

# Journal of Oncology Pharmacy Practice

<http://opp.sagepub.com>

---

## **Alemtuzumab (Campath-1H, Campath1) for the treatment of lymphoid malignancies: chronic lymphocytic leukemia and T-cell prolymphocytic leukemia**

Helen T Wu

*J Oncol Pharm Pract* 2001; 7; 133

DOI: 10.1191/1078155201jp082oa

The online version of this article can be found at:  
<http://opp.sagepub.com/cgi/content/abstract/7/4/133>

---

Published by:



<http://www.sagepublications.com>

**Additional services and information for *Journal of Oncology Pharmacy Practice* can be found at:**

**Email Alerts:** <http://opp.sagepub.com/cgi/alerts>

**Subscriptions:** <http://opp.sagepub.com/subscriptions>

**Reprints:** <http://www.sagepub.com/journalsReprints.nav>

**Permissions:** <http://www.sagepub.co.uk/journalsPermissions.nav>

**Citations** <http://opp.sagepub.com/cgi/content/refs/7/4/133>

# Alemtuzumab (Campath-1H, Campath<sup>®</sup>) for the treatment of lymphoid malignancies: chronic lymphocytic leukemia and T-cell prolymphocytic leukemia

Helen T Wu, PharmD, BCOP

**Objective.** To provide a comprehensive review of the clinical pharmacology and toxicology of the monoclonal antibody alemtuzumab, with particular reference to its use in its approved indication, B-cell chronic lymphocytic leukemia, as well as the non-approved indication, T-cell prolymphocytic leukemia.

**Data Sources.** A MEDLINE search was conducted using the terms 'alemtuzumab' and 'Campath.' All data available from MEDLINE were reviewed. The reference lists from retrieved articles were reviewed and other relevant papers identified. The abstract books from the annual meetings of the American Society of Hematology were also reviewed.

**Data Extraction.** The aim of the review was to be comprehensive and descriptive. Studies containing information deemed to be of interest were reviewed by the author.

**Data Summary.** CD52 is a surface antigen expressed on all B- and T-lymphocytes. Because of the presence of this surface antigen on both normal and malignant lymphocytes, the use of antibody as a treatment option is then possible. Alemtuzumab (Campath-1H, Campath<sup>®</sup>) is a humanized anti-CD52 antibody that has been shown to be active

against certain hematological malignancies, particularly lymphoproliferative diseases in the blood. The overall response rate for patients with chronic lymphocytic leukemia relapsed after fludarabine or alkylating therapy ranged from 33% to 70%, with most patients entering partial remission. The average duration of response is approximately 11–12 months. For patients with T-cell prolymphocytic leukemia failed first-line chemotherapy, overall response rate to alemtuzumab therapy ranged from 76% to 31%, with majority of patients entering complete remission. The average duration of response is approximately 7–9 months. Major adverse effects of alemtuzumab include infusion-related reactions, prolonged lymphopenia, and opportunistic infections (CMV, Herpes zoster, and PCP). Prophylactic use of acyclovir and trimethoprim/sulfamethoxazole are recommended while patient is receiving alemtuzumab and continued for 2 months after alemtuzumab therapy is completed.

**J Oncol Pharm Prac (2001) 7: 133–140.**

**Key words:** alemtuzumab; Campath-1H; chronic lymphocytic leukemia; CLL; T-cell prolymphocytic leukemia; T-PLL

Adult Hematology/Oncology Service, San Francisco Medical Center, University of California, San Francisco, California

Address correspondence and reprint requests to Dr. Helen T Wu, Box 0622, Department of Clinical Pharmacy, University of California-San Francisco, San Francisco, CA 94143-0622  
E-mail: hwwu@itsa.ucsf.edu

