National PBM Drug Monograph
Alemtuzumab (CAMPATH®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Introduction[1,2,3,4]

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in the Western world. It is characterized by proliferation and accumulation of neoplastic B-lymphocyte clones in the blood, lymph nodes, bone marrow, and spleen. The incidence increases with age and is higher in men than women. Median age at diagnosis is 69 years old. The disease can be indolent in some, and those patients will have a normal life span. In others the disease is aggressive and death occurs within five years of diagnosis.

The cause of CLL is unknown. Several cytogenetic abnormalities are associated with CLL including trisomy 12, abnormality of chromosome 13 at band q14, 14q+, deletion of chromosome 6 or 11. The consequence of these abnormalities is unknown. CLL B cells may impair the host immune system and inhibit the activation of normal B cells. T cell and NK cell function may also be abnormal. Hypogammiglobulinemia adds to the general state of impaired immunity, although it is usually not present in early stages. An additional feature of the dysfunctional immune system in CLL is the production of autoantibodies directed against the hematopoietic cells resulting in autoimmune hemolytic anemia, immune-related thrombocytopenia, or granulocytopenia.

The NCI-sponsored Chronic Lymphocytic Leukemia (CLL) Working Group developed guidelines for eligibility, response, and toxicity criteria for standardization of clinical trials.[5] The diagnosis of CLL requires a lymphocytosis in the peripheral blood (≥5000/μl with mature appearance and <55% prolymphocytes) and phenotyping showing B-cell markers along with CD5 antigen, B-cell monoclonal expression, and surface immunoglobulins of low density. A bone marrow aspirate smear showing ≥30% lymphoid cells is not required, but appropriate to assess for site involvement. Clinical staging of the disease in the United States usually follows the Rai staging system which divides patients into three prognostic categories: low risk (Stage 0), intermediate risk (Stages I & II), and high risk (Stages III & IV). As B cells accumulate over time, asymptomatic patients may develop symptoms of lymphadenopathy, splenomegaly, hepatomegaly or B-symptoms.

Treatment of CLL should be delayed except for Rai Stage III and IV (high risk) or if the patient is symptomatic. Treatment early in the disease course delays progression but does not affect overall survival. Initial treatment with oral chlorambucil (an alkylating agent) has been the acceptable therapy for over 50 years but with little impact on outcomes. The purine analogue fludarabine was approved for use as a second line agent. In a recent comparison with chlorambucil for initial therapy, fludarabine produced higher response rates and a longer duration of remission and progression free survival.[6] Overall survival was not enhanced. There is no effective therapy for patients who have failed alkylating therapy and fludarabine. Alemtuzumab, a new anti-CD52 monoclonal antibody was recently approved for the treatment of B-cell CLL in patients who have been treated with alkylating agents and who failed fludarabine therapy.

Pharmacology/Pharmacokinetics[7,8,9,10]

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell surface antigen. CD52 is found on almost all normal and malignant B and T lymphocytes, NK cells, macrophages and monocytes. It is not found on stem cells, erythrocytes, or platelets. A small percentage (<5%) of granulocytes express CD52. The antigen is expressed more in B-cell malignancies than T-cell malignances. The normal function of CD52 on the lymphocytes is unknown. Resistance of the antigen to modulation (shedding, endocytosis, redistribution in cell membrane) is favorable for the success of monoclonal antibody therapy.

Alemtuzumab binds to the CD52 antigen and induces cytotoxicity through complement fixation and antibody-dependent cellular cytotoxicity (ADCC). There is some in vitro evidence that alemtuzumab can induce apoptosis in CLL cells without complement. The significance of this effect in vivo is unknown. Two characteristics have been identified which are important for efficacy: the proximity and high density of the antigen on the cell membrane.

Pharmacokinetics

The pharmacokinetics of alemtuzumab were studied in a multicenter trial in non-Hodgkin's lymphoma and CLL following once weekly IV therapy over a wide dose range. The Cmax and AUC were relatively proportional to the dose administered. The mean t½ was about 12 days.

