Criteria For Non-formulary Use of Alemtuzumab (CAMPATH®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and
the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. These guidelines are intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. They are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

1. Alemtuzumab was approved in May of 2001 for the treatment of patients with B-cell chronic lymphocytic leukemia (CLL) who have been treated with alkylating agents and failed fludarabine therapy. It is the first monoclonal antibody approved for use in CLL. **Severe infusion reactions, hematologic toxicity, and infections require continual evaluation by multiple team members.**

   Criteria for VA use- Restricted to Hematology/Oncology Physicians

Patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and failed fludarabine therapy* OR patients with T-cell prolymphocytic leukemia **AND** Patients are **not known** to have Type I hypersensitivity or anaphylaxis to murine proteins or any other component of the drug product **AND** Patients do not have an active systemic infection or underlying immunodeficiency (e.g. HIV) other than CLL induced immunodeficiency

   * Fludarabine failure is defined as failure to achieve a Complete Response (CR) or a Partial Response (PR) after receiving fludarabine 25mg/m^2 IV daily for 5 days repeated every 4 weeks OR relapse <6 months after achieving a CR or PR with fludarabine.

2. Dosing

   A. Administer diphenhydramine 50mg IV or PO plus acetaminophen 650-1000mg PO 30 minutes before the first dose, before a dose increase, and as needed to minimize infusion reactions
   B. Day 1 the dose is 3mg in 100ml of 0.9% sodium chloride or 5% dextrose over 2 hours; if well tolerated →
   C. Day 2 the dose is 10mg/100ml IV solution over 2 hours; if well tolerated →
   D. Day 3 the dose is 30mg/100ml IV solution over 2 hours
   E. If any dose level is not tolerated, continue daily administration at that level until tolerated, then increase to next level
   F. Subsequent dosing is 30mg/100ml IV solution over 2 hours three times a week i.e. Mondays, Wednesdays, and Fridays for up to 12 weeks.
   G. If patients experience severe infusion-related reactions that prevent dose escalation, pre-treatment with 200mg of hydrocortisone IV may be useful in decreasing those reactions.
   H. **All patients should be started on sulfamethoxazole/trimethoprim DS BID 3 times a week plus acyclovir 400mg BID or an equivalent (e.g. valacyclovir 250mg BID or 500mg QD) from day one of therapy**. **Antifungal prophylaxis should be considered.**

3. Dose Modifications

If serious infections, hematologic toxicity, or other serious toxicity occurs, alemtuzumab should be stopped until the toxicity resolves. In cases of autoimmune hemolytic anemia or thrombocytopenia, therapy should be stopped permanently.

Dose Modification and Re-initiation of therapy for hematologic toxicity

Hematologic Toxicity	Dose Modification and Re-initiation
1st Occurrence of ANC<250/µl and/or platelet count ≤25,000/µl	1. Withhold Campath 2. When ANC≥500/µl AND platelets≥50,000 Resume Campath at same dose 3. If delay is≥7 days, initiate at 3mg and escalate to 10mg then 30mg as tolerated.
2nd Occurrence of ANC ≤250/µl and/or platelets ≤25,000/µl	1. Withhold Campath 2. When ANC ≥500/µl and platelets ≥50,000/µl resume Campath at **10mg** 3. If delay is ≥7 days, restart at 3mg and escalate to **10mg only**
3rd Occurrence of ANC ≤250/µl and/or platelets ≤25,000/µ/	Discontinue Campath permanently
For a decrease of ANC and/or platelets to ≤50% of the baseline value in patients starting therapy with a baseline ANC ≤500/µl and/or baseline platelets ≤25,000/µl	1. Withhold Campath 2. When ANC and/or platelets return to baseline value(s), resume Campath 3. If delay is ≥7 days, initiate therapy at 3mg and escalate to 10mg then 30mg as tolerated

Adapted from package insert. Campath. Richmond, CA: Berlex Laboratories 2001

4. Safety Issues

Before Infusion	• Baseline CBC and platelet count; repeat regularly during treatment (e.g. weekly) • If cytopenias develop, repeat CBC and platelets more frequently (e.g. before each dose)
During Infusion	• BP and heart rate every 15 minutes during infusion; O_2 saturation optional • If patient develops hypotension, fever, rigors, shortness of breath, rash etc. STOP INFUSION. May be restarted when symptoms are controlled • Meperidine IV has been used to treat severe rigors
Long-term Monitoring	• If patient develops a fever, promptly assess for opportunistic infections and treat accordingly • Only irradiated blood products should be used because of the potential for Graft-Vs.-Host reactions • Patients should NOT receive live vaccines for at least 12 months after therapy • Return of neutrophil count to normal may take up to 12 months in some patients • Continue antibiotic/antiviral prophylaxis for 2 months after the end of therapy or until the CD4+ count is >200cells/µl • Document response based on NCI criteria**