## INTRODUCTION

CD52 is a surface antigen expressed on all B- and T-lymphocytes (both normal and malignant), NK cells,

macrophages, monocytes, as well as mature spermatozoa.<sup>1,2</sup> CD52 is not expressed on hemopoietic stem cells.<sup>3</sup> Although the function of CD52 is unknown and the presence of CD52 is of little diagnostic value, antibodies against it have proven to be useful in the treatment of hemopoietic and non-hemopoietic diseases.<sup>1</sup> Alemtuzumab (Campath-1H, Campath<sup>®</sup>), a humanized monoclonal antibody against the CD52 antigen, was first synthesized by Herman Waldmann and colleagues at Cambridge University.<sup>4</sup> Campath-1H binds to the cell membrane of greater than 95% of all normal human blood lymphocytes, as well as to most B- and T-cell lymphomas.<sup>5,6</sup> In an early clinical trial conducted by Hale *et al.*,<sup>7</sup> a tumor regression was noted in two patients with advanced non-Hodgkin's lymphoma (NHL) treated with Campath-1H. Observations in additional NHL patients treated with the rat IgG2b Campath-1G monoclonal antibody indicated a preferential effect on tumor cells in blood and bone marrow over bulky lymph nodes.<sup>8</sup> Hematological malignancies, in particular, chronic lymphocytic leukemia (CLL) and T-cell prolymphocytic leukemia (T-PLL) might therefore be the preferred lymphoproliferative diseases for therapy with anti-CD52 antibodies.<sup>3</sup> Many clinical studies have confirmed the activity of anti-CD52 antibodies in CLL, as well as promising results in treating T-PLL.

Through many licensing transfers since first synthesized, Berlex Laboratories currently licensed Campath-1H, with a generic name alemtuzumab. Alemtuzumab was approved by the US Food and Drug Administration in May 2001 for the treatment of B-cell CLL (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.<sup>9</sup> Although the Food and Drug Administration only approved Campath-1H for treatment of relapsed B-CLL, Campath-1H has been studied for a wide range of diseases including rheumatoid arthritis, multiple sclerosis, graft-versus-host disease (GvHD), solid organ transplant rejection, and NHL.<sup>10</sup> This article will mainly focus on the use of Campath-1H in B-CLL and T-PLL.

## PHARMACOLOGY

Campath-1H is a genetically reshaped human IgG1 anti-CD52 monoclonal antibody, consisting of the hypervariable regions of the parental rat antibody (Campath-1G) inserted into the framework region of normal human immunoglobulin (IgG1) genes.<sup>2,11</sup> Campath-1H, as a humanized antibody, is designed to limit the antiglobulin response from the earlier animal formulation Campath-1G.<sup>10</sup> The exact mecha-

nism that Campath-1H induces cytotoxicity is uncertain. *In vitro*, Campath-1H is active in both complement-mediated cell lysis and antibody-dependent cellular cytotoxicity.<sup>10</sup> It is presumed that both complement-mediated and antibody direct cellular cytotoxicity, as well as the immunosuppressive effect, are important *in vivo*.<sup>10,12</sup> The carbohydrate backbone of IgG is thought to be crucial for the associated complement lysis and antibody direct cellular cytotoxicity.<sup>10</sup> It is observed that CD52(+) cells vary in their sensitivity to lysis induced by Campath-1H.<sup>10</sup> The varying degree of sensitivity may be related to the antigen site and density on different cell types.<sup>10</sup> The most pronounced antitumor effects of Campath-1H were noted in blood, bone marrow, and spleen.<sup>10</sup> Lymph nodes were less affected by Campath-1H therapy.<sup>8,10</sup> The reason for a differential response at various sites is not clear, but may be related to a poor bioavailability of Campath-1H in bulky lymph nodes and thus a low monoclonal antibody saturation on the tumor cell surface.<sup>8</sup> Researchers have also proposed other mechanisms *in vitro*, such as growth inhibition and apoptosis in certain cell lines and diseases related to cross-linking of the Campath-1H antibody with the CD52 receptors, as well as regulation of T-cell proliferation mediated by cytokines.<sup>10,13</sup> However, the relevance of these *in vitro* observations needs to be determined by more studies.

## PHARMACOKINETICS

According to the manufacturer, the pharmacokinetic profile of Campath-1H was studied in rising-dose trial with NHL and CLL patients. Campath-1H was administered once weekly up to a maximum of 12 weeks. Following intravenous (iv) infusions over a range of doses, the maximum serum concentration ( $C_{max}$ ) and the area under the curve (AUC) showed relative dose proportionality. The overall average half-life ( $t_{1/2}$ ) is about 12 days. In CLL patients treated with 30 mg three times weekly, the serum concentration approached steady state in approximately 6 weeks. The rise in serum Campath-1H concentration corresponded with the reduction in malignant lymphocytosis.<sup>2</sup> No pharmacodynamic data are yet available for Campath-1H in the treatment of malignant diseases.