In CLL patients who received 30mg infusions three times a week, peak and trough levels of alemtuzumab increased during the first weeks of therapy and approached steady state at week 6; there was substantial inter-patient variability. The increase in alemtuzumab serum concentration correlated to the reduction in lymphocytes.

FDA Approved Indication(s) and Off-label Uses

Alemtuzumab is indicated 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.
Off-label uses: T-cell prolymphocytic leukemia (T-PLL), T-cell depletion of donor marrow to decrease risk of GVHD, rheumatoid arthritis, multiple sclerosis, and kidney transplantation to prevent rejection

Current VA National Formulary Status

Non-formulary status

Dosage and Administration (see reference 9)

Alemtuzumab is approved for use as an IV infusion three times a week. The initial dose is 3mg administered over 2 hours daily. When this dose is tolerated (infusion related toxicities ≤Grade 2), the daily dose is escalated to 10mg. When this dose is tolerated, the maintenance dose of 30mg is initiated. For most patients, dose escalation to 30 mg is accomplished within 3-7 days. The maintenance dose of 30mg/day is given three times a week (e.g. Monday, Wednesday, Friday) for up to 12 weeks. Single doses greater than 30mg or weekly doses greater than 90mg are associated with an increased risk of pancytopenia.

Concomitant Medications
Premedication is recommended before the first dose, before each dose escalation, and as needed. Premedication used in studies included acetaminophen 650mg and diphenhydramine 50mg 30 minutes before the infusion. In cases of severe infusion reactions, premedication with IV hydrocortisone 100-200mg may be used.

Anti-infective prophylaxis should be used to minimize the risk of serious opportunistic infections. In clinical studies, cotrimoxazole DS BID three times a week and famcyclovir 250mg BID or equivalent was used from the start of therapy. Prophylaxis should continue for 2 months after therapy or until $CD4^+$ count is ≥200 cells/μl.

Dose Adjustments

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/µl	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

Preparation/Administration/Storage

To prepare the infusion, the dose is drawn up into a syringe using a low-protein binding, non-fiber releasing 5µm filter and diluted in 100ml of 0.9% sodium chloride or 5% dextrose and gently inverted to mix. Alemtuzumab contains no preservative and should be used within 8 hours after dilution. The diluted solution may be stored at room temperature or refrigerated and protected from light. The intact vials should be stored refrigerated (2-8°C). Do not freeze.

Dosage forms available

Alemtuzumab is supplied in single-use glass ampoules containing 30mg in 3ml of solution. Each box contains either 3 or 12 ampoules.

Adverse Effects (Safety Data)

Black Box Warning

1. Hematologic toxicity: Serious, and in rare instances fatal pancytopenia/marrow hypoplasia, autoimmune hemolytic anemia, and autoimmune idiopathic thrombocytopenia have occurred. Single doses greater than 30mg and weekly doses of 90mg are associated with a higher incidence of pancytopenia and should be avoided.
2. Infusion reactions: Serious infusion reactions have occurred including rigors, fever, hypotension, shortness of breath, bronchospasm, chills, and/or rash. Patients should be observed closely during infusion. Gradual escalation to the recommended dose is required at initiation and after any interruption for 7 days or more.
3. Infections/opportunistic infections: Serious and sometimes fatal bacterial, fungal, viral and protozoal infections have been reported. Prophylaxis against pneumocystis carinii pneumonia (PCP) and herpes infections decreases but does not eliminate the occurrences. Because of the profound lymphopenia, any blood products administered to patients on alemtuzumab should be irradiated to prevent GVHD.

Precautions

Laboratory Monitoring:

CBC and platelet count weekly during therapy, more often if worsening anemia, neutropenia, or thrombocytopenia is observes. CD4+ should be assessed after therapy until recovery to ≥200cells/µl.

