Z-BEAM Transplantation

a report by
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Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoid malignancies that most commonly occur in individuals over the age of 60 years. Aggressive (high-grade) subtypes progress rapidly but are potentially curable, whereas indolent (low-grade) subtypes grow more slowly but usually relapse after conventional treatment. The introduction of immunotherapy and its combination with chemotherapy greatly improved remission rates compared with chemotherapy alone in NHL; more recently, the combination of immunotherapy plus yttrium-90 (^{90}Y) or iodine-131 (^{131}I) radiation has shown much greater efficacy than immunotherapy alone and may improve overall survival (OS).

The greatest challenge in NHL is keeping patients in remission once they have responded to therapy. Conventional chemotherapy for indolent lymphoma has a high response rate, but relapses will occur. Although patients may respond to salvage therapy, the duration of remissions decreases progressively. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has been shown to increase progression-free survival (PFS) with a two-year probability of 70%;[1] however, the curative potential in these patients is unclear.

Rationale for Using Yttrium-90–Ibritumomab Tiuxetan in Autologous Stem Cell Transplantation

NHL is inherently radiosensitive, providing a rationale for using radiation to treat lymphomas, and the targeted delivery of radiation directly to tumour sites is better tolerated and more efficient than total body irradiation (TBI). The principles of radiolabelled immunotherapy, which allows targeted delivery of a therapeutic dose of radiation not only to the surface of tumour cells at multiple sites but also to neighbouring deeper cells, have been reviewed extensively in recent publications.[2–4] The only radiolabelled immunoconjugates currently approved for the treatment of NHL are ^{90}Y–ibritumomab tiuxetan and ^{131}I–tositumomab (Bexxar®, GlaxoSmithKline, US; only approved in the US), both of which are directed against the CD20 cell surface antigen. ^{90}Y-ibritumomab tiuxetan comprises the anti-CD20 monoclonal antibody ibritumomab, conjugated via the tiuxetan chelator to the pure beta-emitting radioisotope ^{90}Y. It is currently approved for the treatment of adult patients with rituximab-relapsed or -refractory CD20-positive follicular B cell-NHL, and is the only therapy approved for use after rituximab failure. Adverse events with ^{90}Y–ibritumomab tiuxetan are predictable and manageable, with the primary toxicity being transient reversible haematotoxicity, as expected.

No preparative regimens prior to ASCT have been shown to be clearly superior and none has ever been tested in a randomised study. Fractionated TBI has been used in the past, especially in indolent lymphoid malignancies, with encouraging results, but is not recommended for patients above 60 years of age or for those treated with previous radiotherapy.

Therefore, radiolabelled immunotherapy agents such as ^{90}Y–ibritumomab tiuxetan are likely to play an increasingly significant role in ASCT by increasing the efficacy of the conditioning regimen and reducing the relapse risk. Owing to its good tolerability profile, the use of ^{90}Y–ibritumomab tiuxetan at high doses as the sole conditioning agent in place of HDC is also showing promise, and may allow transplantation in patients who cannot tolerate the more aggressive conditioning regimens, such as the elderly or those with co-morbidities (especially cardiovascular disease). The dose-limiting toxicity of radiolabelled immunotherapy is haematotoxicity, which can be circumvented by ASCT and may allow further dose escalation.

Standard-dose Yttrium-90–Ibritumomab Tiuxetan Associated with BEAM Chemotherapy plus Autologous Stem Cell Transplantation

Experience has been gained in several phase II studies with the combination of Zevalin with other conditioning regimens before auto- or allotransplantion.[5] The Groupe d'Etude des Lymphomes de l'Adulte (GELA) in France investigated the Z-BEAM conditioning regimen prior to ASTC in patients with relapsing low-grade NHL.[6] Radiolabelled immunotherapy ^{90}Y–ibritumomab tiuxetan (Zevalin) is effective in B-cell lymphoma and delivers targeted radiation without TBI toxicity. To take advantage of this antilymphoma effect, a conventional dose of ^{90}Y–ibritumomab tiuxetan 15MBq/kg (maximum total dose 1,200MBq) was given without dosimetry on day -14 before ASCT and combined with a standard-dose BEAM regimen starting at day -7.