According to Isaacs *et al.*,<sup>14</sup> approximately 10  $\mu$ g/mL of Campath-1H is required to saturate normal lymphocyte CD52 surface antigen *in vitro*, and the optimal dose to ensure saturation of CD4+ T cells may be a dose of 60 mg.<sup>15</sup> In rheumatoid arthritis and autoimmune disorders, the half-life of Campath-1H

has been estimated between 5 and 9 days with subcutaneous injections.<sup>16</sup> Reported by Morris *et al.*,<sup>17</sup> in non-myeloablative allogeneic transplant patients, 20 mg iv infusion over 8 hours daily for 5 days resulted to peak serum levels after the last infusion in the range of 10–30 µg/mL, then decreased to 5 µg/mL 4 days later, and remained above 1 µg/mL 3 weeks after completion of the last infusion. Although these are valuable information, their applicability to the treatment of malignant diseases is uncertain. There have been no data to show the correlation between drug levels and cytotoxic effect of Campath-1H.

## CLINICAL EFFICACY

### Campath-1H and B-CLL

**Overview of CLL.** CLL is one of the most common types of adult leukemia in the Western Hemisphere. CLL accounts for 25–30% of all adult leukemias, and affects approximately 120,000 patients in the US and Europe. CLL tends to affect more on the elderly population, the median age at diagnosis is more than 60 years, with only 15% of patients under age 50. CLL is a disorder of morphologically mature but immunologically less mature lymphocytes, and is manifested by progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues. Most patients present with no disease-related symptoms at diagnosis. As disease progresses, lymphadenopathy and hepatosplenomegaly become common. Hypogammaglobulinaemia also becomes more common as the disease progresses, as well as a defect in activation of the complement pathways. Patients with CLL exhibit a highly variable course based on the stage of the disease. Some patients may survive many years without treatment, whereas others may die from disease-related complications within a few months, despite appropriate therapy. Infection is the major cause of death in patients with CLL, which can be both disease and treatment related. In the US, 95% of CLL cases are B-cell phenotype, while in Asia, T-cell CLL predominates.<sup>18–20</sup>

Treatment of CLL ranges from periodic observation to a variety of therapeutic options, including alkylating agents, purine analogs, steroids, combination chemotherapy, monoclonal antibodies, and bone marrow transplant. Alkylating agents and new generation of purine analogs (fludarabine, cladribine) are considered to be the standard front-line therapy for CLL. Although these agents have shown to have considerable activity in CLL, these agents can only prolong the survival but not cure the disease. If a patient fails to remit with front-line therapy, then new

treatment is required. In general, CLL is an incurable disease.<sup>18–20</sup>

**Clinical trials.** In 1997, Osterborg *et al.*<sup>8</sup> reported the result of a phase II study on Campath-1H for refractory/relapsed CLL. The study enrolled 29 patients with CLL relapsed after initial treatment ( $N=8$ ) or were refractory ( $N=21$ ) to chemotherapy, at least one alkylating agent-containing regimen. Among all the study patients, 22 patients were rated with Rai stage III or IV diseases, and 13 had B symptoms. The treatment regimen was Campath-1H 30 mg three times weekly, with dose escalation, for a maximum of 12 weeks, which 12 patients received the maximum treatment of 12 weeks, and the other 17 patients received a median treatment of 6 weeks. The overall response (OR) rate was 42% (12/29), with 4% complete response (CR) and 38% partial response (PR). Twelve patients had stable disease (SD, 41%), and 5 patients (17%) had either progression of lymphadenopathy greater than 50% or transformation to a high-grade NHL. The median response duration was 12 months, ranging from 6 to 25+ months. Major adverse effects included rash, infusion-related reactions, neutropenia (10% grade IV), thrombocytopenia (7% grade IV), and infections (suspected PCP 7%, localized HSV reactivation 38%). No prophylactic acyclovir or trimethoprim/sulfamethoxazole was administered during Campath-1H therapy. Infection was attributed to be the main side effect from the study, which was probably related to the long-lasting lymphocytopenia.

