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^{90}Y-ibritumumab tiuxetan (Zevalin)

Introduction

There is currently a range of different treatments available for the treatment of non-Hodgkin's lymphoma (NHL). These include the more traditional therapies such as conventional cytotoxic agents, used alone, in combinations or as high-dose therapy with stem cell support; radiation therapy, which is recognized to be important as NHL is a highly radiosensitive tumour; and the newer biological therapies. Of the biological therapies, immunotherapy with the monoclonal antibody (mAb), rituximab, is perhaps the best established. A further development that combines the recognized benefits of radiotherapy and immunotherapy is the introduction of radiolabelled immunotherapy. This approach utilizes the specificity of an mAb to target the cytotoxic effects of radiotherapy towards antigen-positive tumour cells, thus delivering a high dose of radiation to the tumour and minimizing exposure of other organs and tissues to radiation. In addition, the 'cross-fire' activity of the radiation allows it to penetrate into surrounding tumour tissue, overcoming the problem of limited access in bulky or poorly vascularized tumours.

The most widely studied radiolabelled immunotherapy to date is ^{90}yttrium (^{90}Y)-ibritumomab tiuxetan. This consists of the murine mAb, ibritumomab, which binds to the CD20 antigen that is specifically expressed on B-cells, and tiuxetan, a high-affinity chelator for the radionucleotide, ^{90}Y. ^{90}Y is a beta emitter with a short half-life (64 hours),[1] with a long path length in soft tissue (5.34 mm). Its properties mean that tumour cells that are inaccessible to the radioimmunoconjugate can be killed by energy released from the radioimmunoconjugate bound to neighbouring cells. Unusually, ^{90}Y is a pure beta emitter. This means it can be used in an outpatient setting without patient restrictions in most EU countries.

^{90}Y-ibritumomab tiuxetan is currently indicated for the treatment of adult patients with rituximab relapsed or refractory CD20^{+} follicular B-cell NHL,[2] and it is also being investigated for other treatment options including as first-line, and first-line consolidation therapy. This short review provides an overview of some of the key clinical studies and ongoing clinical trials.

Dose and schedule for ^{90}Y-ibritumomab tiuxetan

^{90}Y-ibritumomab tiuxetan is administered as part of a regimen using reduced pre-doses of ritux-

imab. Rituximab is used to eliminate circulating CD20+ B-lymphocytes and to enable ^{90}Y-ibritumomab tiuxetan to deliver high-energy beta particles specifically to the lymphoma. Treatment consists of two iv doses of rituximab followed by a single dose of ^{90}Y-ibritumomab tiuxetan in the following order[2]:

- day 1: rituximab, 250 mg/m^2 iv
- day 7, 8 or 9: rituximab, 250 mg/m^2 iv, followed by ^{90}Y-ibritumomab tiuxetan iv (10 minute 'slow push'), up to a maximum dose of 1200 MBq.

Safety profile of ^{90}Y-ibritumomab tiuxetan

Studies have shown that when administered at the standard dose ^{90}Y-ibritumomab tiuxetan is well tolerated. The main toxicities are haematological with nadir counts occurring 7-9 weeks after ^{90}Y-ibritumomab tiuxetan therapy as determined in an analysis of safety data for 349 patients with NHL who received ^{90}Y-ibritumomab tiuxetan in five studies.[3] According to this analysis, 30% of patients developed grade 4 neutropenia, 10% developed grade 4 thrombocytopenia, and 4% developed grade 4 anaemia. The median duration of severe (grade 3/4) haematological toxicities was approximately 1-4 weeks. Severe non-haematological toxicities are relatively infrequent; according to this analysis, only 11% of patients reported severe treatment-related non-haematological adverse events, the most frequent being asthenia (2%) and abdominal pain (1%). Most non-haematological toxicities were mild or moderate in severity (grade 1 or 2).[3] In addition, data from a large randomized study comparing ^{90}Y-ibritumomab tiuxetan (n=73) and rituximab (n=70) in patients with relapsed or refractory NHL found that the incidence of non-haematological adverse events was similar for the two treatment groups.[4] The three most common non-haematological adverse events in each group were asthenia (44% *vs.* 41%), nausea (43% *vs.* 19%) and chills (25% *vs*. 29%) for patients receiving ^{90}Y-ibritumomab tiuxetan or rituximab, respectively.[4]