Drug Interactions:
No formal drug interaction studies have been performed.

Immunization:
Patients receiving alemtuzumab are immunosuppressed and should not receive live vaccines. The safety of live vaccines after therapy has not been assessed. The ability to produce a humoral response to any vaccine after therapy has not been assessed.

Carcinogenesis, Mutagenesis/ Impairment of Fertility:
No long-term studies in animals have been performed to assess the carcinogenic or mutagenic potential of alemtuzumab. The effect on fertility in males and females has not been determined.

Immunogenicity:
A small percentage of patients developed antibodies to alemtuzumab. The presence of antibodies may be influenced by several factors including handling of the sample and the underlying disease. Patients with allergies or hypersensitivity to alemtuzumab may have reactions to other monoclonal antibodies.

Geriatric Use:
Of the 149 CLL patients studied 44% were greater than 65 and 10% were greater than 75 years old. No differences in efficacy or safety were seen, but this is an inadequate number of patients for this assessment.

Adverse Events in >5% of B-CLL Study During Treatment or Within 30 days (n=149)

	B-CLL Studies N= 149	
Adverse Event:	**ANY Grade (%)**	**Grade 3 or 4 (%)**
Body as a Whole:		
Rigors	86	16
Fever	85	19
Fatigue	34	5
Pain, Skeletal pain	24	2
Anorexia	20	3
Asthenia	13	4
Edema, Peripheral edema	13	1
Back Pain	10	3
Chest Pain	10	1
Malaise	9	1
Temperature Change Sensation	5	-
Cardiovascular Disorders, General		
Hypotension	32	5
Hypertension	11	2
Heart Rate and Rhythm Disorders		
Tachycardia, SVT	11	3
Central & Peripheral Nervous System		
Headache	24	1
Dysthesias	15	-
Dizziness	12	1
Tremor	7	-
Gastrointestinal Disorders		
Nausea	54	2
Vomiting	41	4
Diarrhea	22	1
Stomatitis, Mucositis	14	1
Abdominal pain	11	2
Dyspepsia	10	-
Constipation	9	1

Adverse Event:	B-CLL Studies N= 149	
	ANY Grade (%)	Grade 3 or 4 (%)
Hematologic Disorders		
Neutropenia	85	64
Anemia	80	38
Pancytopenia	5	3
Platelet, Bleeding, and Clotting Disorders		
Thrombocytopenia	72	50
Purpura	8	-
Epistaxis	7	1
Musculoskeletal		
Myalgias	11	-
Psychiatric		
Insomnia	10	-
Depression	7	1
Somnolence	5	1
Immunosuppression		
Sepsis	15	10
H. Simplex	11	1
Moniliasis	8	1
Infection (other viral or unidentified)	7	1
Respiratory		
Dyspnea	26	9
Cough	25	2
Bronchitis, Pneumonitis	21	13
Pneumonia	16	10
Pharyngitis	12	-
Bronchospasm	9	2
Rhinitis	7	-
Skin/Appendage		
Rash, Maculopapular and erythematous	40	3
Urticaria	30	5
Pruritus	24	1
Increased Sweating	19	1

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

Contraindications

Contraindicated in patients with systemic infections, underlying immunodeficiency (HIV), or known Type 1 hypersensitivity or anaphylaxis to alemtuzumab or any of its components.

Efficacy Measures (see reference 5)

Two major areas of assessment are essential when reviewing clinical trials of third-line therapy in CLL: 1) Did the drug therapy produce a significant clinical response, which indicates clinical benefit to the patient and 2) Were toxicity rates low and/or manageable.

1. Clinical response in the alemtuzumab trials followed the response criteria of the NCI. The criteria is as follows:

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.

Clinically beneficial responses include CR, (n)PR and PR; all others are treatment failures.

