Treatment of Chronic Lymphocytic Leukemia With Alemtuzumab: A Review for Nurses

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Purpose/Objectives: To review the use of the monoclonal antibody alemtuzumab in patients with advanced refractory B cell chronic lymphocytic leukemia (B-CLL) and nursing management during treatment.

Data Sources: Published articles, abstracts, book chapters, Web sites, and training material.

Data Synthesis: Alemtuzumab can achieve disease remission in patients with chemorefractory B-CLL; however, management of high-risk patients presents certain challenges. Infusion-related events can be minimized by stepwise administration and appropriate prophylaxis. Cytopenia can be minimized by drug postponement and cytokine support or red blood cell or platelet transfusions. Patients also are at risk for infection because of lymphopenia, and anti-infective prophylaxis is mandatory at initiation of therapy until at least two months post-treatment.

Conclusions: With satisfactory supportive measures in place, patients with chemorefractory B-CLL can experience the benefits of alemtuzumab therapy without excessive toxicity.

Implications for Nursing: Nurses should be familiar with treatment and prophylactic protocols, be ready to offer supportive therapy to control side effects, and invest time in patient education.

Key Points . . .

- B cell chronic lymphocytic leukemia is the most common leukemia in the Western world.
- Alemtuzumab has a different mode of action than chemotherapy.
- Alemtuzumab can induce responses in patients who have not responded to available therapy.
- Appropriate prophylaxis is vital to successful treatment of high-risk patients.

Goal for CE Enrollees:

To further enhance nurses' knowledge regarding the treatment of patients with B cell chronic lymphocytic leukemia with alemtuzumab.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the mode of action and efficacy of alemtuzumab.
2. Describe the appropriate method of administration of alemtuzumab.
3. Discuss the nursing implications in the care of patients receiving alemtuzumab.

The most common type of leukemia in the Western world is B cell chronic lymphocytic leukemia (B-CLL). Its incidence in the United States is estimated to be more than 8,000 new cases annually (Edwards et al., 1002; Ries et al., 2000). As a disease of the elderly, its prevalence is increasing as the age of the population increases. Key B-CLL characteristics and symptoms of advanced disease are shown in Figure 1. Lymphadenopathy or splenomegaly are seen in about half of patients at diagnosis and become more common as the disease progresses.

About one-third of patients have progressive disease at presentation requiring immediate treatment. In another third, an initially indolent course is followed by disease progression, and the remaining third never require treatment and die from causes unrelated to B-CLL (Dighiero & Binet, 2000).

In the United States, the Rai staging system (Rai et al., 1975), and in Europe, the Binet staging system (Binet et al., 1981) are used to stratify patients according to extent of disease and to identify high-risk patients who require treatment (see Figure 2). Patients eligible for treatment with alemtuzumab (Campath®, Berlex Laboratories, Richmond, CA) for

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Characteristics
- B cell chronic lymphocytic leukemia is the most common leukemia in the Western world.
- It is a disease of the elderly.
- The initial course of disease may be slow.
- The disease remains incurable.
- Cancer cells are slow-growing, mature B lymphocytes (CD5+).
- Excess CD5+ lymphocytes are present in peripheral blood.
- In 99% of patients, cancer cells have the target marker CD52.

Symptoms of advanced disease
- Cancer cells invade bone marrow.
  - Decreased neutrophils and T cells disrupt the ability to fight infection.
  - Decreased red blood cells may cause anemia.
  - Decreased platelets may cause spontaneous or excessive bleeding.
- Splenomegaly, hepatomegaly, lymphadenopathy
- B symptoms, including night sweats, fever, and weight loss
- Flu-like symptoms, including fatigue
- Joint and bone pain
- Loss of appetite and weight

Figure 1. Characteristics and Symptoms of B Cell Chronic Lymphocytic Leukemia

B-CLL have advanced, refractory disease. Their leukemia cells, which are mature CD5+ lymphocytes, continue to multiply and invade bone marrow despite previous chemotherapy. Patients with advanced disease are likely to be elderly because the median age at diagnosis is 65 years (Edwards et al., 2002; Ries et al., 2000). They also are likely to have received prior treatments spanning a number of years. Such patients are very prone to infection because the disease and the effects of previous chemotherapy lower their natural immune defenses. Most patients with advanced disease die because of infections, and the terminal phase of B-CLL involves recurrent episodes of hospitalization with pneumonia or septicemia, excessive bleeding, and wasting (Rai & Keating, 1999). Patients eligible for alemtuzumab treatment are refractory to, or have relapsed after, previous therapy with alkylating agents or purine analogs.