As with radiotherapy, radio-labelled immunotherapy exposes the body to low doses of radiation. This may raise concerns about possible long-term effects of radiation on the bone marrow, which could in turn give rise to myelodysplastic syndrome (MDS) or acute myelogenous leukaemia (AML). To address these concerns, Czuczman *et al.* have analyzed data from 746 patients with NHL treated with ^{90}Y-ibritumomab tiuxetan between 1996 and 2002.5 They found that the incidence of MDS and AML was low (2.3%) and was consistent with that expected on the basis of the patients' treatment history. Most patients had previously received other treatments (median number of previous treatments, 3; range 0-9+); previous treatment with a purine nucleoside analogue was found to be a significant risk factor for MDS or AML (hazard ratio 3.9; p=0.006. Indeed, the frequent use of chlorambucil in the USA during this period may also have contributed to the incidence of MDS and AML. The annualized rates of developing these malignacies were reported to be 0.3% one year after diagnosis of NHL and 0.7% one year after receiving the radioimmunotherapy.[5]

^{90}Y-ibritumomab tiuxetan in relapsed or refractory follicular lymphoma

^{90}Y-ibritumomab tiuxetan has been extensively investigated as treatment for patients with follicular lymphoma who relapse or are refractory to previous therapy, including patients with bulky disease (tumour ≥5 cm).[4,6–9]

The efficacy of ^{90}Y-ibritumomab tiuxetan has been demonstrated in a large multicentre randomized study involving 143 patients that was

first reported in 2002,[4] with subsequent follow-up data reported in 20046. Patients were randomized to receive either ^{90}Y-ibritumomab tiuxetan treatment or rituximab. Patients in the ^{90}Y-ibritumomab tiuxetan group received ^{111}indium-ibritumomab tiuxetan, 5 mCi, (for dosimetry) and rituximab, 250 mg/m^2 iv on day 1 followed by ^{90}Y-ibritumomab tiuxetan, 0.4 mCi/kg iv and rituximab, 250 mg/m^2 iv on day 8, while patients in the rituximab group received four once-weekly doses of rituximab, 375 mg/m^2 iv.[4,6] The initial data revealed that patients receiving ^{90}Y-ibritumomab tiuxetan therapy had a significantly better overall response rate (80% [58/73] *vs.* 56% [39/70]; p=0.002) and complete response (CR)/unconfirmed CR according to International Workshop NHL Response Criteria (IWRC) (34% [25/73] vs 20% [14/70]; p=0.040) than patients receiving rituximab therapy, respectively.3 The increased response rate observed with ^{90}Y-ibritumomab tiuxetan was found to translate into an increased time to progression (TTP), time to next anticancer treatment (TTNT) and duration of response (DR) compared with the rituximab group, as reported in the follow-up publication.[6] This was observed both for the subgroup of patients with follicular lymphoma (n=113) and for all patients (n=143). The differences were not statistically significant as the study was powered to detect a significant difference in the primary endpoint, ORR, but not in secondary endpoints.[6]

Long-term, durable responses can be achieved with ^{90}Y-ibritumomab tiuxetan.9 A retrospective analysis of 211 patients with relapsed or refractory NHL has shown that TTP was reported to be at least 12 months in 37% (n=78) patients, and the median DR for these long-term responders was 28.1 months. This compares favourably with the median DR to previous therapy, which was 12 months for these patients.[9] Further analysis revealed that 59% of the long-term responders had previously received at least two prior regimens, indicating that failure to respond to prior therapy does not preclude achieving a long-term response with ^{90}Y-ibritumomab tiuxetan.[10,11] However, while patients who have failed multiple previous therapies can achieve significant benefit from ^{90}Y-ibritumomab tiuxetan, evidence also suggests that higher ORR and CR can be achieved when ^{90}Y-ibritumomab tiuxetan is used early in the course of treatments.[4,6,8,12,13] Indeed, Emmanouilides et al analyzed data from patients (n=211) in four clinical trials to compare the efficacy of ^{90}Y-ibritumomab tiuxetan when it was used after first-relapse of NHL and when it was used after two or more therapies.13 In all patients (including those with low- or intermediate-grade, follicular, mantle cell or transformed NHL), the CR rate (CR/CR unconfirmed) was found to be higher in first-relapse patients (49% vs 28%; p<0.01), and the median TTP was longer (12.6 *vs.* 7.9 months; p<0.05). The difference was even more pronounced in patients with follicular lymphoma (CR rate: 51% vs 28%; p<0.01; TTP: 15.4 vs 9.2 months; p<0.05, respectively).[13] Furthermore, a small study in which ^{90}Y-ibritumomab tiuxetan was used as first-line therapy reported an ORR of 100% (see section '^{90}Y-ibritumomab tiuxetan first-line').[12]