Bowen *et al.*<sup>21</sup> also described the experience of Campath-1H in fludarabine-resistant/relapsed CLL patients in 1997. It was noted that subcutaneous injection was administered to avoid infusion-related reactions in this small-sized clinical trial. Six CLL patients were treated with Campath-1H with a 30-mg three times a week regimen with dose escalation. Treatment was continued for at least 6 weeks, to a maximum of 12 weeks. Three patients (50%) achieved PR, while the other three patients remained to be nonresponders. The overall median survival from starting Campath-1H was 11 months. Major adverse effects reported were local injection-site reaction after the first dose, rash, and reactivation of CMV infection (50%). All patients received prophylactic trimethoprim/sulfamethoxazole; patients with history of herpes virus infection received prophylactic acyclovir.

Results of several other clinical trials on Campath-1H for refractory/relapsed CLL are available as abstracts and presented at major clinical conferences. Table 1 summarizes the results of these trials. Similar

Table 1. Clinical Trails of Campath-1H in CLL and T-PLL Presented in Abstract Form

Study	Number of patients	Stage of disease/prior therapy	Treatment regimen	Response	Duration of response/time to progression
Steven <i>et al.</i> <sup>23</sup>	23 CLL 18 PLL 5	CLL – failed fludarabine PLL – failed at least one prior therapy 14 patients received prior rituximab	30 mg tiw for up to 12 wk	Only 17 patients were evaluated CR=53% (9/17) SD or DP=47%	Not reported
Nguyen <i>et al.</i> <sup>24</sup>	30 CLL 14 PLL 16	Failed prior regimens, including alkylating agents, purine analogs, and rituximab Rai high risk disease=70% B symptoms=37%	30 mg tiw for 6 wk	CLL OR=64% CR=14% PR=50%  PLL OR=69% CR=38% PR=31%	In responders without further bone marrow transplant, 77% (11/13) disease progression at median of 21 wk
Courte <i>et al.</i> <sup>25</sup>	38 T-PLL	Refractory disease failed fludarabine, some had relapsed after prior response to Campath	30 mg tiw for a maximum of 12 wk	OR=31.6% CR=15.8% PR=15.8%	Median progression-free survival=4.8 mo in responders
Rai <i>et al.</i> <sup>26</sup>	136 B-CLL	B-CLL failed prior therapy including fludarabine	30 mg tiw for 12 wk	OR=39.8% CR=7.4% PR=32.4%	Progression-free survival=7.3 mo in responders
Nabhan <i>et al.</i> <sup>27</sup> Phase I – combination of Campath-1H and rituximab	9 CLL	Relapsed or refractory CLL after alkylating agents and purine analogs	Rituximab=375 mg/m <sup>2</sup> /wk on weeks 1, 3, 4, and 5  Campath-1H=three cohorts on weeks 2–5 3 mg tiw 10 mg tiw 30 mg tiw	Hematologic response=88% CR=0% PR=0%	Not reported
Kennedy <i>et al.</i> <sup>28</sup>	77 B-CLL	Refractory to prior therapy including purine analogs	30 mg tiw to a maximum response	OR=44% CR=25% PR=19%	Median survival for responders up to 23 mo=75%
Keating <i>et al.</i> <sup>29</sup> Phase II	93 B-CLL	B-CLL, s/p alkylating agents and failed fludarabine Rai III–IV=76% B symptoms=30%	30 mg tiw for 4–12 wk  56/93 (58%) received 12-wk treatment	OR=33%  CR=2% (2/93) PR=31% (29/93) SD=59% (55/93)	Projected duration of response=9+ mo for responders
Rai <i>et al.</i> <sup>30</sup> Phase II	24 CLL	CLL failed prior alkylating agents and fludarabine	30 mg tiw, maximum treatment=16 wk	OR=not reported CR=not reported PR=33% Median time to response=4.1 mo	Median duration=9.7 mo

(continued on next page)

Table 1. (continued)

Study	Number of patients	Stage of disease/prior therapy	Treatment regimen	Response	Duration of response/time to progression
		Majority with Rai III–IV disease, and 21/24 (87.5%) with bone marrow infiltration			Median time to disease progression=10.6 mo
Rawstron <i>et al.</i> <sup>31</sup>	10 CLL	CLL refractory to conventional treatment including fludarabine	30 mg tiw for 6 wk  6/10 received the full course, while two patients received 12-wk therapy	OR=7/10 (70%) CR=5/10 (50%) PR=2/10 (20%)	Not reported
Kennedy <i>et al.</i> <sup>32</sup>	29 CLL	CLL refractory to treatment, including purine analog	30 mg tiw until maximum response	OR=17/29 (59%) CR=10/29 (34%) PR=not reported	Median event-free survival=17 mo for responders

OR = overall response.

