Alemtuzumab (Campath® 1-H)

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Targeted monoclonal antibody therapy has become the standard of care in a number of hematologic malignancies. One such antibody, alemtuzumab (Campath® 1-H, manufactured by Millennium Pharmaceuticals, LP, San Antonio, TX, and ILEX Pharmaceuticals, Inc., Cambridge, MA, and ILEX Pharmaceuticals, Inc., Cambridge, MA, and ILEX manufactured by Millennium Pharmaceuticals, Inc. and on an advisory committee for Berlex Laboratories, respectively. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.)

Clinical Efficacy

Alemtuzumab has been used clinically since 1988. Its use in hematologic malignancies began with early pilot studies in patients with advanced non-Hodgkin lymphoma (NHL) when some activity was demonstrated. Phase II studies demonstrated activity in the blood, skin, and bone marrow but less effectiveness against lymphadenopathy and splenomegaly (Lundin et al., 1998). Lower-grade, less aggressive forms of NHL appear to have better response rates than higher-grade NHL. The variable expression of the target antigen CD52 in higher-grade lymphomas is theorized to account for its less than desirable outcomes (Moreton & Hillmen, 2003).

In contrast, alemtuzumab seems to have a more predictable response rate in B-cell chronic lymphocytic leukemia (B-CLL). In a pivotal study, Keating et al. (2002) studied 93 patients with relapsed or refractory B-CLL, all who had failed fludarabine therapy. These heavily pretreated patients then received 30 mg of IV alemtuzumab three times a week for a maximum of 12 weeks. An overall response rate of 33% was achieved, with two of the patients achieving a complete response (CR).

Lundin et al. (2002) studied alemtuzumab as first-line therapy in patients with B-CLL, administering the drug SQ instead of via the traditional IV delivery mode. They treated 38 patients, with an overall response rate of 87%. Among these patients, 7 (19%) achieved a CR. These promising results have continued to generate interest in alemtuzumab for other hematologic malignancies, such as peripheral T-cell malignancies. The World Health Organization included the following diseases in this class: T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia, natural killer cell leukemia, adult T-cell leukemia or lymphoma, and cutaneous T-cell lymphoma, including Sezary syndrome and mycosis fungoides. In a study of 39 patients with T-PLL treated with alemtuzumab, 60% had a CR and 16% had a partial response (PR) (Dearden et al., 2001). This study also demonstrated a prolonged survival in the patients who achieved CR (16 month median) compared to patients with PR (9 month median) or who did not respond (3 month median).

Alemtuzumab also has been studied in the transplant setting. The depletion of T cells by alemtuzumab is an effective mechanism to reduce graft-versus-host disease (GVHD), which remains an obstacle to successful allogeneic stem cell transplant. Kotardis et al. (2000) developed a novel nonmyeloablative conditioning regimen that included a total of 100 mg of alemtuzumab, fludarabine, and melphalan for patients undergoing matched, unrelated stem cell transplants. Forty-three patients were evaluated, with all but one patient having a sustainable graft. At a nine-month follow-up, 33 patients were alive in CR, 7 patients relapsed or progressed, and 4 died from regimen-related complications. Two patients developed grade 2 acute GVHD, and one patient developed chronic GVHD, but no cases of grades 3 or 4 GVHD were documented. More research is needed to evaluate optimal schedules and dosing of alemtuzumab to achieve the goals of decreasing GVHD and improving transplant outcomes.

Adverse Effects

As with most active agents, alemtuzumab has a number of side effects that must be anticipated to control the severity of symptoms and avoid serious complications. The risk of infection because of prolonged lymphopenia...
is a serious concern. The immunosuppression that alemtuzumab causes usually is compounded by the fact that most patients receiving the drug have had previous treatments with other chemotherapy agents that also cause immune compromise. In addition, for patients with B-CLL, the disease itself may predispose them to an increased risk of infection.