Patients relapsed or refractory to rituximab-based regimens

The mAb, rituximab is often used as monotherapy or combination immunochemotherapy and is commonly used in clinical practice for patients with follicular NHL.[14] As such, some patients may become refractory to rituximab, and an important question is whether these patients will then respond to therapy with ^{90}Y-ibritumomab tiuxetan. A few trials have investigated the efficacy and safety of ^{90}Y-ibritumomab tiuxetan in rituximab-refractory patients with NHL, with a high ORR (up to 82.5%).[8,15,16,17] One of these trials was a

Phase II, open-label, multicntre study in patients (n=143) with NHL who were refractory to previous treatment with rituximab (ie nonresponders or patients with a TTP ≤6 months). The ORR achieved with ^{90}Y-ibritumomab tiuxetan was significantly higher than that achieved with prior rituximab therapy (74 vs 32%, $p<0.001$). In particular, 19 of 37 patients (51.4%) who did not respond to their last rituximab therapy responded to ^{90}Y-ibritumomab tiuxetan.[8] In another, more recent trial, ^{90}Y-ibritumomab tiuxetan has produced an ORR of 82.5% and a CR rate of 62.5% in rituximab-refractory patients with indolent B-cell NHL.[17] Forty-five patients were enrolled, approximately half of whom had relapsed after immunochemotherapy (CHOP-R, n=18; other immunochemotherapy regimens, n=7), and one-third of whom had relapsed after rituximab monotherapy (n=15). A CR was achieved by more patients who were previously treated with CHOP-R (77.8%).[17]

Consolidation therapy

Radio-labelled immunotherapy is being investigated as consolidation after chemotherapy1[8,19] or immunochemotherapy[17,20] to improve the quality of response. The value of radio-labelled immunotherapy as consolidation therapy in previously untreated patients with stage II–IV follicular lymphoma (n=90) has been demonstrated with tositumomab/iodine-131 tositumomab.[18] In this study, patients received six cycles of CHOP followed by consolidation with tositumomab/iodine-131 tositumomab and have now been followed for a median of 5.1 years.[18] A complete response was achieved in 39% of patients following CHOP, and the CR rate increased to 69% following consolidation with tositumomab/iodine-131 tositumomab. Consolidation therapy also improved the quality of response as revealed by analysis of molecular responses. Thirty-eight patients had informative bone marrow specimens. Of these, 7 (18%) were PCR negative after completing the CHOP chemotherapy, while a further 24 (63%) became PCR negative after radio-labelled immunotherapy. Achievement of molecular responses (i.e. PCR negativity) has been shown to be associated with better outcome in the context of autologous transplantation,[21] standard therapy[22] and rituximab treatment[23] and therefore can be expected to be associated with improved outcome in this setting. Indeed, estimated 5-year progression-free survival (PFS) and overall survival (OS) were 67% and 87%, respectively, suggesting that consolidation with radio-labelled immunotherapy following chemotherapy can improve survival outcome as well as response rate.[18]

^{90}Y-ibritumomab tiuxetan consolidation after first-line chemotherapy

^{90}Y-ibritumomab tiuxetan is also being investigated as consolidation therapy after first-line chemotherapy (First-line Indolent Trial, FIT). Promising Phase II trial data in 61 untreated patients with follicular lymphoma19 led to recruitment into a larger Phase III FIT trial in 414 patients with newly diagnosed stage III or IV follicular lymphoma who required treatment. Patient accrual was completed in 2006 and results were recently presented during the 2007 American Society of Hematology meeting. This study looked allowed investigators to choose there own standard chemotherapy for patients with previously untreated follicular lymphoma and patients who had achieved PR or CR were randomized to ^{90}Y-ibritumomab tiuxetan consolidation or no further treatment. ^{90}Y-ibritumomab tiuxetan consolidation improved response quality and 77% of patients were converted from PR to CR. For all patients the CR rate in the control group was 53.3% compared with 87.4% with those who received