The goal of this phase II study was to evaluate the efficacy and toxicity of Z-BEAM. Patients <65 years of age with CD20+ low-grade B-cell lymphoma in first or second relapses, or not achieving complete

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Table 1: Hemato Recovery After Autologous Transplantation

Median CD 34+ 10^6/kg: 5.2 (96% received > 3.10^6); n=75	
Delays to	Median days
Neutrophils >0.5g/l	12 (8–31)
Neutrophils >1g/l	12 (8–35)
Platelets >20g/l	12 (3–42)
Median red blood transfusions: 2	
Median platelets transfusions: 4	
Growth factor post-transplantation	
Yes	60 (80%)
No	15 (20%)

Figure 1: Z-BEAM

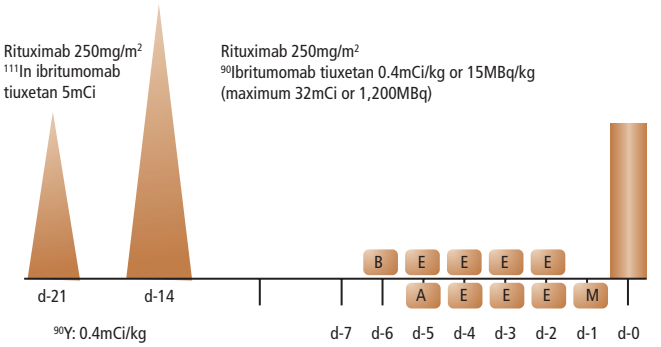

Table 2: Selected Ongoing Phase I/II Studies of Standard-dose Radiolabelled Immunotherapy plus High-dose BEAM Prior to Autologous Stem Cell Transplant

Study	n	Patient Population	Conditioning Regimen	Results
Shimoni et al., Israel	23	DLBCL (n=15) Transformed low-grade (n=7) MCL (n=1)	Z-BEAM	Projected two-year OS 67% (95% CI 46–87) Two-year cumulative relapse 32% (95% CI 17–60) Estimated one-year OS 59% Estimated one-year PFS 49%
Gisselbrecht et al., GELA, France	77	Low-grade refractory/relapsed FL (n=68) or MZL (n=6)	Z-BEAM (n=75)	Median recovery: Neutrophils >0.5g/l 11 days (range: 9–31) Neutrophils >1g/l 12 days (range: 9–35) Platelets >20g/l 12 days (range: 5–42)
Krishnan et al., US	41	DLBCL, FL grade I–III, transformed, MCL	Z-BEAM	Two-year OS 88% Two-year PFS 69%
Khouri et al., US	26	Relapsed FL, DLBCL, MCL	Z-BEAM	Estimated two-year OS 92% Estimated two-year PFS 83%

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZ = marginal zone lymphoma; PFS = progression-free survival; OS = overall survival; R = rituximab; Z = ^{90}Y-ibritumomab tiuxetan (Zevalin®).

remission after first-line treatment, were included in the trial. They had to be chemosensitive to prior salvage therapy, have had no more than three lines of treatment and be eligible for ASCT. The primary end-point was to detect a two-year event-free survival (EFS) rate of at least 80%. Haematological reconstitution was evaluated after transplant and during the first year of follow-up. Between March 2005 and August 2006, 77 patients were included. Patient characteristics at last salvage chemotherapy inclusion were: 68 follicular lymphoma, six marginal zone and one mantle cell plus two transformed histology after pathological review; median age 53 years (range 31–64); follicular lymphoma international prognostic index (FLIPI) low-risk 32, intermediate-risk 20, high-risk 20; and 24 bone marrow involvement. Thirty-nine patients had first relapse, 10 second relapse, 21 partial response (PR), four stable disease and three progressive disease after first-line treatment.