CR = complete response.

PR = partial response.

SD = stable disease.

PD = disease progression.

to the study published by Osterborg *et al.*,<sup>8</sup> the major adverse effects reported in these trials were rash, infusion-related reactions, neutropenia, thrombocytopenia, and infections.

### Campath-1H and T-PLL

**Overview of T-PLL.** T-PLL is a rare lymphoproliferative disorder, representing approximately 3% of T-lymphocyte disorders. Approximately 30 years ago, determination of the B- or T-cell nature of lymphocytes was first introduced in the medical practice. At the same time, a subset of CLL cells, called prolymphocytes because of their less mature cell morphology, was identified based on cytologic examination and the presence of significant splenomegaly. T-PLL is an extremely aggressive disease, with patients often present with very high white blood cell counts. Currently, there is no approved standard treatment for T-PLL. Median survival with the most investigated treatment, deoxycoformycin (DCF/pentostatin), is approximately 6–7 months, with only 10% entering complete remission. Other therapeutic approaches reported include cladribine, fludarabine, chlorambucil and prednisolone, splenectomy, and allogeneic bone marrow transplantation; however, clinical efficacy is not conclusive with any of the treatments. In contrast, Campath-1H has demonstrated good response rate in treating T-PLL. Many clinical trials have studied the use

of Campath-1H in T-PLL patients who have failed front-line therapy and showed promising results.<sup>10–12</sup>

**Clinical trials.** Clinical efficacy of Campath-1H in treating PLL was first described by Pawson *et al.* in 1997.<sup>22</sup> Fifteen patients with T-PLL failed to enter CR with various previous chemotherapy (most of whom had received deoxycoformycin), were treated with Campath-1H 30 mg three times a week (with dose escalation) for 6 weeks or until maximum response. The median length of treatment was 38 days, ranging from 2 to 82 days. In five patients refractory to the 30-mg per injection regimen, dose was increased to 80 mg daily. The results demonstrated a major response of 73% (CR+PR), with 60% of CR. The average duration of response was approximately 9 months, ranging from 5 to 30 months. It was noted that one patient received Campath-1H via subcutaneous route and had a duration of response for 5 months. The major adverse effects were infusion-related reactions, lymphopenia (median 151 days after completion of therapy), infections (cryptococcal meningitis in one patient, CMV reactivation in one patient, localized herpes simplex infection in three patients), and grade 3 or 4 hematologic toxicity (four patients). Prophylactic trimethoprim/sulfamethoxazole and acyclovir were given during therapy and continued until 3 months after therapy. The

authors concluded Campath-1H is an effective treatment for T-PLL; however, Campath-1H alone is not sufficient for long-term remissions.

In 2001, Dearden *et al.* reported the results of 39 T-PLL patients treated with Campath-1H.<sup>11</sup> All but two of the patients had received prior therapy with various agents; none of the patients had achieved CR with previous therapy. Campath-1H regimen was 30 mg three times weekly (with dose escalation) until maximal response. Some patients received daily Campath-1H, and in five cases, the dose was increased to 80 mg. One patient received Campath-1H via subcutaneous injection. Treatment duration lasted from 2 to 82 days, with a median of 35 days. The result demonstrated an overall response (CR+ PR) rate of 76%, with 60% CR. The median disease-free interval was 7 months, ranging from 4 to 45 months. Twelve patients were retreated with Campath-1H following relapse. Of these 12 patients that received a second treatment, five patients (42%) achieved a second CR and one with PR, with responses lasting 5–6 months. Major side effects reported included infusion-related reactions, opportunistic infections (one cryptococcal meningitis, one CMV reactivation, two (5%) herpes zoster, two (5%) PCP pneumonia, and one Legionella pneumonia), and transient grades 3 and 4 hematologic toxicity (13%). Prophylactic acyclovir/valacyclovir and trimethoprim/sulfamethoxazole were given until 3 months following completion of treatment. The authors concluded that Campath-1H is effective in producing remissions in T-PLL. Nevertheless, the use of stem cell transplantation to consolidate responses merits further study.

