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Alemtuzumab for B-cell Chronic Lymphocytic Leukemia

Summary

- ✓ **Alemtuzumab, a humanized monoclonal antibody, is thought to destroy cancer cells through immune system stimulation or apoptosis induction (programmed cell death).**
- ✓ **In case series studies using alemtuzumab as salvage therapy, about a third of patients with B-cell chronic lymphocytic leukemia (B-CLL), who were otherwise refractory to chemotherapy, improved. Anti-tumour activity was also observed when the drug was used as first-line therapy or to treat minimal residual disease.**
- ✓ **Adverse events associated with alemtuzumab included "first-dose" flu-like symptoms, prolonged lymphopenia with a subsequent increased risk of opportunistic infections and viral reactivation (e.g., cytomegalovirus) and transient cytopenias.**
- ✓ **Data from randomized controlled trials (RCTs), focusing on clinical outcomes such as survival and patients' quality of life, are needed to accurately assess the harm and benefit of alemtuzumab.**

The Technology

Alemtuzumab is a humanized monoclonal antibody directed against the cell surface glycoprotein CD52, which is an antigen expressed on most lymphocytes and monocytes, but not on hematopoietic stem cells (precursors of normal blood elements).[1] It has been proposed that alemtuzumab could be used against cancer cells that express CD52 by binding to and destroying these cells through stimulation of the immune system or induction of apoptosis (programmed cell death).[1] This would lead to the removal of malignant lymphocytes from the blood, spleen and bone marrow.

Regulatory Status

Through the Special Access Programme (SAP), alemtuzumab has been available in Canada since May 2002 for the treatment of B-CLL. It is being reviewed by Health Canada for drug approval (Jean-Louis Stril, Berlex Canada Inc., Point-Claire, QC: personal communication, 2004 Dec 8). In the US, the Food and Drug Administration (FDA) approved alemtuzumab in May 2001 for the treatment of B-CLL in patients who have been treated with alkylating agents and have failed fludarabine therapy.[2] The approval was contingent on the completion, by November 2006,[2] of a randomized trial comparing alemtuzumab with chlorambucil in previously untreated patients with the progressing disease. Alemtuzumab is also approved in the European Union for the same indication.[1]

Patient Group

Ninety-five percent of chronic lymphocytic leukemia (CLL) originates from B-CLL. It is the most common leukemia afflicting adults in western countries.[3] In Canada, CLL represents 25% to 30% of the 3,900 new cases of all leukemias estimated in 2004.[1,4] The clinical course is typically indolent, but patients may present with variable symptoms, such as weight loss, extreme fatigue, fever or night sweats without evidence of infection, bleeding, anemia and symptomatic lymph node enlargement.[3,5] The median age at diagnosis of B-CLL is 64 years, with 10% to 15% of patients being under 50 years of age.[1] Individuals aged 35 years or younger are being diagnosed more frequently. The disease is staged according to the presence of lymphadenopathy or splenomegaly and the

features of bone marrow suppression, using either the American Rai system or the European Binet system.[5] Most patients are at an early stage of the disease when diagnosed and about 50% will never progress.[5] Laboratory determinants to evaluate prognosis are increasingly being used.[6] There are, however, no clear data to direct therapy according to prognostic stratification.

Current Practice

Treatment of B-CLL is aimed at controlling the disease and extending survival, but it is not curative.[5] In general, therapies are more appropriately determined by evaluating patients' comorbidities, functional status and preferences.

Oral alkylating agents (e.g., chlorambucil) are first-line therapy in elderly patients with B-CLL and few symptoms,[5] partly because of their low cost, easy application and low complication rates.[3,5] In patients with symptoms that require a more effective induction of remission, purine analogues (e.g., fludarabine) are increasingly used as a valid option for first-line therapy.[3] Fludarabine, compared with chlorambucil, induces a higher overall response rate (63% versus 37%); complete response rate (20% versus 4%) and longer progression-free survival, but it has not shown a survival advantage.[7] Combination of an alkylating agent and fludarabine offers no advantage.[8] Treatment options are scarce in patients who are refractory to purine analogue therapy, constituting a group with poor prognosis and median survival of 10 to 11 months.[6,9]

The Evidence

Alemtuzumab's effects have been studied in case series, most notably in chemotherapy–refractory or relapsed patients (i.e., salvage therapy),[10-13] but also to treat minimal residual disease (i.e., consolidation therapy).[14-17] It has also been studied in drug-naïve patients (i.e., first-line treatment).[18,19] The primary efficacy outcome in all studies was the overall response rates (ORR) as defined by the National Cancer Institute working group (NCIWG)[20] criteria. This included complete remission (CR) and partial remission (PR). Other endpoints included survival, duration of response and safety.