^{90}Y-ibritumomab tiuxetan. This high CR rate was almost identical in all subgroups of pre-treatment chemotherapy despite the difference in CR rate between the different regimens such as single agent Chlorambucil (31%) and CHOP (56%). In summary it appeared that ^{90}Y-ibritumomab tiuxetan was the "equalizer" for less active chemotherapy. ^{90}Y-ibritumomab tiuxetan consolidation significantly (p<0.0001) prolongs median PFS by 2 years compared with no further treatment in patients responsive to first-line induction treatment. For the patients receiving ^{90}Y-ibritumomab tiuxetan the median PFS was 37 months compared to the control of 13.5 months. In the Phase II study, untreated patients with follicular lymphoma received six cycles of standard fludarabine/mitoxantrone (FM) and those achieving an objective response then received ^{90}Y-ibritumomab tiuxetan (14.8 MBq/kg; 0.4 mCi/kg, up to a maximum dose of 1184 MBq; 32 mCi). All patients achieved an objective response following chemotherapy, and 71% achieved a complete response. Following ^{90}Y-ibritumomab tiuxetan, 12(86%) of the 14 evaluable patients initially having a PR, achieved a CR.[19]

^{90}Y-ibritumomab tiuxetan consolidation after immunochemotherapy

Chemotherapy is widely used as first-line treatment for indolent NHL; however, accumulating data suggest that the addition of the immunotherapy (rituximab) to chemotherapy further improves outcome.[24–27] These immunochemotherapy regimens are now becoming accepted as the standard first-line therapy for follicular lymphoma. Given the benefit of ^{90}Y-ibritumomab tiuxetan consolidation after first-line chemotherapy, a logical step has been to investigate the efficacy of ^{90}Y-ibritumomab tiuxetan consolidation after immunochemotherapy. This approach is being investigated in a phase II study, and updated data were recently presented at the American Society for Clinical Oncology 2007 annual meeting.[20,28,29] A total of 60 patients received three cycles of CHOP plus rituximab (CHOP-R), followed by ^{90}Y-ibritumomab tiuxetan, followed by four weekly doses of rituximab.[20] Of 44 evaluable patients, 18 (41%) achieved a CR after CHOP-R and a further 21 achieved a CR after ^{90}Y-ibritumomab tiuxetan consolidation, resulting in a CR rate of 89%. In a second study, 42 patients received 4 weekly doses of rituximab followed by three cycles of CHOP-R, followed by ^{90}Y-ibritumomab tiuxetan consolidation.28 In this study, 28% of patients achieved a CR after CHOP-R and the CR rate increased to 67% after ^{90}Y-ibritumomab tiuxetan consolidation. After a median follow-up of 20 months, 2-year PFS was 77%. Thus the results of both studies suggest that ^{90}Y-ibritumomab tiuxetan consolidation after first-line immunochemotherapy can improve response and therefore may improve survival outcomes.[20,28]

On the strength of these results, a large multicentre phase III study is now underway to investigate the benefit of ^{90}Y-ibritumomab tiuxetan consolidation following immunochemotherapy in the relapsed setting. This study, the Randomized Intergroup Trial ^{90}Y-ibritumomab tiuxetan (RITZ), will enrol patients with relapsed or refractory follicular lymphoma. Patients receive 4-6 cycles of immunochemotherapy and then responding patients are randomized to receive ^{90}Y-ibritumomab tiuxetan consolidation followed by rituximab maintenance therapy or rituximab maintenance therapy alone.

^{90}Y-ibritumomab tiuxetan first-line

Given the efficacy and safety data of ^{90}Y-ibritumomab tiuxetan emerging from its use in relapsed patients and as consolidation therapy,

there is much interest in investigating ^{90}Y-ibritumomab tiuxetan as first-line therapy in follicular lymphoma. Promising results for ^{90}Y-ibritumomab tiuxetan in this setting have also been reported in a small phase II study.[30] Patients received ^{90}Y-ibritumomab tiuxetan followed by rituximab maintenance therapy for 2 years. On day 1, patients with previously untreated low-grade follicular lymphoma received an initial infusion of rituximab (250 mg/m^2) followed by an imaging dose of 111indium-ibritumomab tiuxetan (5 mCi). One week later, a second infusion of rituximab (250 mg/m^2) was given, proceeded by an injection of ^{90}Y-ibritumomab tiuxetan (0.3 or 0.4 mCi/kg, depending upon platelet count). Rituximab maintenance therapy (375 mg/m^2 x 4) was scheduled at 6-month intervals over 2 years. An interim analysis of data for the first 8 evaluable patients showed that 5 (62%) had a complete response and 3 (38%) had a partial response to ^{90}Y-ibritumomab tiuxetan induction. Toxicities were primarily haematologic with grade 3 cytopenia occurring in 3 (38%) patients.[30]

