Emerging Drug List
ALEMTUZUMAB

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Alemtuzumab (MabCampath*)</th>
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<tr>
<td>Manufacturer:</td>
<td>Ilex Pharmaceuticals (distributed by Berlex)</td>
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<td>Indication:</td>
<td>For the treatment of B cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.</td>
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<td>Current Regulatory Status:</td>
<td>The US Food and Drug Administration (FDA) approved alemtuzumab for chronic lymphocytic leukemia (CLL) in May 2001. Alemtuzumab is under review by Health Canada, with approval pending. It is available via Health Canada’s Special Access Programme (Dr. Jean Louis Stril, Berlex Canada, Montreal: personal communication, 2003 Nov 13).</td>
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<td>Description:</td>
<td>Alemtuzumab is a humanized anti-CD52 monoclonal antibody. CD52 is a cell surface antigen expressed on leukocytes (B lymphocytes, T lymphocytes, monocytes, macrophages, thymocytes and granulocytes) and other cell types, for example, skin cells. It has been proposed that alemtuzumab could be used against cancer cells that express CD52 by binding to these cells and destroying them via host-dependent mechanisms. One such cancer is chronic lymphocytic leukemia (CLL), where 95% of patients present with an overabundance of B cells that express CD52. The drug is given as a two-hour intravenous infusion at a dose of 30 mg three times weekly for up to 12 weeks. To minimize the incidence of infusion-related toxicities, alemtuzumab should be initiated at a dose of 3 mg, with a dose escalation as tolerated to 10 mg daily, then to 30 mg daily. The drug’s half-life is approximately 12 days. Peak and trough levels rise during the first few weeks of therapy and approach steady state around week six, although there is variability among patients.</td>
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<td>Current Treatment:</td>
<td>The first-line treatment for B-CLL is the oral alkylating agent, chlorambucil. Fludarabine, a purine analogue, is used in patients who were previously treated for B-CLL. Fludarabine can achieve a response rate of 50%, with a complete response seen in 15% of patients. Combination chemotherapy has also been used for advanced disease, with response rates of 40% to 80%. These regimens include cyclophosphamide, vincristine and prednisone (COP); cyclophosphamide, low-dose doxorubicin vincristine and prednisone (CHOP); and cyclophosphamide, doxorubicin and prednisone (CAP). Cladribine, another purine analogue, has also been used for refractory or relapsed B-CLL. Bone marrow transplantation has a limited role, as B-CLL patients are typically elderly or commonly have marrow involvement.</td>
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<td>Cost:</td>
<td>A document located on the Patented Medicines Pricing Review Board’s web site quotes a Canadian price of $650 per 30 mg ampoule. In the US, the price ranges from US$1,734 to US$2,432 per ampoule.</td>
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Evidence: In a prospective, multicentre, uncontrolled trial, 6 patients (n=93) with B-CLL who had been treated with an alkylating agent and who had failed treatment with fludarabine were eligible. After dose titration, a target dose of alemtuzumab 30 mg was administered intravenously three times weekly for up to 12 weeks. The median participant age was 66 years (range 32 to 86); and 71 patients (76%) had advanced disease [Rai stage III, n=16 (17%) or stage IV, n=55 (59%)]. If disease progression or resolution was noted after four or eight weeks or if no improvement occurred after eight weeks, alemtuzumab was discontinued. After therapy, patients who were considered to be responders or who had stable disease were followed monthly for six months and every three months thereafter. The primary endpoint was the objective response rate (complete response plus partial response) as defined by the 1996 National Cancer Institute Working Group (NCIWG) criteria.7

Among patients, 65 (70%) completed therapy; 20 (23%) were required to withdraw due to an adverse event; and 31 (33%, 95% CI: 23% to 43%) were considered responders (two achieved a complete response and 29 had a partial response). Responses were seen in all prognostic groups except in patients with a World Health Organization (WHO) performance status of 2 at baseline.7 The median time to response was 1.5 months (range 0.4 to 3.7), with a median duration of response of 8.7 months (range 2.5 to >22.6). Median survival was 16 months (95% CI: 11.8 to 21.9).