Median delay between first-line therapy and ASCT was 31 months and median delay between last salvage and ASCT was 4.4 months. Response rates before ASCT were complete response (CR) and complete response unconfirmed (CRu) 77%, PR 22% and stable 1%. As first-line treatment, patients received mostly cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), associated in 29 cases with rituximab. Twenty-nine patients received a second-line chemotherapy with rituximab in 22 cases prior to last salvage chemotherapy; 49 patients after first-line treatment received directly after relapse another line of chemotherapy before ASCT. Overall, among the 77 patients, last salvage chemotherapy regimen included rituximab in 74, and ASCT was performed in 75. The haematological reconstitution after Z-BEAM followed by ASCT in 75 patients was: time to neutrophils >1g/l 12 days (9–35) and time to platelets >20g/l 12 days (range three to 42).

Median number of platelet transfusions was four; median number of red blood cell transfusions was two. Grade 3–4 toxicities were infection (83%), mucositis (47%) and pulmonary (4%). Safety data indicated 35 serious adverse events in 24 patients; these did not appear to significantly differ from those usually seen after ASCT is performed. No cases of toxic death were observed. At weeks 12 and 42 after ASCT, median haemoglobin levels were 11.6g/dl and 11.3g/dl, respectively. Median platelets counts were 111g/l and 148g/l and leukocyte counts were 3.48g/l and 4.80g/l, respectively. After transplant, 91% of the patients were in CR or CRu. Only five adverse events were reported. After a minimum follow-up of one year for all patients, estimated event-free survival (EFS) was 93%. Z-BEAM is a safe conditioning regimen that can be used for B-cell lymphoma. Longer follow-up is necessary to evaluate long-term toxicity and efficacy.

The Z-BEAM regimen is used in other types of lymphoma, for example in those patients who are ineligible for TBI due to older age or prior radiotherapy. The group of City of Hope was a pioneer in their domain and reported their experience[7] of a study of 41 patients with a median age of 60 years. Disease histology were diffuse large B-cell (n=20), mantle-cell (n=13), follicular (n=4) and transformed (n=4) lymphoma. There was a median follow-up of 18.4 months and the estimated two-year OS and PFS were 88.9 and 69.8%, respectively.

Shimoni and others[8,9] have investigated the inclusion of standard-dose ^{90}Y–ibritumomab tiuxetan in the conditioning regimen prior to ASCT in refractory, aggressive NHL expected to have poor outcome with standard conditioning (see *Table 2*). Presence of active disease was determined using positron emission tomography (PET) and computed tomography (CT) scanning. Overall, 11 patients had primary refractory disease, 12 had

refractory relapsed disease and 14 had bulky disease at transplant. Patients received the Z-BEAM conditioning regimen. All patients engrafted rapidly, in a median of 10 days (range 10–22 days).

Overall, 16 of 21 evaluable patients achieved a CR (76%): 11 achieved a CR, nine achieved a PR, of whom five converted to CR with additional radiation therapy to eliminate residual disease. After a median follow-up of 17 months (range six to 27 months), 16 of 23 patients were alive. Non-relapse mortality at day 100 in these heavily-pre-treated refractory patients was 9% (95% confidence interval [CI] 2–33). There was no apparent additional toxicity related to the use of ^{90}Y–ibritumomab tiuxetan and the investigators concluded that its inclusion in this conditioning regimen was relatively safe and improved outcomes in patients with refractory lymphoma.

> Clear eligibility criteria should be included to define a homogenous population of lymphoma patients and those with a poor prognosis.

Escalating-dose ^{90}Y–ibritumomab tiuxetan (0.3–1.2mCi/kg) plus high-dose BEAM was investigated in a phase I trial of relapsed or refractory CD20-positive NHL.[10,11] Based on dosimetry results, patient-specific doses of ^{90}Y–ibritumomab tiuxetan calculated to deliver escalating radiation doses (300–2,100cGy) to critical organs (liver, lung or kidney) were administered. The median age of the patients was 54 years (range 25–72 years) and most had received three or more treatment regimens, including rituximab. The toxicity profile of the ^{90}Y–ibritumomab tiuxetan-containing conditioning regimen was similar to that seen with high-dose BEAM alone. The most common grade III or IV toxicities were infection, fever, stomatitis, nausea, vomiting, diarrhoea, haemorrhage and oedema. Engraftment was rapid and three-year OS and PFS rates were good.