As salvage therapy, data from four published case series,[10-13] involving 182 patients, showed alemtuzumab treatment (30 mg three times weekly for ≤12 or 16 weeks), was associated with an ORR of 31% to 42% with a CR rate of 0% to 6%. Thus, approximately a third of patients with B-CLL improved during salvage therapy with alemtuzumab. In the largest of these trials,[10] responses were rapid with an overall median response time of one and a half months. Among patients, 83% showed responses in the blood and 26% in the bone marrow. Nodal responses were poor with bulky nodes >5 cm.[10] In this study, median survival in all patients was 16 months (32 months in responders).[10] Limited data derived from small case series in patients with relapsed or refractory B-CLL, using the subcutaneous route;[21] or involving combination therapy of alemtuzumab with fludarabine or rituximab (another monoclonal antibody), resulted in an ORR ≤83% and a CR ≤17%.[22,23]

As consolidation therapy, one RCT enrolled 21 patients with B-CLL; 11 to receive alemtuzumab and 10 to receive no further treatment after achieving partial or complete remission after first-line treatment with fludarabine alone or with cyclophosphamide.[17] The study was interrupted because of severe opportunistic infections in seven of the 11 patients treated with alemtuzumab, compared with two placebo recipients. These infections were successfully treated and were unassociated with the cumulative dose of alemtuzumab.[17] In this study, more patients treated with alemtuzumab converted to molecular remission (MRD undetectable by polymerase chain reaction) compared with the control group at a median of seven months follow-up (p=0.048).[17] At 21.4 months median follow-up, patients treated with alemtuzumab showed a significantly longer progression-free survival (no progression) compared with a mean progression-free survival of 24.7 months for the control patients (p=0.036).[17] Other consolidation therapy investigations have yielded similar results.[14-16] Longer follow-up periods

are essential to determine if these benefits translate into prolonged survival.

Alemtuzumab was assessed as first-line therapy in patients with B-CLL.[18,19] In the largest trial, 87% achieved an ORR with 19% achieving a CR.[18] In this study, the median time to disease progression was not reached at 18 months follow-up.

RCTs assessing alemtuzumab in patients with B-CLL are ongoing.[24,25] Good quality trials demonstrating increased survival have not been completed.

Adverse Effects

Adverse events associated with alemtuzumab included acute (first-dose) administration-related reactions, immunosuppression with subsequent infectious complications and hematological toxicities.[2] As salvage therapy, alemtuzumab was given to patients who have already undergone several stages of treatment. Thus, the infections and hematological toxicities of alemtuzumab under these conditions may be higher than expected.[26] First-line therapy with alemtuzumab might also be associated with less toxicity.[25]

Opportunistic infections are a limitation with alemtuzuamb treatment. In the largest of the three trials (salvage therapy), which involved 93 heavily pre-treated patients, opportunistic infections occurred in 55% of the patients; half of them were severe (grade 3 or 4).[10] These infections were at least partly due to profound immunosuppression (a decrease of both B- and T-lymphocytes) during alemtuzumab treatment. Out of 28 deaths occurring within the 180 days of follow-up, 11 were caused by infection that was likely related to treatment.[10] The high number of fludarabine cycles; the short time between the last dose of fludarabine and the start of alemtuzumab; and some patients' characteristics may have played a role. Viral reactivation, especially with cytomegalovirus (CMV), seems to occur frequently and may result in significant morbidity and potential mortality.[27,28] The treatments for CMV are expensive and have a potential for toxicity.

Administration and Cost

In clinical trials, alemtuzumab was titrated ≤2-hour intravenous (IV) infusion at a dose of 30 mg three times weekly for ≤12 weeks. Subcutaneous alemtuzumab achieved concentrations similar to those for IV alemtuzumab with reduced toxicity. It was associated, however, with two out of 32 patients forming anti-alemtuzumab antibodies of unknown clinical significance.[29]

The Patented Medicine Prices Review Board approved alemtuzumab at C$650 per 30 mg/3 mL ampoule.[30] Thus, a 12-week course will cost about C$23,400. The cost of concomitant medications, which include pre-medication with antihistamines, plus acetaminophen and anti-infective prophylaxis, need to be added. Expensive treatment for CMV might also be required.

Concurrent Developments

Rituximab is an antibody that binds to the cell surface antigen CD20, which is strictly expressed in B-CLL malignancies. Rituximab monotherapy has limited efficacy in B-CLL and responses are almost all PRs that are not durable.[6,31]

Targeting the proto-oncogene bcl-2, an anti-apoptosis protein that confers resistance to anti-cancer drugs, is another strategy being investigated.[32] A combination of fludarabine with oblimersen (Genasense™), antisense oligonucleotides directed against bcl-2, is in phase III trials for B-CLL.[6]

Rate of Technology Diffusion

There is potential for increased alemtuzumab use if the drug demonstrates a clinical advantage as first-line therapy in ongoing RCTs.[25]

Alemtuzumab was used off-label in indications such as T-cell prolymphocytic leukemia and other low-grade non-Hodgkin lymphoma; and to deplete T-cells to prevent graft rejection.[33] Decision makers should be aware of alemtuzumab's potential use in these unapproved indications.

Implementation Issues

Safety issues such as opportunistic infection cause concern.[17] Alemtuzumab should be used with appropriate safeguards.

While alemtuzumab is expensive, it is used when no alternative treatment is available (for patients with refractory B-CLL). Data on survival outcomes are needed to accurately estimate its cost-effectiveness.

It is anticipated that in future trials, patients will be stratified based on their leukemia cells' molecular and cytogenetic profiles, to clarify alemtuzumab's role in certain poor risk groups.[11]

Available data indicate that salvage therapy with alemtuzumab is associated with control of leukemia in approximately a third of patients, but it is also associated with harm. Without good quality data from RCTs, it is impossible to establish the role of alemtuzumab in patients with B-CLL.

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