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ORIGINAL ARTICLE

Experience with alemtuzumab in treatment of chronic lymphocytic leukaemia in the Netherlands

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ABSTRACT

Background: Alemtuzumab (MabCampath®) is a monoclonal antibody against CD52, indicated as third-line treatment of chronic lymphocytic leukaemia (CLL). As most important side effect opportunistic infections are mentioned. It is, however, unknown whether these complications often lead to problems in general patient care in the Netherlands.

Methods: To gain insight into the use and complications of alemtuzumab therapy, the alemtuzumab-treated CLL patients in 15 hospitals in the Netherlands were evaluated by means of a questionnaire.

Results: In the period from 31 October 2001 until 17 November 2005, 27 patients with CLL or prolymphocytic leukaemia (PLL), RAI stage I to IV, Binet stage A to C, received 32 treatments with alemtuzumab. The time from diagnosis until start of alemtuzumab treatment was 6 ± 4.5 years (mean ± SD). The treatment lasted 11 ± 7 weeks. Of the treatments, 41% could be administered for the full 12 weeks.

The most frequent adverse events were fever (72%), shivering (47%), fatigue (22%) and dyspnoea (16%). Haematological side effects consisted of leucopenia (75%), thrombocytopenia (44%), and anaemia (13%). Infectious complications occurred in 12 of 32 (38%) treatments: pneumonia (25%; of which one *Pneumocystis carini* pneumonia and four *Aspergillus* infections), sepsis (9%; of which one *Listeria*), herpes zoster (9%), herpes simplex (6%), CMV reactivation (6%), meningitis (3%) and Guillain Barre (3%).

The overall response was 53%, with complete remission in 13%, partial remission in 41%, stable disease in 25% and progressive disease in 13%, and lasted for 8.3 ± 7.3 months.

Conclusion: Treatment with alemtuzumab is often terminated prematurely, leading to a suboptimal treatment effect. Fear of severe uncontrollable opportunistic infections seems unjustified.

KEYWORDS

Alemtuzumab, CLL, infections, side effects

INTRODUCTION

Chronic lymphocytic leukaemia (CLL), with an incidence of 3 to 5 per 100,000 per year, is the most common form of leukaemia in adults. Survival depends on the clinical stage, the presence or absence of somatic mutations in genes coding for the heavy chain of immunoglobulins (IgV_H genes)[1] and cytogenetic abnormalities.[2]

At present the first line of treatment for CLL is chlorambucil. When progression occurs fludarabine or combination chemotherapy is chosen as the next line of therapy. Patients who have become resistant to fludarabine have a higher risk of infection and an unfavourable prognosis, with a median survival of only ten months.[3] Recent developments with monoclonal antibodies open new perspectives for third-line treatment of this unfavourable prognostic group of CLL patients.

Alemtuzumab (Mabcampath®) is a monoclonal antibody targeted to CD52, an antigen present on both normal and malignant B and T lymphocytes and on monocytes, thymocytes and macrophages. Binding of alemtuzumab to CD52 initiates complement activation via the classical pathway. The membrane attack complex which is formed in this way leads to lysis of the lymphocyte. Besides this complement-dependent cytotoxicity (CDC), alemtuzumab also works by an antibody-dependent cellular cytotoxicity (ADCC), by forming a complex between CD52-positive cells and Fc receptors on NK cells, monocytes and macrophages, leading to cell destruction. As a third mechanism of action alemtuzumab induces apoptosis of CD52-positive cells.[4,5]

At present alemtuzumab is not only indicated as third-line treatment of CLL after failure of conventional treatment including fludarabine, it is now also being used upfront in the first-line in a randomised Dutch study of high-risk CLL patients. The response rate reported in the literature is 33%; 2% complete remission (CR) and 31% partial remission (PR).[6] Acute, infusion-related side effects are fever, rigors/chills, nausea, vomiting, hypotension, rash, dyspnoea, cough and diarrhoea. Haematological toxicity with pancytopenia and infections are more long-lasting complications. Opportunistic infections, such as *Pneumocystes carinii* pneumonia and cytomegalovirus (CMV) pneumonitis, have been reported as the most important side effect of alemtuzumab.

It is not clear whether these complications often lead to problems in clinical care. To gain insight into the use and complications of alemtuzumab therapy in the Netherlands, the treatment of fludarabine-resistant CLL patients with alemtuzumab was evaluated using a questionnaire.

