Hematology Meeting Reports 2007; 1(5):93–102

An update on ^{90}Y-ibritumomab tiuxetan in autologous stem cell transplantation

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A B S T R A C T

Relapsed or refractory non-Hodgkin's lymphoma (NHL) remains a major treatment challenge. One treatment strategy entails high-dose therapy (HDT) coupled with autologous stem cell transplantation (ASCT). In order to improve response rate, rituximab, an anti-CD20 monoclonal antibody, is widey used in combination with chemotherapy prior to or following ASCT. In addition, radiolabeled immunotherapy represents a further possible treatment refinement in this setting. Among the forms of radiolabeled immunotherapy available, ^{90}yttrium(Y)-ibritumomab tiuxetan was the first to be approved for clinical use and has accumulated support as a treatment for relapsed or refractory NHL. One of the expanding areas of interest for ^{90}Y-ibritumomab tiuxetan concerns its use in ASCT conditioning regimens. In this setting, ^{90}Y-ibritumomab tiuxetan may offer improved efficacy and sparing of toxicity associated with high-dose chemotherapy and external beam total body radiation. Various dose schedules and combinations are currently under investigation and, although these have not been optimally defined, results to date show these are feasible and can provide a therapeutic advantage. The relative merits of these different approaches for treatment of NHL may be influenced by patient and disease factors.

Introduction

Non-Hodgkin's lymphoma (NHL) encompasses a heterogenous disease group that can be broadly classified as indolent or aggressive. Indolent or low-grade lymphomas have a chronic course with a relatively good prognosis and a median survival of 7 to 8 years while aggressive lymphomas have an overall greater likelihood of initial cure.[1] Studies suggest that, depending on prognostic factors, conventional chemotherapy can cure up to almost 50% of all aggressive NHL, but it is acknowledged that no cure is the rule for indolent lymphomas, although 20% of the patients can be free of disease at 20 years.[2–4] However, regardless of histological grade, persistent or recurrent lymphomas respond poorly to retreatment with standard-dose chemotherapy. In patients with indolent NHL, relapse may be associated with transformation to a higher-grade, more aggressive histology. Other challenges associated with relapsing indolent lymphomas are lower remission rates and shorter duration of remission after each successive therapy.[5]

For patients with recurrent aggressive lymphomas, autologous stem cell transplantation (ASCT) with bone marrow transplantation or peripheral stem cells is considered standard treatment.[6] In the PARMA trial, 5-year median event-free survival and overall survival (OS) rates were

significantly higher in patients who received ASCT compared with chemotherapy plus involved-field radiation therapy.[7] Similarly, among patients with low-grade recurrent lymphomas, high-dose therapy (HDT) as a conditioning regimen prior to autologous stem cell transplantation (ASCT) has been seen to produce long-term disease-free survival (DFS).[8–11] However, despite the encouraging results seen with HDT and ASCT, many patients are unsuitable candidates for therapy because of advanced age, comorbidity and resistance to chemotherapy. Lymphomas (particularly those with low-grade histology) are highly radiosensitive, meaning that total body irradiation (TBI) has been commonly used as part of conditioning regimens for ASCT. TBI delivers high doses of radiation to normal tissues but is associated with high toxicity rates compared with high-dose chemotherapy alone.[12] Furthermore, the reinfusion of tumour cells in the autologous transplant may contribute to relapse. These issues have prompted an ongoing search for alternative or refined treatment options for patients with relapsed or resistant NHL.

Among these new options, the anti-CD20 monoclonal antibody, rituximab, can induce a response (complete or partial) in about one-third of selected relapsing patients.[13,14] Its potential role in enhancing the effect of chemotherapy has been proven in several randomized studies.[15,16] Adjuvant rituximab following ASCT offers the ability to address the minimal residual disease (MRD) that predisposes NHL patients to relapse.[17] The detection and erradication of MRD is crucial to long-term treatment success, as currently the majority of patients who achieve a complete response (CR) will relapse within months.[16,18-20] Radiolabeled immunotherapy, consisting of radiolabelled monoclonal antibodies, has also emerged as a potential treatment for patients with relapsed B-cell lymphomas. Radiolabeled immunotherapy involves the use of constant and continuously decreasing low-dose-rate radiation, which appears to predominately utilise apoptosis as a cellular mechanism.[21] This contrasts with the cellular effects of external beam radiotherapy and chemotherapy, which tend to rely on cell necrosis for their therapeutic effects.[22-24] Modern immunotherapy schedules incorporate dose fractionation to help overcome the problem of nonuniform radiation dose to different regions of the tumour, which is in turn related to heterogenous binding of monoclonal antibodies within tumours.[25]