Rai Staging System
- Low risk (stage 0)
  - Lymphocytosis in blood and bone marrow only
- Intermediate risk (stage I/II)
  - Lymphocytosis plus lymphadenopathy, hepatomegaly, or splenomegaly
- High risk (stage III/IV)
  - Lymphocytosis and anemia or thrombocytopenia

Binet Staging System
- Low risk (stage A)
  - Hemoglobin > 10 g/dl and/or platelets > 100 x 10^9/l
  - < 2 node-bearing or enlarged areas
- Intermediate risk (stage B)
  - Hemoglobin > 10 g/dl and/or platelets > 100 x 10^9/l
  - > 3 node-bearing or enlarged areas
- High risk (stage C)
  - Hemoglobin < 10 g/dl or platelets < 100 x 10^9/l
  - Any number of node-bearing or enlarged areas

Figure 2. Staging Systems for Chronic Lymphocytic Leukemia

Alemtuzumab

Mechanisms of Action

Alemtuzumab works by a completely different mode of action than chemotherapy. Chemotherapy drugs need to enter cancer cells to kill them. In contrast, monoclonal antibodies (MAbs) are molecules that have been generated to react with specific target antigens on the cell surface. Alemtuzumab is a MAb that can bind to the CD52 antigen present on normal B and T cells and trigger cell lysis. In vivo, lysis occurs mainly by antibody-dependent cell-mediated toxicity, plus complement-mediated lysis, and possibly apoptosis (Rai & Stephenson, 2001) (see Figure 3).

Because 100% of patients with B-CLL test positive for CD52 (Gilleece & Dexter, 1993) and CD52 is highly expressed on these leukemia cells, alemtuzumab is very effective at purging such cells from blood and bone marrow. Importantly, CD52 is absent from hematopoietic stem cells (Gilleece & Dexter), allowing for normal differentiation to continue despite treatment with alemtuzumab. The unique mechanism of action of alemtuzumab not only makes it highly effective in eliminating malignant cells from the major sites of disease in B-CLL but also creates highly specific management issues. Therefore, nurses must deal with adverse events to allow patients to proceed smoothly through therapy.

Clinical Efficacy

Alemtuzumab is approved for use as third-line therapy in patients who have been treated with alkylating agents and have not responded to fludarabine therapy. Overall response rates of 33%–44% and complete remission (CR) rates of 2%–13% have been reported (Hoffman, Jansen, & Rai, 1999; Osterborg et al., 1997; Rai et al., 2002). The largest study of alemtuzumab to date is a multicenter phase II clinical trial (Keating et al., 2002). Ninety-three patients with advanced disease who had undergone a median of three prior therapies were enrolled. The patients' median age was 66 years, and the median time from initial diagnosis was 6.1 years. Three-quarters of patients had very advanced disease (Rai stage III/IV). Even though these patients were in the high-risk stage, responses to alemtuzumab in blood and bone marrow were dramatic. Overall objective response (see Figure 4) in the