2. Toxicity with alemtuzumab is extensive and potentially serious. It is difficult, however, to separate out toxicity from the disease, from prior chemotherapy with fludarabine, or from alemtuzumab because the toxicities of each overlap. In particular, the incidence of immunosuppression (resulting in opportunistic infections) and the hematologic toxicities could be due to the CLL, prior therapy with fludarabine, or alemtuzumab. The ability to manage these toxicities, no matter what the cause, plays an important role in the decision to administer alemtuzumab in this population.

Clinical Trials

Trial	Inclusion	Drug Therapy	Measured Outcomes	Results
Österborg 1997[11] Open MC phase II N=29 22 Rai stage III/IV	-CLL (NCI criteria) - >18yo WHO PS≤1 -Any stage requiring therapy -Failed or relapsed on conventional 1st or 2nd therapy (3 had prior fludarabine)	2hr infusion TIW Maximum 12 weeks Titrate to final dose (30mg) as tolerated	Efficacy (NCI criteria) Safety	• CR 4% + PR 38% = 42% overall • Med response duration 12mos(6-25+) • 17 withdrew after 6 weeks, 4 due to infection • AE: fever/rigors 28% Hypotension 21% Rash 65% • Infection: Local HSV reactivation 38% Oral candidiasis 17% PCP 7% Pneumonia/Sepsis 27%
Österborg 1996[12] N=9 Case –series	Any stage requiring therapy -disease related symptoms -progressive lymphocytosis -anemia or thrombocytopenia -massive splenomegaly or bulky lymphadenopathy	- First 5 pts -2 hr infusion TIW for max 18 weeks- - Next 4 pts SC TIW for max 18 weeks -Initial dose 3mg; escalate rapidly to final 30mg dose	Efficacy (NCI) Safety (WHO)	• CR 33% • PR 55% • PD 11% • Duration 8+ -24+ mos (2 relapses) • AE: Fever/rigors 89% Nausea/Rash 33% CMV pneumonitis 11% (1/9)
Bowen 1997[13] N=7 MC phase II (6) Case-series (1)	Resistant to or relapsed following Fludarabine (includes CLL and B-prolymphocytic leukemia)	10mg SC, then 30mg TIW for at least 6 wks-max 12 wks Prophylaxis: cotrimoxazole and acyclovir	Efficacy: CR: absence of detectable disease including BM PR: ≥ 50% reduction in detectable disease	• CR 14% (1/7) [relapsed at 3 mos] • PR 43% (3/7) • AE: Local inj-site reactions 100% Rash 1/7 DVT 1/7 • Infection: CMV reactivation 3/7 Sepsis 1/7
Dyer 1997[14] N=6 Case-series	In vivo purging of residual cells (PR) after 6 cycles of a purine analogue (fludarabine or deoxycoformycin) preventing stem cell collection	10-20mg over 2-4 hours interval ?? For 4-6 weeks or until no residual disease in BM Prophylaxis: cotrimoxazole and acyclovir	In vivo purging of residual CLL cells to allow stem cell harvest	• CR 5/6 • 2/5 harvested stem cells were contaminated with CLL cells-autologous transplant completed • 3/5 harvested stem cells –no contamination • PR 1/6--MUD transplant • CMV infection 1/6
		ABSTRACTS		
Österborg 1995[15] N=30	Heavily pre-treated (21) Untreated (9)	30mg IV or SC TIW Max 18 weeks	Efficacy (clearing of leukemia cells from blood and BM) Safety	• Pre-treated: CR+PR= 40% • Untreated: CR+PR=89% • Elimination of CLL Blood 97% BM Pre-treated 45% Untreated78% LN- less affected • Duration of response :8+ -24+mos • AE: only Heme toxicity mentioned • Long lasting lymphopenia
Rawstrom 1997[16] N=10	Refractory to conventional therapy including Fludarabine	30mg TIW for 6 weeks (18 doses)	Efficacy Safety	• CR 50% • PR 20%