The most recent report for Campath-1H in T-PLL was published by Keating *et al.* in 2002.<sup>12</sup> Seventy-six patients with T-PLL were enrolled; four of these patients were chemotherapy naive before entering the study. Campath-1H was initiated as a 3-mg test dose, then escalated to 30 mg three times weekly as tolerated. Nine patients received higher doses (60–90 mg) in an attempt to reach or to consolidate a CR. Treatment lasted 4–12 weeks with a median of 39.5 days. In the 72 previously treated patients, the objective response rate (CR+ PR) was 50%, with 37.5% CR. In the four chemotherapy naive patients, three patients (75%) achieved a CR. The overall median duration of CR was 8.7 months, ranging from 0.1 to 44.4 months. In 13 patients with relapsed disease and received a second course of Campath-1H, 1 achieved a second CR, 3 remained to have stable disease, and 1 achieved PR. The major adverse effects included infusion-related reactions, infections (4% CMV, 1% varicella zoster, 1% PCP), transient hematologic toxicity (6% grade 3 or 4 neutropenia, 22% grade 3 or 4

thrombocytopenia), and prolonged lymphopenia. Two treatment-related deaths were reported, one with sepsis and pneumonia related to severe neutropenia, the other one with pneumonia during a second course of Campath-1H therapy. Prophylactic trimethoprim/sulfamethoxazole and famciclovir were given during therapy and continued for at least 2 months after completion of therapy. The authors concluded that Campath-1H is an active drug in T-PLL for whom the first-line therapy has failed.

The results of several other clinical trials are available as abstracts. Table 1 summarizes the results of these trials. Similar to the other trials, the major adverse effects reported in these trials were infusion-related reactions, neutropenia, thrombocytopenia, and infections.

## ADVERSE EFFECTS

The most commonly reported adverse events of Campath-1H are infusion-related effects, hematologic toxicities, and infections. Infusion-related adverse effects include rigors (90%), fever (83%), nausea (47–54%), vomiting (33–41%), rash (30–40%), fatigue (20–35%), dyspnea (17–26%), and hypotension (15–32%). Hematologic toxicities include lymphopenia, severe neutropenia (64–70%), severe anemia (38–47%), and severe thrombocytopenia (50%). Infections (43%) reported include sepsis, pneumonia, and opportunistic infections such as pneumocystis carinii (PCP), herpes simplex (HSV), CMV, candidiasis, aspergillosis, and mucormycosis. Less commonly reported adverse effects (10–20%) include peripheral edema, hypertension, tachycardia/SVT, headache, dyesthesias, dizziness, anorexia, diarrhea, and stomatitis/mucositis. Rare adverse events include (1–10%) chest pain, autoimmune thrombocytopenia, positive Coombs' test without hemolysis, pancytopenia/marrow hypoplasia, antibodies to alemtuzumab, and autoimmune hemolytic anemia.<sup>2</sup>

Many of the side effects are related to the mechanism of action. Campath-1H eradicates all normal lymphocytes of both B- and T-cell lineage. The resulting lymphopenia can be profound and long-lasting, which can result in an increase of opportunistic infection in heavily pretreated patients. Many studies have reported HSV and suspected PCP as significant adverse effects, with a wide varying range (PCP 2–31%, HSV 20–71%).<sup>10</sup> It is recommended by the manufacturer that patients should receive sulfamethoxazole/trimethoprim DS (Septra<sup>®</sup>, Bactrim<sup>®</sup>) twice daily three times per week for PCP prophylaxis, and famciclovir 250 mg twice daily, or equivalent,

for HSV prophylaxis during Campath-1H therapy. Prophylaxis should continue for 2 months after completion of Campath-1H therapy or until the CD4 count is  $\geq 200$  cells/ $\mu$ L, whichever occurs later.

## DOSAGE, ADMINISTRATION, AND COST<sup>2</sup>

Dose escalation is required; usually accomplished in 3–7 days. Per manufacturer's recommendation, do not exceed single doses  $> 30$  mg or cumulative doses  $> 90$  mg/week although higher doses have been used in some clinical trials. Premedicate with diphenhydramine and acetaminophen 30 minutes before initiation of infusion. In case where severe infusion-related events occur, treatment with hydrocortisone 200 mg can be used in decreasing the infusion-related events. The initial dose for adult B-CLL is 3 mg/day as a 2-hour infusion; if tolerated well, then increase to 10 mg/day and continue until tolerated; when 10 mg dose is tolerated, increase to 30 mg/day. In most patients, escalation to 30 mg can be accomplished in 3–7 days. Per manufacturer's recommendation, maintenance dose is 30 mg/day, three times per week for up to 12 weeks for B-CLL. No recommendation is provided for treatment of other hematological diseases. Dosage adjustments/discontinuation of therapy are needed for occurrence of severe neutropenia and thrombocytopenia.