Mechanism of Action 1:
Complement-mediated lysis

Mechanism of Action 2:
Antibody-dependent cell-mediated toxicity

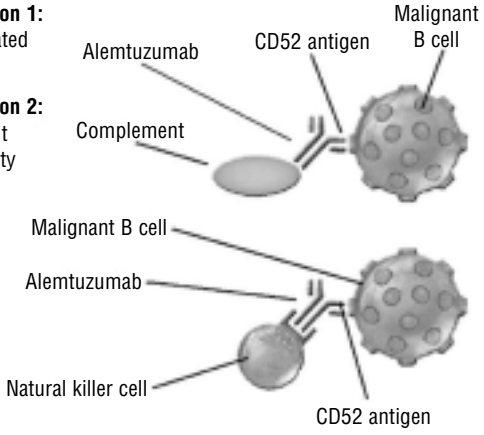

Figure 3. Alemtuzumab's Mechanisms of Action

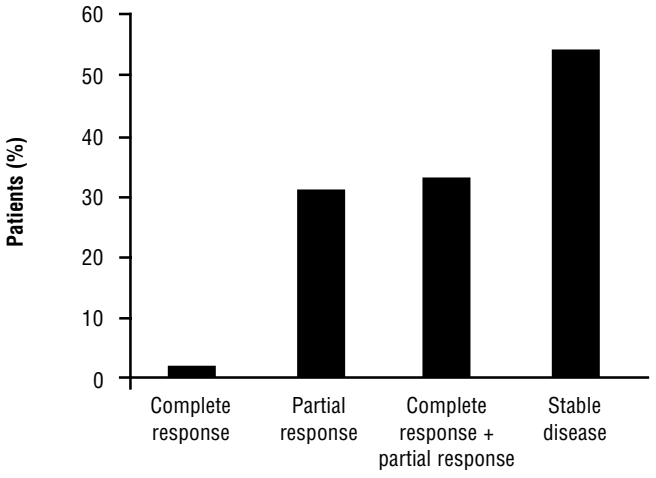

Figure 4. Response to Alemtuzumab

Note. Based on information from Keating et al., 2002.

intent-to-treat population (n = 93) was 33% (CR 2%, partial response 31%), according to National Cancer Institute-sponsored Working Group guidelines (Cheson et al., 1996). Median time to progression for responders was 9.5 months. Median survival was 16 months (95% confidence interval: 11.8, 24.8 months). Nineteen of 31 responders (61%) were alive 34 months after alemtuzumab therapy, and median survival had not yet been reached.

Infusion-Related Adverse Reactions

During the administration of alemtuzumab, a range of acute, infusion-related adverse reactions may occur (see Figure 5). Infusion-related events are most likely to occur during the initial or repeated dose-escalation infusions and have been seen most often at the 10 mg dosage, although rigors (seen in 90% of patients) and fevers (85% of patients) may be persistent throughout the course of treatment. These events may be severe in a small number of patients but generally are of grade one or two severity. Some infusion-related events may be related to rapid cytokine release after therapy with MAbs (Hainsworth, 2000), which may produce flu-like symptoms, rigors, bronchospasm, and hypoxia. Patients with particularly high tumor burden in the peripheral circulation also may be at risk for acute infusion-related reactions in the form of tumor lysis syndrome, in which release of intracellular products by cell lysis causes toxic effects, such as hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia. Such effects are more common and severe after treatment with the anti-CD20 MAb rituximab (Byrd et al., 1999). In patients with extensive lymphocytosis, electrolytes and renal function should be monitored daily during the first infusions of alemtuzumab, and allopurinol (not to exceed 800 mg per day, individual doses) should be initiated if indicated. In addition, adequate oral or IV hydration is essential to protect renal function.

Observations from several clinics suggest that, although infusion-related events with rituximab occur almost as soon as infusion begins, those associated with alemtuzumab tend to occur toward the end of infusion. Anecdotal reports exist of very high temperatures (> 102°C) beginning four hours after alemtuzumab infusions (A. Lynn, personal communication, June 3, 2002). Infusion-related events are likely to be more common and more severe if alemtuzumab infusions are given more than three days apart (Keating et al., 2002).

Infusion-related toxicity rapidly decreases with time, with, except for rashes, a substantial decrease in incidence from week one to weeks two through four.

Infusions should be stopped and physician contacted* if patient experiences
- Chills
- Rigors
- Shortness of breath
- Pain
- Dizziness
- Pruritus
- Vital signs out of the parameters given on treatment order.

Figure 5. Infusion-Related Symptoms

* In the event of grade three or four side effects, infusion should be stopped immediately.

Hematologic Side Effects

Anemia (hemoglobin < 9 g/dl) may be present before treatment because of invasion of bone marrow by cancer cells. Anemia may increase in the early stages of alemtuzumab treatment (weeks two through eight). Patients may benefit from irradiated leukocyte-depleted blood product transfusion or use of the growth factor erythropoietin to stimulate red blood cell production. Patients who respond to alemtuzumab generally experience resolution of existing anemia and the associated extreme fatigue.