MATERIALS AND METHODS

With the help of Schering BV, a list of physicians and accompanying hospitals in the Netherlands that had prescribed alemtuzumab in the period from 2001 until 2005 was composed. These physicians were approached for a retrospective investigation of the medical records of CLL patients treated with alemtuzumab in the above-mentioned period. The investigation was performed by means of a questionnaire, constructed on the basis of the literature.[6]

Information was collected on the demographical characteristics of the patients, the clinical stage of CLL at the start of treatment, cytogenetic abnormalities and IgV_H mutational status. Previous treatments including fludarabine treatment and whether or not patients were fludarabine resistant, which was defined as no response to or progression during or within six months after fludarabine, was recorded. The duration and intensity of the treatment with alemtuzumab was also described.

The treatment effect of alemtuzumab was reported as complete remission (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukaemia.[7]

Side effects were reported according to the common toxicity criteria.[8] (Sub)acute infusion-related side effects, haematological toxicity and infectious complications were recorded. Infections were defined as the state produced by the establishment of an infective agent in or on a suitable host as assessed by the responsible physician and it was attempted to specify *Aspergillus* infections in possible, probable and proven ones.[9] *Pneumocystes carinii* pneumonia was defined as an opportunistic infection possibly caused by *P. carinii* characterised by a nonproductive cough, shortness of breath, fever, bilateral interstitial infiltrates and hypoxaemia and responding to treatment aimed at this infection.

RESULTS

Thirteen of the 28 hospitals approached for this investigation dropped out. Nine hospitals had not treated CLL patients with alemtuzumab, in one hospital the treatment of the only patient had just started, and three hospitals refused to cooperate. The remaining 15 hospitals, one university hospital, six teaching hospitals and eight general hospitals reported on all their consecutive CLL patients treated with alemtuzumab, a total of 29 patients.

Two of these 29 patients were not included, one because he had not been treated with alemtuzumab and one because no information on the treatment with alemtuzumab could be recovered. The other 27 patients, mean age 63 years (range 49-77), 20 male, 7 female, received 32 treatments with alemtuzumab from 31 October 2001 until 17 November 2005. In these patients the diagnosis was made of either CLL (24; 89%) or PLL (3; 11%), Rai stage I (2; 7%), stage II (2; 7%), stage III (5; 19%), stage IV (17; 63%), unknown (1; 4%), Binet stage A (1; 4%), stage B (3; 11%), stage C (22; 82%), and unknown (1; 4%). Cytogenetic abnormalities were sparsely recorded. Cytogenetics were normal in four patients, one had a 6 q deletion, one a 13q deletion, and one patient had a 13q deletion, an 11q deletion and a 17p deletion. In the other 20 patients cytogenetics were not performed. The IgV_H mutational status was not known in any of the patients.

On average, patients had received three lines of previous treatment (range 0-8). Twenty-three patients (85%) had received fludarabine previously, 16 (59%) chlorambucil, 15 (56%) cyclophosphamide, vincristine and prednisone (CVP) and 12 (44%) patients had received chlorambucil combined with prednisone before. One patient (4%) had not received prior therapy and received alemtuzumab as upfront treatment. Twenty patients (87% of the fludarabine-treated patients) were fludarabine resistant.

The time from diagnosis until start of alemtuzumab treatment was 6 ± 4.5 years. In 27 of 32 treatments (84%) the loading dose of 3, 10, 30 mg was given, in one patient 3 mg was administered twice and for four treatments the loading dose could not be retrieved. Of the treatments, 24 (75%) followed the recommended dosage of 30 mg three times weekly for four to 12 weeks. In three of the treatments (9%) the highest achievable dosage was less than 30 mg, namely 10 mg. In five treatments (16%) the highest achievable dosage was unknown. All other 24 (75%) treatments reached the intended dosage of 30 mg. In two treatments the dosage had to be reduced to 10 mg, once because of

thrombocytopenia and once because of thrombocytopenia and anaemia; this dose reduction was effective as both the thrombocytopenia and anaemia recovered. In 28 (88%) treatments the frequency of administration was three times weekly, for the remaining four treatments the frequency of administration was unknown.

Median follow-up was 13 months (range 2-37). Treatment lasted 11 ± 7 weeks, with a minimum of two and a maximum of 42 weeks; this last treatment was given together with fludarabine once every three weeks. The therapy was terminated prematurely in 17 treatments (53%); prematurely was defined as shorter than 12 weeks. The reason for early termination of treatment could not be retrieved in three cases (18 %). In five treatments (29%) the treatment was stopped because of fever or other side effects, in three (18%) there was progressive disease, in two (12%) complete response, in two (12%) severe haematological toxicity, in one (6%) haemolytic anaemia and one patient went on for allogeneic bone marrow transplantation. The treatment could be completed in 13 cases (41%) (for 12 weeks or longer), from two patients (6%) the duration of treatment could not be recovered. Alemtuzumab was predominantly (18 treatments, 56%) administered intravenously, in three treatments (9%) subcutaneous administration was used and in 11 treatments (34%) the route of administration was unknown.