 Opportunistic infections, such as cytomegalovirus (CMV) and pneumocystis carinii pneumonia (PCP), are a significant concern when using alemtuzumab. Patients generally are treated with prophylactic antibiotics to avoid this complication. Patients are monitored weekly or biweekly for CMV reactivation during treatment and for six months after completion of therapy. In a review of 1,538 patients who received alemtuzumab, CMV infections occurred in 3.6% and was the cause of death in three cases (2.2%) (Williams, Roach, Rugg, & Brettmann, 2001). Montillo et al. (2002) observed no infectious episodes during treatment and for 24 weeks after treatment in nine patients with B-CLL treated with SQ alemtuzumab. However, weekly CMV monitoring revealed three patients (33%) with CMV reactivation post-treatment without development of clinical CMV disease. Treatment with ganciclovir restored antigenemia to negative in two to three weeks.

Hematologic toxicity is another common side effect associated with alemtuzumab. Lundin et al. (2002) found that 39% of patients experienced toxicity. The National Cancer Institute grade 2 anemia and 21% developed grade 4 neutropenia after a median period of four months. Rieger, von Grunhagen, Fietz, Thiel, and Knauf (2004) found similar results. This has led some investigators to inquire into different doses and schedules for alemtuzumab as well as prophylactic use of growth factor support for the anticipated fall in blood counts. As with most monoclonal antibodies, infusion-related toxicities are common and include fevers, rigors, hypotension, dyspnea, and nausea. These reactions are believed to be related to cytokine release during administration. Infusion reactions usually resolve or improve when patients have achieved the plateau dose of 30 mg thrice weekly; however, infusion reactions can occur 8–10 weeks into therapy. This is more likely if patients have had more than four days off treatment.

Alemtuzumab traditionally has been administered as an IV over two hours. This mode of drug delivery has invariably been associated with the infusion reactions mentioned previously, some of which may be severe. Such reactions are minimized by premedication regimens that usually involve acetaminophen, antihistamines, and corticosteroids. Meperidine, benzodiazepines, oxygen, and antiemetics often are used for symptom management during IV infusions.

**Novel Use of Alemtuzumab**

Investigations into the use of SQ alemtuzumab have been conducted recently. The considerable infusion-related side effects associated with IV alemtuzumab have prompted investigators to look at alternative routes of administration. Bowen et al. (1997) conducted a pilot study using SQ alemtuzumab after observing that patients who received the drug for rheumatoid arthritis experienced less first-dose side effects. This route of administration is thought to be better tolerated, more convenient, and just as efficacious as IV dosing. With better tolerability, patients most likely will receive the full dosing regimen of alemtuzumab, therefore requiring less premedication, less time in treatment rooms, and less nursing resources, all of which make the SQ route of administration more cost effective. To date, alemtuzumab has been studied at the same dose range, starting with 3 mg, increasing to 10 mg, and then reaching a plateau dose of 30 mg thrice weekly for up to 12 weeks. With this mode of delivery, only transient injection site skin reactions were noted, and traditional infusion reactions were rare or absent. Transient grade 4 neutropenia required the drug be held in seven patients; these patients were supported effectively with granulocyte-colony-stimulating factor. CMV reactivation occurred in four patients and was treated promptly with ganciclovir. Only one patient developed PCP, but this patient did not receive prophylaxis because of allergies. Long-term follow-up of these patients has shown that a non–dose-dependent lymphopenia persists; however, it is not associated with any increased risk of late occurring infections or the emergence of autoimmune disorders (Lundin et al., 2004).

**Summary**

Alemtuzumab is an exciting targeted therapy for patients with CD52-sensitive malignancies. The drug is being used in a variety of hematologic malignancies in different dosing schedules and different routes of administration. The Cancer and Leukemia Group B is conducting a study using alemtuzumab as consolidation treatment for patients with B-CLL. The group also is conducting a phase I and II dose-escalation study using alemtuzumab during intensification therapy in adults with untreated acute lymphoblastic leukemia. A national pharmaceutical protocol is actively accruing participants for a trial in which alemtuzumab is used in combination with fludarabine for relapsed and refractory B-CLL. The SQ route of administration is gaining popularity because it is highly effective with fewer side effects than IV infusions. Nurses administering alemtuzumab are in a unique position to...
ensure patient safety and tolerance of the therapy. By understanding the mechanism of action and the potential complications associated with alemtuzumab, nurses will be better able to provide optimal care to patients as the use of targeted monoclonal therapy continues to progress.

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References