients and dismal prognosis. Many recent initiatives and therapeutic options have provided further opportunity to enroll these patients onto clinical trials. The large international initiatives such as the European ACT-1 and ACT-2 phase III trials are an excellent start for a better understanding and outcome for patients with an aggressive T-cell lymphoma. Obviously, such trials should undergo close monitoring for toxicity if incorporating alemtuzumab combinations.

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HCK-N, PIL, WLJvP and GWvI were responsible for the conception and design of the study. ML, WLJvP and HCK-N collected and assembled data. HCK-N, WLJvP, JO and GWvI were responsible for data analysis and interpretation. All authors wrote the manuscript and approved the final version of the manuscript.

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**disclosure**

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