Trial	Inclusion	Drug Therapy	Measured Outcomes	Results
		Prophylaxis: cotrimoxazole and fluconazole		• 40% received 18 doses • 20% received 36 doses (2nd course) • 20% are half-way thru 1 course • 10% stopped after 6 doses • 10% responded after 5 doses and went to harvest stem cells • 1 pt died 2° to thrombocytopenia
Keating 1999[17] MC phase II International N=93 **CAM211 Pivotal Trial**	Prior Alkylating therapy and No response or refractory to Fludarabine (Failed to achieve a CR or PR on fludarabine **or** relapsed <6 months after the last dose of fludarabine) Rai Stage III/IV or Stage 0-II with progressive disease: rapid doubling of lymphocyte count, progressive lymphadenopathy and/or splenomegaly, B-symptoms	30mg IV over 2 hours TIW X4-12 weeks Prophylaxis: cotrimoxazole and acyclovir	Efficacy Safety	• CR 2% + PR 31% = overall RR 33% • AE: Fever/rigors 89% Nausea/vomiting 50% Rash 33% Fatigue 29% Dyspnea 24% Neutropenia/thrombocytopenia 50% • Infections: Pneumonia 5% CMV 2% Candida 2% Septicemia 2% Other 4% PCP 2% • Median follow-up 9 months • 22/31 responders still alive • 28(30%) died 9 with infections
Kennedy 1999[18] N=29	CLL refractory to purine analogues	30mg IV over 2 hours TIW until max response	Efficacy (NCI criteria)	• CR 34% + PR 24% = 59% overall • Median follow-up 12 months • 7 responders → PBSCT; 2 have no detectable CLL by MRD Flow post transplant • 1 died from transplant complications
Ferrajoli 2000[19] N=45 30=B-cell CLL 2=mantle cell lymph. 4= T-cell PLL 1= LGL 1=SLVL 4=mycoses fungoides	Hematologic malignancies expressing CD 52 in >20% of neoplastic cells and have failed or predicted to have <20% response to conventional therapy	3mg IV D1, 10mg D2, 30mg D3, then 30mg TIW X 12 weeks Prophylaxis: cotrimoxazole and famciclovir	Efficacy Toxicity	• 34 evaluable • CR 9% (1-CLL) • PR 26% (5-CLL) • SD 18% (6-CLL) • PD 47% (11-CLL) • AE: Fever/chills 88% Hypotension 18% Dyspnea 18% Rash 12% • Infections: CMV 12% H. Zoster 6% Other 6%
Rai 2000[20] N=24 Phase II Majority Rai III/IV **Campath 009 Study Group**	Failed aklylating therapy and Fludarabine	10mg IV daily up to 5 days then 30mg TIW For maximum 16 weeks	Efficacy (NCI criteria) Toxicity	• PR 33% • Med overall survival 27.5mos (7.4-42+) • AE: Fevers/rigors/Hypotension/ NV mostly grade 1 or 2 • 9 d/c therapy b/o infection • highest incidence of major infections in first month AFTER therapy ended
Rai 2001[21] N=136 Compassionate use	Refractory to Fludarabine including some who relapsed after prior response to	3mg IV over 2 hours, then ↑ to max 30mg TIW X maximum 12 weeks	Efficacy Safety	• CR 7.4% + PR 32.4%= overall 39.8% • PD 61%

Trial	Inclusion	Drug Therapy	Measured Outcomes	Results
	alemtuzumab	Prophylaxis: cotrimoxazole and famciclovir		• 8 died • 26 d/c therapy 2° AE • Med survival 7.6 mos • AE : Fever 65% Rigors 71% Nausea 45% • Infections: 32% Candida 5% Pneumonia 5% H. Simplex 4% H. Zoster 1% CMV reactivation 1% Pseudomonas reactivation 1/136