Support for the use of radio-labelled immunotherapy is offered by tositumomab/ iodine-131 tositumomab.31 A phase II study involving 76 highly-selected previously-untreated patients with follicular lymphoma revealed that 75% (n=57) achieved a complete response, of which 70% were in remission for 4.3-7.7 years. This suggests that many patients can achieve long-term remissions following a single course of radio-labelled immunotherapy.

Summary and future perspectives

There is now an expanding body of evidence that is establishing the efficacy and safety of ^{90}Y-ibritumomab tiuxetan in the management of follicular lymphoma. When given as salvage therapy in patients with relapsed or refractory disease, ^{90}Y-ibritumomab tiuxetan induces objective responses in approximately 80% of patients and 30% achieve complete remission. These responses rate compare favourably with those reported for rituximab and translate into survival benefits. In this setting, ^{90}Y-ibritumomab tiuxetan is effective in heavily pre-treated patients and patients with bulky disease, as well as in patients with better prognostic factors. ^{90}Y-ibritumomab tiuxetan is therefore a valuable option for patients relapsing or refractory to first-line chemotherapy / immunochemotherapy. ^{90}Y-ibritumomab tiuxetan has also demonstrated significant clinical benefit when used as consolidation therapy after first-line chemotherapy or immunochemotherapy. In this setting, ^{90}Y-ibritumomab tiuxetan has been shown to improve on the quality of response achieved with first-line chemotherapy or immunochemotherapy, converting PRs to CRs and possibly inducing molecular responses in some patients. This is expected to improve survival, as is being investigated in the ongoing Phase III FIT study (assessing the benefit of ^{90}Y-ibritumomab tiuxetan after first-line chemotherapy) and the ongoing RITZ study (assessing the benefit of ^{90}Y-ibritumomab tiuxetan consolidation after first-line immunochemotherapy followed by rituximab maintenance therapy).

As a radiolabeled immunotherapy, ^{90}Y-ibritumomab tiuxetan is also being investigated in other NHL tumour types and is discussed by other authors in this supplement. Results are encouraging and suggest a role for ^{90}Y-ibritumomab tiuxetan in mantle cell lymphoma32 and as conditioning therapy for autologous stem celltransplant.[33,34] Additionally, ^{90}Y-ibritumomab tiuxetan has also demonstrated promising activity in the treatment of the aggressive lymphoma, diffuse large B-cell lymphoma (DLBCL), both as salvage therapy following chemotherapy and as consolidation following

immunochemotherapy.[35,36,37] A large international phase III study (ZEvalin as consolidation therapy in Aggressive Lymphoma; ZEAL) is currently underway to assess the benefit of ^{90}Y-ibritumomab tiuxetan consolidation following immunochemotherapy in previously-untreated patients with DLBCL.

In all settings, ^{90}Y-ibritumomab tiuxetan has been found to be well tolerated. The main short-term toxicities are haematological toxicities, which are generally mild and manageable. Data to date suggest that the long-term risk of MDS or AML is relatively low and acceptable. Further monitoring of the risk of these malignancies is, however, warranted, particularly once ^{90}Y-ibritumomab tiuxetan starts to be used earlier in the course of NHL. Given its favourable safety profile and ease of administration, ^{90}Y-ibritumomab tiuxetan may also be a possible option in early disease for patients who find a wait and watch approach difficult to accept. This is supported by preliminary data suggesting that ^{90}Y-ibritumomab tiuxetan is highly effective as first-line therapy.

^{90}Y-ibritumomab tiuxetan is clearly an important addition to the clinician's armamentarium in the fight against follicular lymphoma. Further studies are ongoing to investigate the benefit of ^{90}Y-ibritumomab tiuxetan in other settings for the treatment of follicular lymphoma and other CD20-positive lymphomas.

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