Early studies of radionuclides coupled to immunotherapies in NHL investigated a number of antibodies (e.g. anti CD20, anti-CD37, anti-CD22, OKB7) primarily linked to ^{131}iodine(I).[26] However, ^{90}Y-ibritumomab tiuxetan was the first radioimmunoconjugate to be approved for clinical use (for relapsed or refractory/low-grade or transformed NHL, including that refractory to rituximab). ^{90}Y-ibritumomab tiuxetan produces high response rates and long-term durable responses, superior to that of immunotherapy alone.[27-29] For example, a randomised trial in 143 NHL patients found that ^{90}Y-ibritumomab tiuxetan produced a greater overall response rate and longer median duration of response than rituximab alone (80% *vs*. 56%, p=0.002; 16.7 *vs*. 11.2 months, p=0.44).[29] Furthermore, ^{90}Y-ibritumomab has produced responses in patients with follicular NHL refractory to rituximab, illustrating the value of the radioisotope component.[30] Such responses are explained by the ability of the radioisotope to take advantage of a crossfire effect and kill tumour cells in bulky or poorly vascularized tumours without the direct binding of the antibody.[31] In addition, evidence suggests that failure to respond to prior therapy does not preclude achieving a long-term response with ^{90}Y-ibritumomab, and that patients previously treated with ^{90}Y-ibritu-

momab tiuxetan can undergo other forms of treatment without an apparent negative impact on their efficacy.[27,32,33]

Rationale for radiolabeled immunotherapy prior to ASCT in NHL

HDT combined with ASCT has become standard treatment for relapsed or refractory NHL. However, there are several obstacles associated with this strategy, including residual disease (MRD, as mentioned above) after HDT, the possibility of tumour cell reinfusion and severe toxicity, which may be caused by attempts to intensify HDT and TBI to overcome resistant disease. Improvements in the benefit-to-risk ratio of external-beam TBI has occurred from advances in the science of dose fractionation (administration of total radiation dose as multiple doses over time) which have enabled an increase in the total radiation dose that can be given, while decreasing late toxicities and immunosuppression.

Rituximab has provided promising results in numerous studies as a potential adjuvant to chemotherapy either prior to or following ASCT in patients with recurrent or refractory NHL.[17,34] Evidence of the elimination of lymphoma cell contamination is suggested by the clearance of bcl-2-positive cells from stem cell harvests. In terms of clinical response, pretransplantation treatment with rituximab has been associated with improved complete response rate, which is one of the main predictors of increase survival, including an almost 50% improvement in three-year overall survival in patients with diffuse large B-cell lymphoma (75% *vs*. 52%; p=0.025).[34] As a component of pretransplantation conditioning regimens, radiolableled immunotherapy can be considered to extend the therapeutic benefits of rituximab. Compared with immunotherapy alone, radiolabeled immunotherapy provides the added advantages of radioisotope emission, which act over a multicellular range and thereby distribute the radiation more uniformly throughout the malignant tissue.[25] Hence, the rationale for radiolabeled immunotehrapy prior to ASCT in relapsed/refractory NHL relates to both sparing of toxicity associated with highly myeloablative HDT regimens and the potential superiority of radiolabled immunotherapy in terms of prevention of long-term relapse. Clinically, the specific application of these different benefits may be determined by patient factors such as age and fitness. Although myelotoxicity remains the major dose-limiting effect with ^{90}Y-ibritumomab tiuxetan, this can be overcome by ASCT.[35]

Clinical studies of radiolabled immunotherapy and ASCT in patients with NHL

One of the earliest reported uses of radiolabeled immunotherapy in combination with ASCT was by Press and Eary in 1995.[36] In this phase II study, 21 patients with relapsed B-cell lymphomas were treated with therapeutic infusions of ^{131}I-tositumomab followed by ASCT. Dosimetry is required in order to determine the dose delivered to the tumor and vital organs. Of the treated patients, 18 had objective responses including 16 complete remissions. These results possibly reflect the deliberate intention to administer myeloablative doses. In a later pilot study using high-dose ^{131}I-tositumomab in combination with high-dose chemotherapy and ASCT, these objective response data were confirmed with observed OS and PFS rates of 83% and 68%, respectively.[37] Results with ^{131}I-tositumomab from both studies compared favourably with response rates seen in a nonrandomized control group in the later trial who received external-beam TBI, cyclophosphamide and etoposide followed by

ASCT (OS 53% and PFS 36% at 2 years).[37] Importantly, toxicity was manageable with only a minority of patients (15%) experiencing grade III-IV toxic effects primarily infections and mucositis.