An uncontrolled follow-up trial was published in abstract form.8 Alemtuzumab 30 mg was given intravenously three times weekly for up to 12 weeks or until a maximum response was seen, whichever occurred first. Efficacy data are available for 152 patients with B-CLL. Using the NCIWG criteria, an objective response rate was achieved in 43% of patients (5% achieved a complete response and 38% had a partial response).

Additional objective response data are available from a published trial involving 24 patients who had been refractory to fludarabine and another study sub-population of 32 patients (selected from a larger study of 125 patients) who had received an alkylating agent and failed. These are described in the American product monograph and at the FDA's web site. In the published trial and CLL subset, overall response rates are 29% (95% CI: 11 to 47) and 21% (95% CI: 8 to 33) respectively, with all being partial responses.

In four additional published studies involving 90 patients with B cell or T cell lymphoma, overall response rates range from 31% to 67% (the 67% rate is noted in four of six patients in one study). Other trials exploring the use of alemtuzumab in refractory CLL are presented in abstract form. Additional studies focus on the subcutaneous administration of alemtuzumab.
Two published trial reports and three trials published in conference abstract form describe the use of alemtuzumab as a first-line agent for patients with CLL.\textsuperscript{15,22-25} Alemtuzumab has also been given to treat residual disease after chemotherapy in four small trials, two of which are published in full.\textsuperscript{26-29} In addition, four small studies, two of which are published in full, explore the use of combination therapy using rituximab or fludarabine in patients with refractory or relapsed CLL.\textsuperscript{30-33}

Adverse Effects: Of 28 (30\%) deaths occurring during the prospective, multicentre, uncontrolled trial\textsuperscript{2} or within the 180 days of follow-up, 14 deaths (15\%) were judged to be drug-related.\textsuperscript{3}

All these deaths were caused by cytopenias and in most cases, cytopenia-related opportunistic infections. In the same trial, 65 serious adverse events in 46 patients were reported. Among these, 49 were thought to be drug-related. Most of the serious adverse events were due to opportunistic infection (29 patients). Other adverse events were infusion-related (10 events reported); were due to febrile neutropenia (16 events reported); or were hematological (12 events reported). Because immunosuppression may persist for several months after the end of treatment, prophylaxis with antibiotics (e.g., co-trimoxazole and famciclovir) was mandatory.\textsuperscript{3}

Infusion-related adverse events, such as rigors, fever, nausea, vomiting and rash, were the most commonly observed adverse events (90\% of patients reported at least one of these symptoms). Therapy had to be discontinued in 6\% of patients.\textsuperscript{3,6} Infusion-related reactions, except rash, decreased in intensity over time and were minimized by pre-treatment with oral antihistamines, acetaminophen and corticosteroids.\textsuperscript{3,6} Dyspnea (28\%), hypotension (17\%) and hypoxia (3\%) were also reported.\textsuperscript{6}

Commentary: CLL, which accounts for 25\% to 30\% of leukemias, occurs mainly in patients over the age of 50. Alemtuzumab was approved in the US in 2001 as salvage therapy in patients with B-CLL who have been treated with alkylating agents and who have failed fludarabine. This approval was based on data from two uncontrolled trials demonstrating a 33\% objective response rate.\textsuperscript{3} Deaths and serious morbidity related to the use of the drug were reported in these trials, but in the setting of malignant disease, this toxicity may be considered to be acceptable.\textsuperscript{3}

There is no direct evidence from controlled trials that suggests there is an increased survival with this new drug compared to or combined with first- or second-line agents. Its approval in the US, however, was conditional upon the manufacturer conducting a comparative trial against chlorambucil in 284 previously untreated patients with progressing disease.\textsuperscript{3} Once the results of this clinical trial are available, alemtuzumab’s place in therapy may become clearer.
References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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