Thrombocytopenia (platelets < 100 x 10^9/l) also is common prior to treatment with alemtuzumab and may worsen as a consequence of therapy. It may be very rapid in onset. Such platelet reduction may increase the chances of episodes of spontaneous bleeding, such as nosebleeds, increased bruising, or petechiae. Patients should be warned against taking aspirin, which also reduces blood-clotting times. Platelet counts measured within two hours of infusions may be very low, and platelet transfusions given within this period have little effect. However, platelet counts following subsequent infusions do not drop as rapidly or as severely, and counts will return to pretreatment levels within 48 hours after infusion.

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) is seen in about a quarter of patients with advanced disease. Worsening of neutropenia after alemtuzumab infusions may be significant. Some treatment centers stop treatment if ANC falls below 250/ml. Supportive therapy with granulocyte–colony-stimulating factor may be beneficial. This is routine practice at some centers. Patients who experience fevers after dose escalations of alemtuzumab have been completed should be evaluated for viral infections, particularly cytomegalovirus (CMV), associated with treatment-induced lymphopenia.

Opportunistic Infections

The spectrum of pathogens most commonly seen in patients with B-CLL is extensive, particularly after chemotherapy with alkylating agents and fludarabine therapy. Infectious complications occur in as many as 80% of patients with B-CLL as a consequence of disease (Morrison, 1998) and as a result of the immunosuppressive effects of prior therapies (Anaissie et al., 1998; Cheson, 1995). Alemtuzumab therapy in B-CLL may

increase this already heightened risk of infection. In the Keating et al. (2002) trial, a total of 55% of patients had infections (28% of patients had mild or moderate infections and 27% of patients had severe infections) and 12% had opportunistic infections during treatment. Septicemia occurred in 14 patients (15%). Severe (grade three or four) infection rates were much lower (10%) in responders. Five deaths were caused by infection and likely were related to treatment. Alemtuzumab therapy decreases CD4+ T cell counts during and for a prolonged period after treatment. Reduced CD4+ T cell counts, particularly counts less than 200/ml, have been implicated as increasing the risk of opportunistic infections in patients with AIDS (Kovacs & Masur, 2000). Decreases in ANC after alemtuzumab therapy also increase the risk of developing infections, such as herpes simplex, oral candidiasis, *Pneumocystis carinii* pneumonia, and CMV reactivation. In the absence of anti-infective medication, patients treated with alemtuzumab developed infections more often and with a wider range of organisms, including candidiasis, CMV, and gram-positive organisms (Lundin et al., 1998; Osterborg et al., 1997; Rai et al., 2002).

CMV reactivation may be life-threatening if unchecked. Tests to detect CMV-reactive antibodies are not diagnostic and should not be used for treatment decisions. A CMV-specific qualitative polymerase chain reaction (PCR) test result should be obtained prior to therapy with alemtuzumab. Therapy should be initiated only if this test is negative (CMV guidelines are available from Berlex Laboratories [Keating et al., 2003]). When a patient becomes febrile during treatment with alemtuzumab, the qualitative PCR test should be repeated. If, at any time, qualitative PCR is positive, the result should be confirmed by quantitative PCR. If the quantitative test is below the laboratory threshold, alemtuzumab may be continued, but a quantitative PCR test should be repeated weekly. If a rising titer is detected or if the titer exceeds the laboratory threshold, alemtuzumab should be discontinued and parenteral therapy with ganciclovir may be required. In addition, nurses should bring test results plus patient complaints and vital signs to the attention of physicians because some patients may need to be treated for opportunistic infections despite negative cultures.

Prophylaxis: Prophylactic therapy is a mandatory part of the alemtuzumab treatment protocol. The schedule of prophylaxis calls for sulfamethoxazole-trimethoprim double-strength twice daily three times per week and famciclovir (or an equivalent) twice daily. Pentamidine may be used for patients who are allergic or intolerant to sulfonamides. Preferably, antimicrobial prophylaxis should be initiated on day one of treatment, but certainly no later than day eight, and continued for a minimum of two months after completion of alemtuzumab therapy. Antifungal prophylaxis may be given at the discretion of the physician.

Administration

Preparation of infusion: The shelf life of undiluted alemtuzumab is 12 months when stored in a refrigerator at 2–8°C and protected from light. Alemtuzumab does not contain antimicrobial preservatives. The concentration of undiluted alemtuzumab is 10 mg/ml, and the ampule should not be shaken before dilution. The IV solution should be prepared as shown in Figure 6. Pregnant women should not handle alemtuzumab.