Despite the apparent favourable efficacy and good tolerability of ^{131}I-based radiolabeled immunotherapy conditioning, post-treatment radiation isolation is an issue for patients and close contacts.[26] In contrast, ^{90}Y is a pure β-emitter which, compared with ^{131}I, delivers more energy to the tumour site, has a longer path length (5.0 mm *vs*. 0.8 mm) and a more favourable half-life (2.67 days *vs*. 8 days).30 Dosimetry is not directly possible with ^{90}Y so, when performed, ^{111}Indium used, but, in contrast to ^{131}I, standard ^{90}Y doses are used in most countries, without the need for individual dosimetry. From a practical perspective, with the use of ^{90}Y-labelled immunotherapy does not necessitate sophisticated radioprotection measures with only acrylic shielding required during preparation and administration, and only the universal safety precaution of avoidance of contact with bodily waste required by medical personnel. Clinical experience with ^{90}Y-ibritumomab tiuxetan in heavily pre-treated patients with relapsed or refractory B cell NHL who had undergone ASCT indicated that ^{90}Y-ibritumomab tiuxetan is both feasible and safe following transplantation.[38,39] There is now an increasing number of studies examining ^{90}Y-ibritumomab tiuxetan in conventional and escalated dose schedules combined with HDT as well as in myeloablative dose schedules prior to ASCT.

Conventional dose studies of ^{90}Y-ibritumomab tiuxetan and ASCT

Several studies have examined standard outpatient dosing of ^{90}Y-ibritumomab tiuxetan with HDT such as high-dose cyclophosphamide and etoposide or BEAM (carmustine, etoposide, cytarabine and melphalan) followed by ASCT.[40,41] Individualised dosing requires experienced nuclear medicine physicians and a weight-based standardised dosing schedule has provided practical and economic advantages.[42] In a pilot study that attempted to improve outcomes in 12 older (≥55 years), poor-risk patients with aggressive B cell lymphoma undergoing ASCT, Fung et al. utilized a preparative regimen that included standard dose ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg) 14 days before high-dose BEAM and ASCT.[40] The regimen was well tolerated and only one patient had died of progressive disease during a median follow-up of 9 months. All 11 remaining patients were without evidence of lymphoma when examined using CAT and PET scans at the final follow-up visit. These findings led the investigators to conclude that the combination of ^{90}Y- ibritumomab tiuxetan and high-dose BEAM followed by ASCT could be safely administered without dosimetric guidance, allowing for targeted intensification of the conditioning regimen in a relatively straightforward manner.[40] Standard-dose ^{90}Y-ibritumomab tiuxetan and BEAM prior to ASCT has also been administered to patients with relapsed mantle cell lymphoma (MCL) with treatment contributing to robust OS and DFS rates (79% and 59% estimated at 2 years, respectively), with good tolerability.[41] However, as these trials were small and conducted over a relatively short period of follow-up, larger studies are required to fully evaluate the immediate and long-term effectiveness and toxicity of this therapeutic approach. To this end, a phase II study conducted by GELA (Groupe d'Etude des Lymphomes de l'Adulte) has recently completed enroling patients with low-grade B-cell lymphoma (mostly follicular) onto combined treatment with ^{90}Y-ibritumomab tiuxetan and BEAM (Figure 1). Preliminary results from the first 30 patients

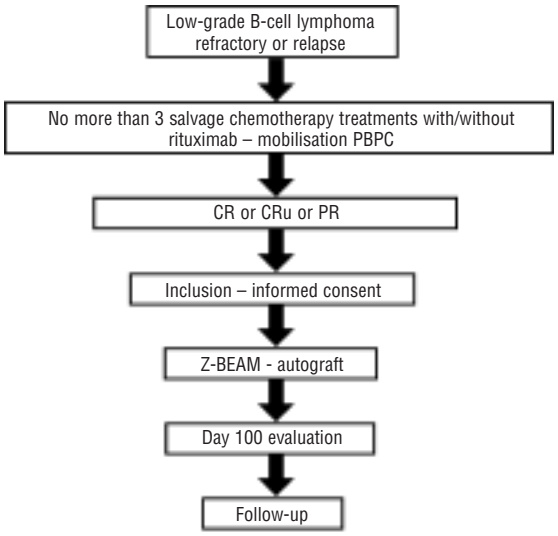

Figure 1: ^{90}Y-ibritumomab tiuxetan –BEAM consolidation in relapsing low-grade B cell lymphoma in the GELA study. Presented at the annual meeting of the European Group for Blood and Marrow Transplantation (*Prague, 2005*).

included in this study, presented at the annual meeting of the European Group for Blood and Marrow Transplantation (Prague, 2005), have suggested that immediate toxicity does not differ from that observed with a high-dose chemotherapy conditioning regimen and ASCT.