MC=multicenter; PS=performance status; CR complete response; PR partial response; SD stable disease; PD progressive disease; TIW three times a week; BM bone marrow; MUD matched unrelated donor; LN lymph node; PBSCT peripheral blood stem cell transplant; MRD Flow Minimal Residual Disease 4-color Flow Cytometry; LGL large granular lymphocytosis; SLVL splenic lymphoma with villous lymphocytes

Acquisition Costs

Drug /Vial Size/Package Size	Price/Package Size
Alemtuzumab 30mg/3ml SDV 1X3 vials	$2632.89
Alemtuzumab 30mg/3ml SDV 4X3 vials	$10,531.52

Initial and Maintenance Costs

Drug	Dose	Cost/Week/patient ($)	Cost/12 weeks/patient ($)
Alemtuzumab	30mg	2632.89	31,594.68

(See purchasing data information in separate document)

Conclusions

There are no established cures for CLL. The treatment strategy for almost 40 years for patients in Rai Stages III and IV or progressive disease in Stages I and II has been to start with an alkylating agent, primarily chlorambucil, on a continuous or intermittent schedule until a maximum response is achieved. That response is seldom a complete response and relapse is inevitable. The purine analogue fludarabine was approved as second-line use after relapsed or refractory disease. In these patients, fludarabine produces good responses that are durable; relapse is inevitable. Second remissions in those who responded with initial therapy are possible. Recently, in comparative trials as first-line therapy, fludarabine produced a higher response rate and longer duration of response when compared to chlorambucil. The overall survival was not changed.[22,23]

When patients quickly relapse from fludarabine or their disease becomes refractory, there is little to offer that induces a substantial response. Standard combination chemotherapy rarely yields good response rates (0-22%) and none are complete responses. Bone marrow transplant has been investigated and may offer some patients long-term responses; unfortunately, the majority of CLL patients are not within the appropriate age range for receiving a transplant. Recent studies based on in vitro synergy used the combination of fludarabine and cyclophosphamide, which produced high response rates in previously untreated patients and in fludarabine refractory patients. The duration of the response in previously untreated patients has exceeded that obtained with fludarabine alone. Myelosuppression and infections are prominent toxicities.

Two monoclonal antibodies have shown activity in CLL. Rituximab (antiCD20) was approved for use in B-cell lymphomas expressing CD20. CLL cells express less CD20 than lymphomas and early trial results were disappointing. A change in the pharmacokinetic indices in CLL patients versus lymphoma patients led researchers to try higher and/or more frequent doses in CLL in order to achieve therapeutic serum concentrations. Increasing the dose and/or frequency resulted in higher response rates.[24,25] Approval of

alemtuzumab (antiCD52) by the FDA is based on the CAM211 pivotal trial in the United States and supportive trials 005 and 009. Trial 005 was conducted in Europe, and trial 009 in the United States; Burroughs Wellcome conducted both trials between 1993 and 1995. The results of the CAM211 trial and the 009 trial were published as abstracts. The European 005 trial results have never been published. The best information on the trials is available in the transcripts of the Oncologic Drugs Advisory Committee meeting when the drug was approved.[26] In addition, there are numerous open-label series (see Clinic Trials above) with less rigorous inclusion criteria and response criteria.

Clinical Efficacy

In the single-arm CAM211 trial, the response rate was considered a surrogate endpoint for survival. All patients had been treated previously with at least one alkylating agent followed by at least one course of fludarabine, making alemtuzumab a third-line treatment. Third line treatment with combination chemotherapy produced response rates of 0-22% with a median survival of less than 12 months. The response rate in CAM211 of 33% (2% CR + 29% PR) exceeded the 20% response set as a threshold. Other efficacy parameters included a median progression free survival of 4 months and a median survival of 15.9 months. Patients with disease symptoms (B-symptoms, fatigue, symptoms of hepato- or splenomegaly) also showed improvement. Alemtuzumab was most effective at eliminating malignant lymphocytes in the bone marrow and peripheral blood; it was much less effective in treating bulky nodal disease. The drug has been used to consolidate or 'purge' residual disease following bone marrow transplant or fludarabine therapy.