Day 1: 3 mg IV infusion[a]
Day 2: 10 mg IV infusion[a]
Day 3: 30 mg IV infusion[a]
Subsequent dosages: 30 mg IV three times a week[b]

Figure 6. Dose-Escalation Plan

[a] Monitor vital signs every 15 minutes and increase dose only in the absence of grade two or higher acute infusion-related events.

[b] For example, Monday, Wednesday, and Friday

Premedication and dose escalation: Premedication is necessary prior to the first dose of alemtuzumab, at each escalation of the dose, and with every subsequent dose. Diphenhydramine 25–50 mg (or an equivalent) should be given orally one hour before therapy or via IV 30 minutes before infusion. Acetaminophen 650 mg also is given one hour prior to infusion.

On the first day of therapy, the recommended dose is 3 mg of alemtuzumab IV over a period of at least two hours. If the dose is not well tolerated (e.g., rigors that do not respond to narcotics), the 3 mg dose is repeated on the following day (see Figure 7). Generally, escalation to the recommended therapeutic dose of 30 mg can be achieved in three to seven days. Single doses should not exceed 30 mg, nor should weekly cumulative doses exceed 90 mg. Treatment at 30 mg should then be given three times a week for as long as 12 weeks (Keating et al., 2003).

Patient monitoring: The protocol for administering alemtuzumab stresses the need for close monitoring of patients during infusions. Although impending reactions may provide few warning signs, anecdotal evidence suggests that the majority of patients appear to know when rigors are about to begin and may experience an aura.

Because treatment for infusion-related events must be administered promptly, the necessary drugs should be immediately available in the clinic throughout infusion. Even when nurses are not restricted in their use of such drugs, physicians should be available to advise or order the administration of appropriate medications in the event of acute reactions.

Infusion-related events also may occur toward the end of the two-hour infusion period or some time thereafter. Patients need to be advised of the possibility of delayed reactions and provided with appropriate medication prior to discharge from the clinic. The most suitable time to remind patients of the need to persist with prophylactic medications is when they leave the clinic after the final infusion.

During the dose-escalation period (and subsequently if the patient experiences adverse effects), the patient should be observed closely and frequently. Vital signs should be measured

- Withdraw 3, 10, or 30 mg alemtuzumab into a syringe under sterile conditions.
- Filter through a sterile, low protein-binding, nonfiber-releasing 5 µm filter into 100 ml 0.9% sodium chloride or 5% dextrose in water.
- Once diluted, use within eight hours.
- Do not use if
  - The product has been exposed to freezing temperatures.
  - The packaging freeze indicator has been activated.
  - Any particulate matter or discoloration is noticed.

Figure 7. Preparation Instructions

every 15 minutes during infusion and, if any of the signs detailed in Figure 5 are observed, for as long as eight hours after infusion. Oxygen saturation also should be monitored. The patients should be encouraged to drink plenty of water because dehydration worsens side effects. After dose escalation has been completed, the observation period can be reduced to two hours. At this stage, some patients may return to their workplaces after treatment. If so, replacing antihistamines that cause sedation with those that cause less sedation or decreasing doses appropriately may be advisable. This is an important intervention because alemtuzumab is administered as an outpatient treatment, and many patients expect to continue normal lifestyles, including returning to work, after treatment. However, patients should be cautioned to arrange transportation because driving is not advised.

If acute rigors are observed, infusion should be stopped and medication administered (IV diphenhydramine 50 mg plus meperidine 25–50 mg, if required). Infusion may be restarted when adverse effects subside. If no improvement occurs, hydrocortisone 50 mg may be effective. At some centers, antiemetics and H_2 blockers are used to reduce nausea and rashes and chills, respectively.

In subsequent infusions, a prophylactic regimen should be administered as a preventive measure. When the infusion is tolerated, the prophylactic medications can be withdrawn over a number of infusions in the following order: steroids, midinfusion diphenhydramine, and meperidine.