5. Adverse effects

The most *serious* adverse effects include **hematologic toxicity** (consisting of a sometimes-fatal pancytopenia or autoimmune hemolytic anemia or autoimmune thrombocytopenia, any of which warrants permanent discontinuation of the drug), **infusion reactions** (consisting of hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash), and **infections** (opportunistic infections which are sometimes fatal), all of which carry a **black box warning** in the package insert. Mortality in 15% of patients in the pivotal trial was probably due to the drug.

The most *frequent* adverse effects include grade I-II infusion reactions, nausea, vomiting, neutropenia, anemia, thrombocytopenia, cough, shortness of breath, hypotension, and rash.

6. Summary of pivotal trial

- 93 patients with B-cell CLL treated with alkylating agents and at least one course of fludarabine who relapsed (<6 months since last fludarabine dose) or were refractory to fludarabine (failure to achieve a CR or PR)
- After initial dose escalation, therapy continued at 30mg over 2 hours three times a week for up to 12 weeks
- Response Rate 33% (CR 2% + PR 31%) and median survival of 16 months
- Opportunistic infections in 29%
- Grade III or IV anemia in 47%
- Neutropenia or worsening of pre-treatment neutropenia in 70%
- Grade III or IV thrombocytopenia or worsening of pre-treatment thrombocytopenia in 52%
- Infusion reactions in 89%
- Dose delays in 32% (often due to infection or hematologic toxicity)
- Discontinuation of therapy in 24% because of adverse effects

**** NCI sponsored Chronic Lymphocytic Leukemia (CLL) Working Group Response Criteria:**

Complete Response requires all of the following for at least 2 months

1. Absence of lymphadenopathy by physical exam or radiographic techniques.
2. No hepato- or splenomegaly by physical exam or radiographic techniques.
3. Absence of constitutional symptoms.
4. Normal CBC- PMN's ≥1500/µl & platelets >100,000/µl & hemoglobin > 11 g/dl & peripheral blood lymphocytes ≤4000/µl
5. Bone marrow biopsy and aspirate 2 months after clinical and laboratory CR to document response. Sample should be normocellular for age with <30% of nucleated cells being lymphocytes. If hypocellular, repeat in 4 weeks.
6. If all of the above criteria are satisfied, an abdominal CT scan may be used to confirm the clinical and hematologic impression if clinically indicated
7. If all of the above criteria are satisfied but there are nodules identified histologically in the bone marrow, patients may have a shorter time to progression and should be classified as nodular PRs (nPR) and included with the PRs.
8. Patients who achieve a CR but have a persistent anemia or thrombocytopenia unrelated to the disease but likely due to treatment should be considered a PR because long-term outcomes may differ from more routine complete responders

Partial Response requires the following for at least 2 months plus the documentation of any constitutional symptoms:

1. ≥50% decrease in peripheral blood lymphocyte count from baseline **AND**
2. ≥50% reduction in lymphadenopathy **AND/OR**
3. ≥50% reduction in the size of the liver and/or spleen **PLUS ONE OR MORE OF THE FOLLOWING FEATURES**
4. PMN's ≥1500/µl or 50% improvement over baseline
5. Platelets >100,000/µl or 50% improvement over baseline
6. Hemaglobin >11 g/dl or 50% improvement over baseline without transfusions

Progressive Disease requires at least one of the following

1. ≥50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive exams 2 weeks apart (1 node must be ≥2cm); appearance of new palpable lymph nodes
2. ≥50% increase in the size of the liver and/or spleen; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
3. ≥50% increase in the absolute number of circulating lymphocytes
4. Transformation to a more aggressive histology (e.g., Richter syndrome or prolymphocytic leukemia with >55% prolymphocytes)
5. In the absence of above criteria the presence of a ≥2g/dl decrease in hemoglobin or ≥50% decrease in platelets and/or absolute granulocyte count will not exclude a patient from continuing therapy.

Patients who do not achieve a CR or PR and do not have findings consistent with PD will be considered to have stable disease.

References:

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Cheson BD, Bennett JM, Grever MR, Kay NE, Keating MJ, et el. National Cancer Institute-sponsored working group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87(12):4990-4997.

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