



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, Inc., Cambridge, MA, and ILEX Pharmaceuticals, LP, San Antonio, TX, and distributed by Berlex, Inc., Montville, NJ), has shown promising results in a number of clinical trials. Alemtuzumab traditionally has been administered via IV and frequently is associated with significant infusion reactions. This has led investigators to evaluate a new approach to administration. Subcutaneous (SQ) administration of alemtuzumab is as effective as IV administration but with fewer infusion-related side effects (Lundin et al., 2002; Montillo et al., 2002).

Alemtuzumab is a humanized monoclonal antibody that targets the cell surface antigen CD52. CD52 is expressed on more than 95% of all normal B and T lymphocytes. It is also highly expressed on a variety of malignant cells but not on hematopoietic stem cells. Alemtuzumab's proposed mechanism of action is trifold: CD52 antibodies are thought to initiate the destruction of cells through antibody-dependent cell-mediated cytotoxicity, the activation of complement cascade (complement-dependent cytotoxicity), and induction of apoptosis (Villamor, Montserrat, & Colomer, 2003). Treatment with alemtuzumab renders patients lymphopenic within the first two to four weeks of treatment. Because the CD52 surface antigen is expressed on a number of different malignant cells, alemtuzumab has been studied in a variety of different hematologic diseases.

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 effectivity 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. Kottaridis 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

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