Efficacy of alemtuzumab

Best response to alemtuzumab is described in *table 1*. The overall response rate was 53%. The duration of the response was 8.3 ± 7.3 months. One patient (4%) died while on treatment with alemtuzumab. The cause of death is unknown. Six patients died within six months after the start of alemtuzumab treatment, the cause of death was not retrievable in five patients, in one patient it was due to progressive disease and an *Aspergillus* infection. In total 13 of 27 (48%) patients have died. Of seven patients the cause of death could not be recovered, in one patient it was due to progressive disease, one patient died of an *Aspergillus* infection, in three patients death was due to both progressive disease and an infection (one *Aspergillus* infection, one *Listeria* infection and one meningitis with unknown pathogen) and one patient died of graft-versus-host-disease after allogeneic bone marrow transplantation.

Table 1. *Efficacy of alemtuzumab*

Response	Treatments (n=32)	% of total number of treatments
Complete remission	4	13
Partial response	13	41
Stable disease	8	25
Progressive disease	4	13
Unknown	3	9

Patients died on average nine months after termination of alemtuzumab treatment (minimum 2 weeks, maximum 20 months).

(Sub)acute side effects to alemtuzumab

Side effects occurring during or directly after administration of alemtuzumab are described in *table 2*. Fever was the most frequent. In seven of 32 treatments fever recurred with every administration of alemtuzumab, in two of 32 it only occurred in the first three weeks of treatment and in three only in the first two weeks of treatment.

Haematological side effects to alemtuzumab

Leucopenia occurred in 24 of 32 (75%) treatments with alemtuzumab. Thrombocytopenia occurred or aggravated in 14 of 32 (44%). Two (6%) of these were clinically relevant, with the number of platelets <10 x 10^9/l. In one patient a thrombocytopenia grade IV was present before the start of treatment with alemtuzumab. The nadir of thrombocytes was on average encountered after four weeks

Table 2. *Toxicity of alemtuzumab*

Side effects	Occurring in no. of treatments (n=32) (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade unknown
Subacute side effects						
Fever	23 (72)	-	6	7	1	9
Rigor/chills	15 (47)	-	6	2	-	7
Fatigue	7 (22)	-	1	5	1	-
Dyspnoea	5 (16)	-	1	2	1	1
Diarrhoea	5 (16)	1	1	1	2	-
Nausea	3 (9)	-	3	-	-	-
Injection site reaction	3 (9)	-	1	2	-	-
Rash	2 (6)	-	-	1	-	1
Vomiting	2 (6)	1	1	-	-	-
Headache	2 (6)	-	2	-	-	-
Haematological toxicity						
Anaemia	32 (100)	9	10	5	1	7
Thrombo-cytopenia	27 (84)	-	6	11	3	7
Infectious complications						
Pneumonia	8 (25)					
Sepsis	3 (9)					
Herpes zoster	3 (9)					
Herpes simplex	2 (6)					
Sinusitis	2 (6)					
CMV reacti-vation	2 (6)					
Otitis media	1 (3)					
Guillain-Barré	1 (3)					
Meningitis	1 (3)					
Candidiasis	1 (3)					

and recovered in almost all cases, in four treatments (13%) an improvement of thrombocyte count compared with the start of treatment was even achieved.
Anaemia was also present at the start of treatment in 25 cases. Anaemia aggravated in four treatments (13%) (measured from baseline to nadir), with a mean nadir four weeks after the start of treatment. Two of these four treatments resulted in an improvement in the anaemia at the end of treatment. In 10 of 32 treatments (31%) an improvement of haemoglobin count was eventually reached.

Infectious complications with alemtuzumab treatment
Pneumocystis carinii pneumonia prophylaxis with cotrimoxazole and cytomegalovirus prophylaxis with valaciclovir was given in 25 of 32 treatments (78%), from the remaining seven it is unknown whether prophylaxis was administered.
Infectious complications with alemtuzumab treatment are described in *table 2*. In 12 of 32 treatments (38%) infections occurred. The most frequently encountered infection was a pneumonia which occurred in eight of 32 treatments. During these eight treatments, four patients had only one pneumonia, two patients had two, one patient had three and one patient even had four pneumonias. The pathogens responsible for the pneumonias were *Pneumocystis carinii* in one, a fungal infection in three of which two were possible and one was a proven *Aspergillus* infection, a combination of a bacterial and fungal infection (possible *Aspergillus*) in one, a bacterial infection in two and for eight pneumonias the pathogen was unknown.
Sepsis occurred in three patients and was caused by an *E. coli*, a streptococcus group A and a *Listeria* species.
Viral infections occurred in five (16%) of patients, three herpes simplex and two herpes zoster infections.