Safety

There are numerous toxicities associated with alemtuzumab. The most serious events included 84 drug-related adverse reactions: 10 were infusional, 16 were infectious, 30 were infections with neutropenia, and 12 were hematologic. There was no difference found in patients who developed serious adverse effects and the amount of previous chemotherapy.

Opportunistic infections occurred in 29% of patients. Of the 47 documented opportunistic infections, 29 were serious. Antibiotic prophylaxis in 87 patients changed the pattern of infections, decreasing the risk for PCP. There were 12 fungal infections, 16 viral infections (despite antiviral prophylaxis) and 1 PCP infection.

Hematologic toxicity: 47% of patients had at least one episode of grade3/4 anemia during therapy. Pre-study neutrophil counts were grade 3 or 4 in 18%. On study, 70% had a worsening of their grade 3or 4 neutropenia or developed at least one grade 3or 4 episode. The median number of days of grade 3 or 4 neutropenia is 28 days (2-161). Pre-study grade 3 or 4 thrombocytopenias were present in 19%. On-study 52% had a worsening of grade 3/4 or developed at least once instance of grade 3 or 4.

Dose delays occurred in 30 patients for 7-53 days (median 12). When greater than 7 days, delays were primarily due to hematologic toxicities or infections.

Mortality: There were 28 patients who died on-study or within 180 days after the study. Half of the deaths were drug related and half were due to progression.

Discontinuation of therapy: Therapy was discontinued in 22 patients because of adverse effects. 5 were related to the infusion, although it was noted that hypotension during infusion improved over the course of therapy. One patient had grade 4 bronchospasm after receiving 10mg of alemtuzumab.

Infusional toxicity: occurs in 88-89% of patients and consists primarily of fever and rigors especially at the start of therapy. Nausea and vomiting can occur in 30-50%, hypotension in 15%, and rash or urticaria in 30 and 22%, respectively. Premedication with acetaminophen and diphenhydramine may help to reduce the incidence and severity.

Recommendations

The Oncologic Drugs Advisory Committee (ODAC) raised several issues during the approval process that still need to be explored with further trials. Although the ODAC voted that the toxicity profile was acceptable because of the benefits gained, discussions centered on infections and mortality. The number of opportunistic infections was a concern for several members, especially the inability, based on the data from the pivotal trial, to distinguish between the disease and the new treatment as the cause for the infections. Prophylaxis against PCP later in the trial did reduce the number of infections from *pneumocystis*, and prophylaxis for fungal infections may be necessary. The entry criteria for the study included "refractory" patients (the definition of refractory in the studies was vague) who were exposed to a drug with a 15% drug related mortality rate when they may have had a median survival of 2 years without therapy. The limited pharmacokinetic data presented by the sponsor indicates that the half-life of the drug increases as the tumor burden decreases. The committee theorized whether individualized dosing or decreases in the dose frequency would possibly limit some of the adverse events. Finally, there was much discussion about what a phase III or IV confirmatory study should focus on: confirming the results of the pivotal trial or confirming when and how to best use the drug in the scope of therapy for CLL.

Alemtuzumab appears to have activity in CLL patients refractory to fludarabine. Infusional, hematologic, and infectious adverse events can be serious, and use of this drug should be restricted to hematology/oncology physicians familiar with the management and prevention of the adverse events. The use of the drug in patients with multiple co-morbidities has not been evaluated. Until there is more data on this drug, especially in populations similar to the VA, the recommendation is to leave this drug as non-formulary but make it available for use by attending hematologists/oncologists. Criteria for non-formulary use should be developed. Usage patterns and published clinical data should be monitored over the next 12 months at which time the drug should be reviewed again.

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