Postponement or dose modification: Treatment with alemtuzumab may cause hematologic toxicities, temporarily reducing the numbers of normal, essential blood cells. In the event of such toxicity (i.e., platelet count < 25,000/ml or ANC < 250/ml), alemtuzumab therapy should be withheld until blood counts rebound. After the first postponement resulting from hematologic toxicity, alemtuzumab therapy may be reinitiated at 30 mg. If hematologic toxicity occurs a second time, reinitiate therapy using 10 mg, provided that treatment did not need to be withheld for more than seven days. When treatment is withheld for longer than seven days, therapy must be reinitiated using the 3 mg dose. If a third postponement is indicated because of severe or life-threatening complications, alemtuzumab therapy should be discontinued permanently.

Timing of treatment discontinuation: Assessments are carried out at weeks 4, 8, and 12 to determine responses at various disease sites. Treatment may be discontinued permanently if patients experience a CR in which nodal disease, bone marrow, and blood are cleared of malignant cells. Patients can be retreated with alemtuzumab if they experience a relapse. If patients experience good partial response (marrow infiltration reduced to 15%–20%), treatments may be stopped and reinstated after 6–12 months.

Patient Education

Patients need to be given clear and comprehensive information about the nature, timing, and length of possible side effects before treatment is started. Compliance with prophylactic medication for infectious complications is of the highest importance. Positive features of treatment, such as the likely resolution of night sweats, reduced fever, better appetite, and decreased fatigue, also should be emphasized. Patients should be told that, during the first week, infusions may take as long as six hours and that they will be kept for observation. Patients may anticipate severe side effects unnecessarily if they previously have experienced acute vomiting or hair loss as a consequence of conventional chemotherapy. Alemtuzumab therapy does not cause hair loss; episodes of nausea or vomiting generally are mild and, therefore, can be managed using antiemetics.

Reassurance that effective medical treatments and premedications are available for infusion-related side effects can allay anxiety. Quality of life may decrease during the first few weeks of treatment (e.g., infusion-related symptoms, fatigue caused by anemia, episodes of spontaneous bleeding caused by thrombocytopenia), and patients may become disheartened. They should be encouraged to persevere because quality of life is likely to improve after this time. Nurses may help patients' motivation by teaching them to follow day-to-day changes in white blood cell counts because the period during which infusion-related side effects are most common and severe also is the time when the numbers of cancer cells can show the most dramatic reduction. Nurses also should point out that infusion-related side effects are most likely to occur during the initial dose-escalation infusions and tend to subside over time. Patients should be informed that they may not be able to drive home from their appointments during the first week and possibly during the entire period of therapy. In patients at high risk for tumor lysis syndrome, allopurinol therapy should be initiated and explained.

Patients and family members or caretakers should be warned to contact a doctor or nurse immediately if patients develop a temperature higher than 100.4°F (38°C), cough or sore throat (even without a temperature), or wound that does not heal, looks swollen, or is warm to touch. Patients should be advised to drink plenty of fluids and avoid products containing aspirin. Keeping a diary of medications taken and symptoms experienced also is useful.

Summary

For patients with advanced disease who have not responded to chemotherapy with alkylating agents and therapy with fludarabine, alemtuzumab offers a chance to achieve disease remission and improve survival. Without treatment, such patients might be expected to survive only nine months; with treatment, median survival can been increased to almost 16 months. Alemtuzumab also can improve quality of life (e.g., reduce anemia-related fatigue and discomfort caused by bulky nodes, alleviate symptoms such as night sweats) for patients who respond and for those whose disease stabilizes. Patients often express enthusiasm with improving laboratory tests and increased energy levels. For patients to gain the most benefit from treatment, alemtuzumab administration must be carried out according to the recommended protocols and appropriate prophylaxis must be given as indicated in this article. Nurses and patients should be educated about potential infusion-related side effects and aware of the signs and symptoms of opportunistic infections and cytopenia that may occur so that patients can be treated early for these adverse events. With these precautions, alemtuzumab treatment can be not only successful but also well tolerated.

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References

Anaissie, E.J., Kontoyiannis, D.P., O'Brien, S., Kantarjian, H., Robertson, L., Lerner, S., et al. (1998). Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Annals of Internal Medicine, 129,* 559–566.

Binet, J.L., Auquier, A., Dighiero, G., Chastang, C., Piguet, H., Goasguen, J., et al. (1981). A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer, 48,* 198–206.

Byrd, J.C., Waselenko, J.K., Maneatis, T.J., Murphy, T., Ward, F.T., Monahan, B.P., et al. (1999). Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. *Journal of Clinical Oncology, 17,* 791–795.

