Radioimmunotherapy of lymphoma

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SUMMARY

Radiolabeled monoclonal antibodies for the treatment of follicular low-grade non-Hodgkin's lymphoma have been available for several years in the United States and more recently throughout Europe. Since their introduction to treatment of refractory or relapsed patients, they have been evaluated for efficacy earlier in the course of the disease including so-called 1st line therapy in conjunction with initial chemotherapy and as consolidation therapy in patients who have achieved remission following a course of chemotherapy. It can be expected that these agents will become more widely available. Two agents are currently distributed commercially: Bexxar® consisting of 131I-labeled tositumomab and cold (unlabeled) tositumomab and Zevalin® consisting of 90Y-labeled Ibritumomab and cold rituximab. All 3 antibodies recognize a cell surface antigen, CD20, found on normal and malignant B lymphocytes characteristic of follicular lymphoma. The nomenclature: "…tumomab" indicates that it is a tumor murine monoclonal antibody while "…ximab" indicates that it is a chimeric molecule in which a portion of the murine IgG has been removed and replaced with an equivalent component of human IgG. Rituximab is available in many countries for use as an immunotherapeutic either alone in relapsed patients or in conjunction with standard chemotherapeutic regimen. Because of the limited access to the radiolabeled products in Australia, Harvey Turner and colleagues in Perth radioiodinated rituxan (the non-radioactive component of Zevalin®), developed a protocol similar to Bexxar® and obtained gratifyingly similar good results.Clinical use depends upon evidence of CD20 expression (usually available from biopsy material at diagnosis), confirmation of less than 25% of marrow involvement, platelet counts >100,000 and preferably 150,000 and granulocyte count > 3500. For either product, dosing is based on platelet count and body weight [up to 137% ideal weight). Zevalin® dosage is 15 MBq (0.4 mCi)/kg if platelets exceed 150K; 11 MBq (0.3 mCi)/kg between 100K-150K. Bexxar® administration is based on whole body radiation absorbed dose determined by measuring whole body counts on 3 occasions after administration of 185 MBq (5 mCi) of the 131I-tositumomab. In all instances, cold antibody is infused prior to the labeled component. In early studies, 67-80% of the patients achieved a partial or complete response of greater duration than in their prior treatment. More recently, when used as the 1st line or consolidation therapy, near 100% overall response rates have been observed.

Key words: *Lymphoma, Non-Hodgkin; Lymphoma, Follicular; Radioimmunotherapy; Antibodies, Monoclonal, Murine-Derived; Antibodies, Monoclonal; Radiopharmaceuticals*

During the period from 1960 to 1996, despite improvements in chemotherapy regimens, there was no improvement in the median probability of survival following diagnosis in patients with Low Grade Lymphoma, principally Follicular and Small Cell Lymphoma (the two most common histopathologic forms of Low Grade Non-Hodgkin's Lymphoma). Although therapy can often be delayed in the asymptomatic individual, once symptoms appear and require intervention, the pattern of the so-called "low grade lymphoma paradox" is observed; that is clinical disease relapse despite a good clinical response (seemingly a Complete Response [CR]) for months or years following chemotherapy with a median interval of Progression Fee Survival [PFS] approaching 10 years. Following relapse and re-treatment, the PFS is shorter than after the initial response. With each relapse, the subsequent PFS is shorter and shorter until in one report (prior to the introduction of immunotherapy), the duration of response was approximately 3 months (1). The introduction of immunotherapy using rituximab, a murine derived monoclonal antibody that recognizes the CD20 epitope which is regularly expressed on normal B cells and malignant clones derived from B cells, has improved the duration of PFS. Rituximab promotes apoptosis via several cytotoxic mechanisms. Although initially used following relapse of disease or in patients who had failed to respond to chemotherapeutic regimens, the clinical role of rituximab has progressed to where at the present time, it is now a routine component of most chemotherapeutic regimens. CHOP [Cyclophosphamide-Hydroxydaunorubicin-Oncovin (vincristine)-Prednisone] which had been the most frequent chemotherapeutic combination to treat follicular low grade lymphoma] has been succeeded by CHOP-R in which a course of rituximab infusions follows each cycle of CHOP. CVP has been replaced by CVP-R.