Tolerability

These preliminary data indicate that ^{90}Y–ibritumomab tiuxetan at standard- and high-/escalating-dose was well tolerated as a component of transplant-conditioning regimens. Toxicity profiles were similar to those seen with other high-dose regimens such as TBI, etoposide and cyclophosphamide, with no additional toxicity and no adverse events or allergic reactions specifically attributed to ^{90}Y–ibritumomab tiuxetan. Adverse events observed following ^{90}Y–ibritumomab tiuxetan plus HDC and transplant were as expected and included skin rashes, nausea/vomiting, mucositis, infection and cardiac, pulmonary and hepatic toxicity. In studies where ^{90}Y–ibritumomab tiuxetan was the sole myeloablative agent, adverse events were as expected for monotherapy (neutropoenia, infections) and were relatively mild. The most frequent, severe complications normally seen with conventional HDC conditioning were not observed. Tolerability findings were similar in ^{131}I–tositumomab studies; abnormal levels of thyroid-stimulating hormone were also frequently observed following ^{131}I–tositumomab-based conditioning.

Conventional chemotherapy for NHL is associated with an increased risk of myelodyspalstic syndrome. This usually develops within 10 years of treatment exposure. Analysis estimated the risk of myelodysplastic syndrome or acute myeloid leukaemia in NHL patients receiving high-dose chemotherapy and ASCT to be between 5 and 10%. Clinical data for ^{90}Y–ibritumomab tiuxetan in 746 patients reported 17 myelodysplastic syndromes, with an annualised rate of 0.7% from the time of treatment, indicating that there is no increase in risk compared with conventional chemotherapy.[12]

Current and Future Directions for Yttrium-90–Ibritumomab Tiuxetan in Autologous Stem Cell Transplantation

There is still a substantial need to further improve conditioning regimens in SCT through a safe treatment modality. The high relapse rates observed after ASCT suggest that most conditioning regimens are inadequate and more effective options are needed. Radiolabelled immunotherapy, in particular ^{90}Y–ibritumomab tiuxetan, has shown great promise as part of conditioning regimens both as high-dose monotherapy and at standard- and escalated-dose alongside HDC, and appears to offer an effective and well-tolerated alternative to TBI.

Future research to evaluate the role of ^{90}Y–ibritumomab tiuxetan alone with peripheral blood SC support should take a stepwise approach, focusing initially on phase II studies in patients with different histological NHL subtypes. Clear eligibility criteria should be included to define a homogenous population of lymphoma patients and those with a poor prognosis. Research also needs to be carried out with ^{90}Y–ibritumomab tiuxetan as first-line therapy and following relapse. Subsequently, these results can be compared with a standard regimen in historical controls before making the decision to move on to randomised studies in poor-prognosis NHL patients. ■