Cheson, B.D. (1995). Infectious and immunosuppressive complications of purine analog therapy. *Journal of Clinical Oncology, 13,* 2431–2448.

Cheson, B.D., Bennett, J.M., Grever, M., Kay, N., Keating, M.J., O'Brien, S., et al. (1996). National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. *Blood, 87,* 4990–4997.

Dighiero, G., & Binet, J.L. (2000). When and how to treat chronic lymphocytic leukemia. *New England Journal of Medicine, 343,* 1799–1801.

Edwards, B.K., Howe, H.L., Ries, L.A., Thun, M.J., Rosenberg, H.M., Yancik, R., et al. (2002). Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. *Cancer, 94,* 2766–2792.

Gilleece, M.H., & Dexter, T.M. (1993). Effect of Campath-1H antibody on human hematopoietic progenitors in vitro. *Blood, 82,* 807–812.

Hainsworth, J.D. (2000). Monoclonal antibody therapy in lymphoid malignancies. *Oncologist, 5,* 376–384.

Hoffman, M., Jansen, D., & Rai, K. (1999). Analysis of response to Campath-1H in patients with B-CLL progressing after fludarabine therapy [Abstract P129]. *Hematology and Cell Therapy International Workshop on Chronic Lymphocytic Leukemia, 42,* 109.

Keating, M., Coutre, S., Rai, K., Osterborg, A., Faderl, S., Kennedy, B., et al. (2003). *Management guidelines for clinical use of alemtuzumab in B-cell chronic lymphocytic leukemia.* Manuscript submitted for publication.

Keating, M.J., Flinn, I., Jain, V., Binet, J.L., Hillmen, P., Byrd, J., et al. (2002). Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. *Blood, 99,* 3554–3561.

Kovacs, J.A., & Masur, H. (2000). Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. *New England Journal of Medicine, 342,* 1416–1429.

Lundin, J., Osterborg, A., Brittinger, G., Crowther, D., Dombret, H., Engert, A., et al. (1998). CAMPATH-1H monoclonal antibody in therapy for previously treated low-grade non-Hodgkin's lymphomas: A phase II multicenter study. European Study Group of CAMPATH-1H Treatment in Low-Grade Non-Hodgkin's Lymphoma. *Journal of Clinical Oncology, 16,* 3257–3263.

Morrison, V.A. (1998). The infectious complications of chronic lymphocytic leukemia. *Seminars in Oncology, 25,* 98–106.

Osterborg, A., Dyer, M.J., Bunjes, D., Pangalis, G.A., Bastion, Y., Catovsky, D., et al. (1997). 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. *Journal of Clinical Oncology, 15,* 1567–1574.

Rai, K., Freter, C.B., Mercier, R.J., Cooper, M.R., Mitchell, B.S., Stadtmauer, E.A., et al. (2002). Alemtuzumab in previously treated chronic lymphatic leukemia patients who also had received fludarabine. *Journal of Clinical Oncology, 20,* 3891–3897.

Rai, K., & Keating, M. (1999). Chronic lymphocytic leukemia. In J.F. Holland & E. Frei (Eds.), *Cancer medicine* (pp. 2697–2718). Oxford, UK: Blackwell Science.

Rai, K.R., Sawitsky, A., Cronkite, E.P., Chanana, A.D., Levy, R.N., & Pasternack, B.S. (1975). Clinical staging of chronic lymphocytic leukemia. *Blood, 46,* 219–234.

Rai, K.R., & Stephenson, J. (2001). Monoclonal antibodies in cancer: The development of Campath-1H. In *Campath-1H: Emerging frontline therapy in chronic lymphocytic leukemia.* New York: Parthenon.

Ries, L.A., Wingo, P.A., Miller, D.S., Howe, H.L., Weir, H.K., Rosenberg, H.M., et al. (2000). The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. *Cancer, 88,* 2398–2424.

For more information . . .

- Chronic Lymphocytic Leukemia Education Network
  www.healthtalk.com/cllen
- Chronic Lymphocytic Leukemia Foundation
  www.cllfoundation.org
- Cancer.gov: Chronic Lymphocytic Leukemia
  http://www.cancer.gov/cancerinfo/pdq/treatment/CLL

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