Radioimmunotherapy uses an anti-CD 20 antibody to deliver a β-emitting radionuclide to B-cells, thus providing whatever direct cytotoxic effect as a result of immunoglobulin fixation combined with a delivery of a local radiation flux, thus altering the life cycle of cells even if they have not been bound with antibody. As expected, radioimmunotherapy has resulted in further improvement in clinical responses compared to immunotherapy alone.

Zevalin®

This presentation will review the product Zevalin® which is the only commercial product currently available in Europe. Zevalin® is actually a regimen: a combination of the unlabeled anti-CD 20 antibody, rituximab, followed by an infusion of an Yttrium-90 [^{90}Y] labeled antibody, ibritumomab. Ibritumomab is a murine antibody from which rituximab, a chimeric

antibody, is derived. The anti-CD 20 portion is similar in both the rituximab and inbritumomab molecules. Rituximab infusion precedes administration of the radiolabled immunoglobulin in order to occupy the abundant CD 20 binding sites on circulating and splenic B-cells. Although somewhat counter-intuitive, tumor uptake of the radiolabeled form of the antibody is actually greater when non-radiolabeled immunoglobulin is infused prior to the infusion of the radiolabeled form. Initially, clinical studies involved the infusion of an Indium-111 labeled ibritumomab preceded by a rituxin infusion in order to obtain dosimetry data and confirm biodistribution of the radiolabeled immunoglobulin (Figure 1).

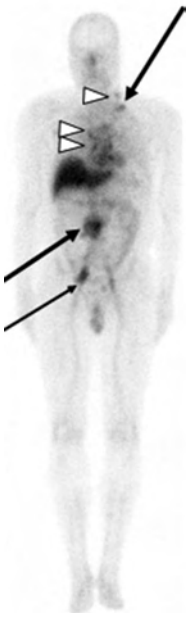

Figure 1. Planar anterior whole body scan obtained 72 hours after IV administration of 185 MBq ^{111}In-ibritumomab tiuxetan which had been preceded by an infusion of rituximab. White arrowheads indicate targeting of relatively small lymph nodes in the left neck and the right mediastinum. Black arrows indicate larger nodal masses in the left supraclavicular space, the mid-abdominal peri-aortic space and overlying the right iliac vessels. Note also that at 72 hrs, there is persistence of minimal cardiac blood pool and great vessel activity and no uptake in uninvolved organs other than the liver. In cases of mal-distribution, renal uptake has been seen as well as complete clearing of the vascular structures and soft tissues with most of the activity localizing in the liver.

Currently, within both the European and United States communities, use of the Indium-labeled form of the immunoglobulin followed by imaging is not required. Nevertheless, since the initial clinical trials involved the infusion of a potentially therapeutic amount of rituxin [450 mg/m^2], the entire regimen still consists of the initial infusion of rituximab alone followed one week later by a repeat infusion of rituximab followed by ^{90}Y-ibritumomab (15 MBq/kg if platelets are 150k/uL; 11 MBq/kg if platelets are >100k/uL, <150mm^2; maximum dose 4.44GBq).

In the initial efficacy trials comparing rituximab to Zevalin® in patients with indolent low grade lymphoma who had relapsed after chemotherapy, the Zevalin® regimen had an overall response rate [ORR] of 82% compared to rituximab alone which had an ORR of 33% with no Complete Responses [CR], By contrast, the Zevalin® treated group had 26% CR (2).