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Pregnancy and lactation. **Undesirable effects:** The radiation dose resulting from therapeutic exposure may result in secondary malignancies and in development of hereditary defects. It is necessary to ensure that the risks of the radiation are less than from the disease itself. The majority of patients may be expected to experience adverse reactions. The frequencies of the adverse reactions reported below (very common ≥10%, common ≥1 to <10%, uncommon <1%) are based on clinical trial data irrespective of causality. Anaphylactic reactions and hypersensitivity. Anaphylactic and other hypersensitivity reactions have been reported in less than 1% of patients following the intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of Zevalin®. Haematological adverse reactions. Haematological toxicity has been very commonly observed in clinical trials, and is dose-limiting. Median time to blood platelet and granulocyte nadirs were around 60 days after start of treatment. Grade 3 or 4 thrombocytopenia was reported with median times to recovery of 13 and 21 days and grade 3 or 4 neutropenia with median times to recovery of 8 and 14 days. Infections. During the first 13 weeks after treatment with Zevalin®, patients very commonly developed infections. Grade 3 and grade 4 infections were reported commonly. During follow-up, infections occurred commonly. Of these, grade 3 w as common, grade 4 uncommon. Secondary malignancies. Myelodysplasia/acute myeloid leukaemia (AML) has been reported in five out of 211 patients assigned to treatment with Zevalin®. The risk of developing secondary myelodysplasia or leukaemia following therapy with alkylating agents is well known. Since all of these patients were pre-treated with alkylating agents, available results provide insufficient data on whether Zevalin® contributes to an increased risk of myelodysplasia, or on the extent of risk. Incidence of adverse reactions by body system. Blood and lymphatic system disorders, very common: Anemia, leukocytopenia, neutropenia, thrombocytopenia; common: Febrile neutropenia, lymphocytopenia, pancytopenia. Gastrointestinal disorders, very common: Nausea; common: Abdominal pain, constipation, diarrhoea, dyspepsia, throat irritation, vomiting. General disorders and administration site conditions, very common: Asthenia, pyrexia, rigors; common: Flu syndrome, hemorrhage while thrombocytopenic, malaise, pain, peripheral edema. Immune system disorders, common: Hypersensitivity. Infections and infestations, common: Infection, Oral moniliasis, Pneumonia, Sepsis, Urinary tract infection. Metabolism and nutrition disorders, common: Anorexia. Musculoskeletal, connective tissue and bone disorders, common: Arthralgia, back pain, myalgia, neck pain. Neoplasms (benign and malignant), common: Tumour pain. Nervous system disorders, common: Dizziness (except vertigo), headache, insomnia. Psychiatric disorders, common: Anxiety. Respiratory, thoracic, and mediastinal disorders, common: Cough, rhinitis. Skin and subcutaneous tissue disorders, common: Pruritus, rash, sweating increased. **Special warnings and special precautions for use:** Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides. This radiopharmaceutical may be received, used and administered only by authorised persons in designated settings. Its receipt, storage, use, transfer, and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals. 90Y-radiolabelled Zevalin® should not be administered to patients who are likely to develop life-threatening haematological toxicity signs. Zevalin® should not be administered in the patients mentioned below as safety and efficacy has not been established: = patients in whom more than 25% of the bone marrow has been infiltrated by lymphoma cells, = patients who have received prior external beam radiation involving more than 25% of active bone marrow, = patients with platelet counts <100,000/µl or neutrophil counts <1,500/µl, = patients who have received prior bone marrow transplant or stem cell support, = children and adolescents under 18 years of age. Special caution is required with respect to bone marrow depletion. Patients who had received murine-derived proteins before Zevalin® treatment, should be tested for human anti-mouse antibodies (HAMA). Patients who have developed HAMA may have allergic or hypersensitivity reactions when treated with Zevalin® or other murine-derived proteins. Severe infusion reactions may occur during or following rituximab infusion, which may be associated with chest pain, cardiogenic shock, myocardial infarction, pulmonary edema, ventricular fibrillation, apnea, bronchospasm, dyspnea, hypoxia, angioneurotic edema, flushing, hypotension, acute respiratory distress syndrome, and lung infiltration. Infusion–related reactions due to Zevalin® are less common and less severe. Anaphylactic and other hypersensitivity reactions have been reported in less than 1% of patients following the intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g. adrenaline, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of Zevalin®. After use of Zevalin®, patients should generally be tested for HAMA before any further treatment with mouse derived proteins. Severe mucocutaneous reactions, including Stevens-Johnson Syndrome with fatal outcome, have rarely been reported in association with the Zevalin® therapeutic regimen, which includes rituximab and radiolabelled Zevalin®. Long-term animal studies on the effect on fertility and reproductive function have not been performed. Due to the nature of the compound, females of childbearing potential, as well as males, should use effective contraceptive measures during treatment with Zevalin® and for 12 months afterwards. The safety of immunisation with any vaccine, particularly live viral vaccines, following therapy with Zevalin® has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied. **Date of revision of the text:** March 2007 **Please note!** For current prescribing information refer to the package insert and/or contact your local Bayer Schering Pharma organization. Bayer Schering Pharma AG, 13342 Berlin, Germany

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