Radioimmunotherapy with Yttrium-90 Ibritumomab Tiuxetan for Patients with Relapsed CD20+ B-cell Non-Hodgkin’s Lymphoma

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Current Treatment Options in Oncology 2002, 3:275–282
Current Science Inc. ISSN 1527-2729
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Opinion statement

The clinical development and US Food and Drug Administration approval in 1997 of the monoclonal anti-CD20 antibody rituximab have been major treatment advances for patients with B-cell non-Hodgkin’s lymphoma (NHL). Rituximab produces responses in approximately 50% of cases of relapsed, low grade NHL. Most of these responses are partial remissions; cure remains elusive. One way to enhance the effectiveness of monoclonal antibodies is to chelate radionuclides such as yttrium-90 (90Y) to the antibody. 90Y is a high-energy, beta-emitting radioisotope that delivers most of its radiation over a path length of 2 to 5 mm. Therefore, the antibody delivers, or targets, the radiation only to CD20+ cells, sparing normal cells from the radiation. Ibritumomab is the murine anti-CD20 antibody that was engineered to develop the human chimeric antibody rituximab. Tiuxetan is a linker/chelator that is attached to the antibody to form ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals, San Diego, CA). Zevalin can be reacted with 111Indium (111In) for imaging and 90Y for therapy. Phase I studies of Zevalin have determined that patients with a baseline platelet count greater than 150,000 × 10^6/L receive 0.4 mCi/kg. Patients with a platelet count of 100 to 149,000 × 10^6/L should receive 0.3 mCi/kg. Zevalin has a higher overall response rate (ORR) than its cold antibody counterpart rituximab, as demonstrated in two separate clinical trials. The first trial (IDEC 106-04) randomized 143 rituximab-naïve patients with relapsed NHL to receive rituximab or Zevalin. The ORR for Zevalin was 80% compared with 56% for rituximab (P = 0.002). The second trial (IDEC 106-06) tested the efficacy of Zevalin in patients who were rituxan-refractory; the ORR was 74%. The main toxicity of Zevalin was reversible myelosuppression. These studies indicate that radiolabeled anti-CD20 antibodies can produce a higher ORR than rituximab. Single-dose Zevalin is another treatment alternative for patients with relapsed low grade NHL. It is well-tolerated even by older adults. The exact role of Zevalin in the therapy of NHL is undetermined. New studies are underway to explore whether patients can safely receive a second dose of Zevalin and to combine Zevalin with high-dose chemotherapy and stem cell rescue. The outcome of these studies will be helpful in deciding how best to integrate this new modality into the treatment paradigm of NHL.
Introduction

The incidence of non-Hodgkin’s lymphoma (NHL) continues to increase without explanation [1]. In 2001, there were approximately 65,000 new cases of lymphoma in the United States. Although usually chemosensitive, most cases of NHL relapse after the initial treatment. For a minority of patients, autologous bone marrow or stem cell transplantation will result in prolonged disease-free survival or cure. For those who progress after salvage chemotherapy or transplantation, continuation of chemotherapy is often problematic because of the development of resistance. In addition, patients have increased susceptibility to the toxic side effects of the drugs. For many of these patients, NHL becomes a chronic disease that requires intermittent treatment and constant vigilance.

The availability of biologic agents such as monoclonal antibodies directed against lymphocyte antigens has made it possible to effectively treat patients who were heavily pretreated with chemotherapy or who had chemorefractory disease. Rituximab, a mouse/human chimeric antibody to the CD20 antigen, has achieved widespread use since it was approved in 1997 [2*]. Rituximab has an excellent safety profile consisting of infusion-related events but no significant myelosuppression [3]. Rituximab produces an overall response rate (ORR) of approximately 50%, although only 6% of these responses are complete [4].

Attempts to enhance the efficacy of these antibodies has been focused in two main areas, combinations of rituximab with chemotherapy [5,6] and linkage of a radioactive particle to the antibody to provide radioimmunotherapy (RIT). Ibritumomab is the murine immunoglobulin G1 monoclonal anti-CD20 antibody from which rituximab was engineered. To chelate radioisotopes to the antibody, a tiuxetan linker was attached to the ibritumomab to form Zevalin (IDEC Pharmaceuticals, San Diego, CA). Zevalin can be reacted with 111indium (111In) for tumor imaging or with yttrium-90 (90Y) for therapy. Extensive clinical trials have been conducted with other radioimmunoconjugates [7,8,9*, 10●, 11,12]. The most experience is with 131iodine-labeled tositumomab (Bexxar; Corixa, Seattle, WA) [9*,10●,13●,14●,15]. This review focuses on the clinical results obtained with Zevalin RIT.

Treatment

Indications

- The experience with Zevalin has been in the setting of a clinical trial. All the trials have required the patients to be in the relapse phase of disease and have the following eligibility criteria:
  - Relapsed low or intermediate grade NHL.
  - Measurable tumor greater than 2 cm in diameter.
  - Presence of CD20+ lymphoma cells.
  - Performance status 0, 1, or 2.
  - Bone marrow containing less than 25% involvement with NHL.
  - Platelet count greater than 100,000; absolute neutrophil count greater than 1500.
  - No central nervous system lymphoma.
  - No prior high-dose therapy with stem cells.
  - External beam radiation to less than 25% of bone marrow.
  - No prior radioimmunotherapy.
  - Blood absolute lymphocyte count less than 5000.
  - No evidence that the NHL is related to the AIDS virus.
- The criteria that the bone marrow contain less than 25% lymphoma has made it difficult to enroll patients with small lymphocytic NHL and mantle cell NHL because they frequently have extensive marrow involvement. Studies have not been performed in the patient group with more than 25% marrow involvement. Zevalin is indicated for patients with relapsed CD20+ low grade NHL. Table 1 briefly reviews the data from five clinical trials that support this indication.