Alemtuzumab is available as a 30-mg single-use glass ampoule in 3 mL solution. Alemtuzumab should be used within 8 hours after dilution. After withdrawing the necessary amount from the ampoule into a syringe, the syringe must be filtered with a low-protein binding, non-fiber releasing 5- $\mu$ m filter prior to dilution. The manufacturer recommends a dilution with 100 mL sterile 0.9% sodium chloride, or D5W for each infusion.

The average whole sale price (AWP) for each 30 mg (3 mL) vial is US\$1537.50. Estimated drug cost for a 6-week treatment course is US\$28,000, or US\$56,000 for a 12-week course therapy.

## CONCLUSION

Many clinical trials have shown Campath-1H to be active against B-CLL and T-PLL in patients failed previous alkylating or purine analog chemotherapy. In a small number of chemotherapy naive patients, Campath-1H also demonstrates good efficacy as first-line therapy. However, the activity is not universal in all patients, nor is the duration of response long-lasting. In addition, the use of Campath-1H is

associated with some significant toxicity, mainly infections and myelosuppression. Therefore, Campath-1H is used as a salvage therapy to prolong survival, but not as a curative treatment option. Perhaps more investigation should be conducted to explore possible roles of Campath-1H in the treatment of these diseases. Possible options could include identifying the subset of patient population with B-CLL and T-PLL who are most likely to respond to Campath-1H, exploring combination of Campath-1H with other chemotherapeutic agents or monoclonal antibodies either as front-line or second-line therapy, and establishing pharmacodynamic profile, which should all benefit patients tremendously in the future.

## REFERENCES

- 1 Ginaldi L, De Martinis M, *et al.* Levels of expression of CD52 in normal and leukemic B and T cells: correlation with *in vivo* therapeutic responses to Campath-1H. *Leuk Res* 1998; **22**: 185–91.
- 2 Campath Package Insert, Berlex Laboratories 2001.
- 3 Dyer MJS. The role of Campath-1 antibodies in the treatment of lymphoid malignancies. *Semin Oncol* 1999 Oct; **26**(Suppl 14): 52–57.
- 4 Riechmann L, Clark M, Waldmann H, *et al.* Reshaping human antibodies for therapy. *Nature* 1988; **332**: 323–27.
- 5 Dyer MJS, Hale G, Marcus R, *et al.* Remission induction in patients with lymphoid malignancies using unconjugated Campath-1 monoclonal antibodies. *Leuk Lymphoma* 1990; **2**: 179–93.
- 6 Salisbury JR, Rapson NT, Codd JD, *et al.* Immunohistochemical analysis of CDW52 antigen expression in non-Hodgkin's lymphomas. *J Clin Pathol* 1994; **47**: 313–17.
- 7 Hale G, Dyer MJS, Clark MR, *et al.* Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody Campath-1H. *Lancet* 1988; **1**: 1394–99.
- 8 Osterborg A, Dyer MJS, Bunjes D, *et al.* Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukemia. *J Clin Oncol* 1997; **15**: 1567–74.
- 9 Dumont FJ. Alemtuzumab. *Curr Opin Invest Drugs* 2001 Jan; **2**: 139–60.
- 10 Flynn JM, Byrd JC. Campath-1H monoclonal antibody therapy. *Curr Opin Oncol* 2000; **12**: 574–81.
- 11 Dearden CE, *et al.* High remission rate in T-cell prolymphocytic leukemia with Campath-1H. *Blood* 2001; **98**: 1721–26.