DISCUSSION

In this study the effect and complications of alemtuzumab therapy in the treatment of CLL patients in the Netherlands was evaluated. Although most hospitals that were approached participated in this investigation, the results need to be critically appraised as some of the information could not be retrieved retrospectively.
The patients in this study where heavily pretreated, mostly including fludarabine, and were in an advanced stage of the disease at the start of alemtuzumab treatment. In this unfavourable prognostic group of patients with a median survival of ten months.[3,6] an overall response (OR) was reached of 53%, with an average response duration of nearly 8.5 months. Keating *et al*. treated 93 CLL patients, previously treated with fludarabine, with alemtuzumab and obtained an OR of 33%, with a response duration of 9.5 months.[6] However, in that study all patients were fludarabine resistant, whereas in ours only 11 were. Others have shown comparable results in previously treated CLL patients, an OR varying between 33 and 57%[10-14] and a median response duration of 12 to 15.4 months.[10,11]
In our study only one patient (4%) died during treatment with alemtuzumab. In total 13 of 27 patients (48%) died. In four of these patients an infection, probably related to the use of alemtuzumab, played a role in the death. Also in other studies relatively few patients died while on treatment with alemtuzumab, between 0%[10] up to 9%.[13] Mortality is predominantly seen after completion of the treatment and can rise to 68%.[6]
Alemtuzumab treatment was terminated prematurely in 53% of cases, in 47% due to side effects. The (sub) acute side effects such as fever and rigors/chills usually diminish during treatment[6,10-12] and are well controlled by paracetamol and an antihistamine. Treatment was seldom stopped definitively because of these side effects.[11] As in our study, these side effects are less often seen and less severe after subcutaneous administration.[15-17]
Haematological toxicity consisted of leucopenia, anaemia and thrombocytopenia. Anaemia aggravated in four treatments (13%) but in 31% it eventually improved. Thrombocytopenia occurred or aggravated in 14 (44%) treatments and recovered in almost all cases. In four treatments (13%) an improvement in the thrombocyte count was seen compared with the start of the treatment, an effect which is also seen in literature.[11]
The most important complications of alemtuzumab therapy are infections. In 25% of treatments one or more pneumonias were observed. Also in other studies especially pulmonary infections are described.[6,10-12] Although in eight of 15 pneumonias no pathogen was retrieved, five opportunistic infections were seen in the other seven, four fungal infections and one *Pneumocystis carinii* pneumonia.
In our study only two CMV reactivations were observed. However, a CMV-PCR was only performed in seven treatments, in 25 it was either not done or unknown. This incomplete information admits no reliable conclusions about CMV reactivation. In literature CMV reactivation varies between 7%[6] and 66%.[18,19]

Opportunistic infections seen after alemtuzumab therapy are partly related to the disease itself.[20,21] Patients who are resistant or partially responsive to fludarabine appear to have the highest risk of infections[22] and retain a severe immunodeficiency for a long period of time.[23] The risk of infections varied between 23 and 79% for patients previously treated for CLL,[11,19,24-29] while this was only 8.7% in patients treated with alemtuzumab as first-line therapy.[16] Therefore, it seems that the incidence of infections rises with the number of lines of treatment

and with less responsiveness, and can not be directly related to alemtuzumab treatment alone. At this moment a phase III study has started within the HOVON (Dutch Haemato-Oncology Association) study group on the treatment of previously untreated high-risk CLL patients with fludarabine, cyclophosphamide, with or without alemtuzumab.[30] This randomised trial will give insight into both the response to this combination therapy and the additional toxicity of alemtuzumab.

The experience with alemtuzumab treatment of CLL patients in the Netherlands is promising. A good response rate is reached in an unfavourable prognostic group of patients. The most important side effects are opportunistic infections. Effective monitoring and pre-emptive treatment of CMV reactivation and prevention of *Pneumocystis carinii* pneumonia with cotrimoxazole and herpes infections with valaciclovir is of vital importance to prevent serious complications.

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ERRATA

NETH J MED 2007;65(6):219-21
PHOTO QUIZ
Neck swelling following a vigorous neck massage

The third author's name was misspelled and the affiliation was not included. The correct heading should be:
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REVIEW
Prevalence and clinical significance of organ-specific autoantibodies in type 1 diabetes mellitus
L.C.G. de Graaff, J.W.A. Smit, J.K. Radder

On pages 240 and 242 'EMA-negative' was mentioned when this should have been 'PCA-negative'.