In a subsequent randomized trial comparing Zevalin® to rituximab in patients who had relapsed or been refractory to chemotherapy but were rituximab naïve, , Zevalin® had an 89% ORR compared to a 56% ORR in patients receiving only rituximab alone. Zevalin® had a 30% CR compared to 16% for rituximab (3). In general, patients with a CR have a longer PFS than patients only achieving a PR. The initial indication for use of Zevalin®, however, was in patients who had failed to respond to chemotherapy with rituximab or who had relapsed after responding to this regimen (Figure 2).

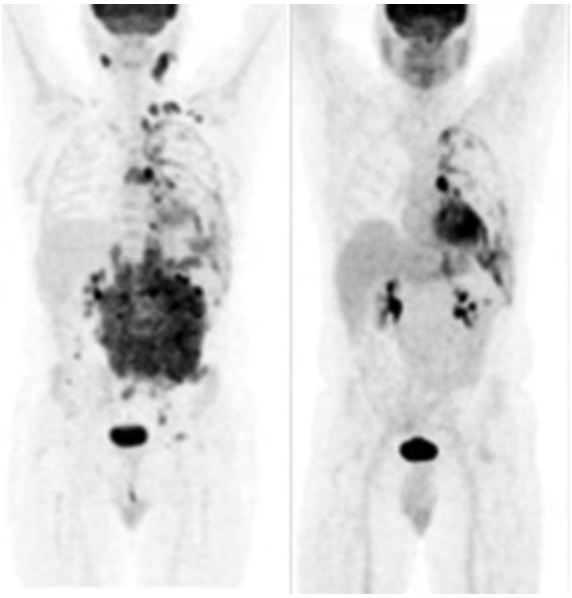

Figure 2. ^{18}FDG (fluoro deoxyglucose) PET volume [MIP] images pre-antiCD20 RIT demonstrating a very large abdominal lymphoma and smaller foci of nodal involvement in the mediastinum, left supra-clavicular area, left neck and right sub-mandular region. Repeat imaging at 5 ½ months demonstaring complete resolution of lymphoma activity. Persistant FDG-avid foci in the left chest represents granulation tissue from prior pleurectomy for tumor involvement. Patient is a 49 year old man who had been initially treated with CHOP in 1993; relapse in 1998 with a good response to rituximab. The patient was retreated with chemotherapy but relapsed in 2002 and again one year later.

More recently, it has been demonstrated that the use of Zevalin® in patients who did respond, that is they achieved a CR or PR following traditional chemotherapy such as CHOP, CHOP-R, CVP, CVP-R, or fludarabine, increases the median PFS three-fold (36 months vs 13 months). In patients achieving a CR, the median PFS in the group who received Zevalin® was 54 months (4).

The principal toxicity of Zevalin® therapy is hematologic with reduction of platelet count being the greatest concern. Patients should be monitored with complete blood and platelet counts weekly after infusion. In general, the platelets nadir from 4-7 weeks and generally return to about 80% of the ptre-therapy level. Many patients can be managed with observation alone but platelet infusions may become necessary. The absolute neutrophil count also may decline to 1000 cells/mm^2.

SUMMARY AND CONCLUSIONS

In general, clinical responses [CR; PR] with RIT used after relapse are greater, and of greater duration, than alternative or repeat chemotherapies.

- RIT is safe and effective even after multiple relapses following chemotherapy and/or rituximab [Rituxin®] therapy.

- The CR and ORR are even better when used as 1st line treatment in conjunction with chemotherapy or as "Consolidation" therapy.
- The principle toxicity of RIT of *Zevalin*® is hematologic; secondary to bone marrow irradiation from labeled antibody in blood and specific deposition on tumor cells in the bone marrow.
- Patients should be followed with weekly CBC and Platelet Count: supportive measures such as growth factors &/or transfusions may be required but serious consequences are rare.
- In the event of relapse (disease recurrence) after radioimmunotherapy, patients tolerate subsequent therapy as well or better than equivalent patients who have not received Radio Immuno Therapy.
- Radiation exposure of family members and health care personnel is low.

Conflict of interest

We declare no conflicts of interest.

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