- 12 Keating MJ, Cazin B, *et al.* Campath-1H treatment of T-cell prolymphocytic leukemia in patients from whom at least one prior chemotherapy regimen has failed. *J Clin Oncol* 2002; **20**: 205-13.
- 13 Bannerji R, Kitada S, *et al.* Campath-1H antibody induces transmembrane signaling *in vitro* and *in vivo* in patients with chronic lymphocytic leukemia (CLL) and promotes tumor clearance in part through caspase mediated apoptosis. *Blood* 2001; **98**: 808a. Abstract 3359.
- 14 Isaacs JD, Watts RA, *et al.* Humanised monoclonal antibody therapy for rheumatoid arthritis. *Lancet* 1992; **340**: 748-52.
- 15 Brett S, Baxter G, *et al.* Repopulation of blood lymphocyte subpopulations in rheumatoid arthritis patients treated with the depleting humanized monoclonal antibody, Campath-1H. *Immunology* 1996; **88**: 13-19.
- 16 Isaacs JD, Manna VK, *et al.* Campath-1H in rheumatoid arthritis: an intravenous dose-ranging study. *Br J Rheumatol* 1996; **35**: 231-40.
- 17 Morris E, Rebello P, *et al.* Pharmacokinetics of Campath-1H *in vivo* T cell depletion in non-myeloablative allogeneic transplants: relevance for early adoptive immunotherapy. *Blood* 2001; **98**: 478a. Abstract 1998.
- 18 Kalil N, Cheson BD. Chronic lymphocytic leukemia. *The Oncologist* 1999; **4**: 352-69.
- 19 [www.cancernet.nci.nih.gov](http://www.cancernet.nci.nih.gov) (PDQ<sup>®</sup>), Chronic Lymphocytic Leukemia.
- 20 Kalil N, Cheson BD. Management of chronic lymphocytic leukemia. *Drugs Aging* 2000 Jan; **16**: 9-27.
- 21 Bowen AL, Zomas E, *et al.* Subcutaneous Campath-1H in fludarabine-resistant/relapsed chronic lymphocytic and B-prolymphocytic leukemia. *Br J Haematol* 1997; **96**: 617-19.
- 22 Pawson R, Dyer MJ, *et al.* Treatment of T-cell prolymphocytic leukemia with human CD52 antibody. *J Clin Oncol* 1997; **15**: 2667-72.
- 23 Steven L, McCune J, *et al.* Alemtuzumab (Campath) in relapsed or refractory CLL or PLL. *Blood* 2001; **98**: 290b. Abstract 4907.
- 24 Nguyen DD, Cao TM, *et al.* Campath-1H for relapsed/refractory chronic lymphocytic leukemia (CLL) and prolymphocytic leukemia (PLL): the Stanford University Experience. *Blood* 2001; **98**: 291b. Abstract 4908.
- 25 Courte S, Rai KR, *et al.* Efficacy and safety of alemtuzumab (Campath-1H) used on compassionate basis in refractory T-PLL. *Blood* 2001; **98**: 366a. Abstract 1542.
- 26 Rai KR, Courtre S, *et al.* Efficacy and safety of alemtuzumab (Campath-1H) in refractory B-CLL patients treated on a compassionate basis. *Blood* 2001; **98**: 365a. Abstract 1538.
- 27 Nabhan C, Tallman MS, *et al.* Phase I study of rituximab and Campath-1H in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood* 2001; **98**: 365a. Abstract 1536.
- 28 Kennedy B, Rawstron A, *et al.* Eradication of detectable minimal disease with Campath-1H therapy results in prolonged survival in patients with refractory B-CLL. *Blood* 2001; **98**: 367a. Abstract 1544.
- 29 Keating MJ, Byrd J, Rai K, *et al.* Multicenter study of Campath-1H in patients with chronic lymphocytic leukemia (B-CLL) refractory to fludarabine. *Blood* 1999; **94(Suppl 1)**: 705a. Abstract 3118.
- 30 Rai K, Mercier RJ, Cooper MR, *et al.* Campath-1H is an effective salvage therapy for fludarabine failing CLL patients. Results of a phase II trial. *Blood* 2000; **11**: 153a. Abstract 703.
- 31 Rawstron AC, Davies FE, Evans P, *et al.* Campath1H therapy for patients with refractory chronic lymphocytic leukaemia (CLL). *Blood* 1997; **90**: 529a. Abstract 2356.
- 32 Kennedy B, Rawstron AC, Evans P, *et al.* Campath-1H therapy in 29 patients with refractory CLL: "true" complete remission is an attainable goal. *Blood* 1999; **94**: 603a. Abstract 2683.