Escalated dose ^{90}Y immunotherapy

Despite the potential practical and tolerability advantages of conventional doses of ^{90}Y-ibritumomab tiuxetan, the high relapse rates associated with NHL and the less favourable prognosis of relapsed disease warrants investigation of more intensive conditioning regimens prior to ASCT. Currently, the recommended maximum total dose of ^{90}Y-ibritumomab tiuxetan is 1184 MBq or 32 mCi, which corresponds to 0.4 mCi/kg. However, recent phase I/II trials incorporating high-dose ^{90}Y-ibritumomab tiuxetan in combination with HDT prior to ASCT have yielded encouraging results. A phase I trial employed careful dosimetry, using ^{111}Indium, of ^{90}Y-ibritumomab tiuxetan to provide CD20^{+} NHL patients with escalating radiation exposure (100, 300, 500, 700, 900 cGy) to critical organs.[43] ^{90}Y immunotherapyFRIT was combined with high-dose BEAM followed by rituximab 250 mg/m^2 administered 22 days prior to transplantation. Toxicities (including infection, stomatitis, nausea, vomiting, haemorrhage and oedema) were similar to those reported with high-dose BEAM alone, and engraftment occurred at a median of 10 days. The OS for all treated patients at all dose levels was reported to be 60% at 3 years and PFS at 2 and 3 years was 47%. Hence, data suggested that ^{90}Y-ibritumomab tiuxetan could be safely combined with BEAM chemotherapy and ASCT at a dose that delivered a high level of radiation (700 cGy) to critical organs.

In another phase I/II trial, ^{90}Y-ibritumomab tiuxetan (at an expected maximum radiation dose of 1000 cGy to the target organ) was combined with high-dose etoposide (40–60 mg/kg) and cyclophosphamide (100 mg/kg) followed by ASCT.[44] In this trial, 31 patients with poor-risk or recurrent CD20-positive NHL received ^{90}Y-ibritumomab tiuxetan at a median dose of 71.6 mCi (2649.2 MBq). There were two deaths and five relapses and, at a median follow-up of 22 months, the 2-year estimated overall survival and relapse-free survival rates were 92% and 78%, respectively (Figure 2). Overall, this regimen was well tolerated with mucositis, neutropenic sepsis and nausea commonly reported but generally mild to moderate in severity. This toxicity profile was similar to that previously observed in patients receiving TBI, etoposide and cyclophosphamide. The median times to reach an absolute neutrophil count >500/μL and platelet count >20 000/μL were 10 days and 12 days, respectively. It was concluded that high-dose ^{90}Y-ibritumomab tiuxetan can be combined safely with high-dose etoposide and cyclo-

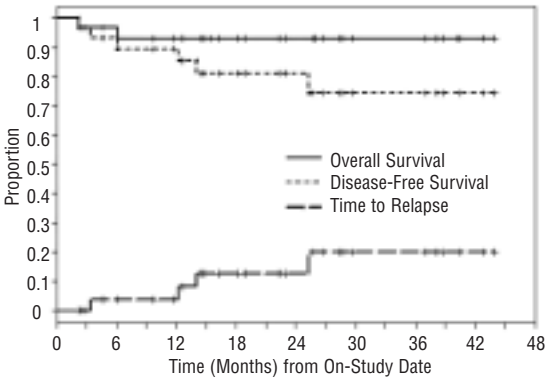

Figure 2: Kaplan-Meier estimated 2-year DFS and OS of 31 patients who underwent high-dose ^{90}Y-ibritumomab tiuxetan and ASCT in NHL.[44] Reproduced with permission from Nademanee A, *et al.* A phase 1/2 trial of high-dose yttrium-90-ibritumomab tiuxetan in combination with high-dose etoposide and cyclophosphamide followed by autologous stem cell transplantation in patients with poor-risk or relapsed non-Hodgkin lymphoma. *Blood 2005;106: 2896–902.*

phosphamide without an increase in transplant-related toxicity or delayed engraftment.[44] Other specific advantages of ^{90}Y-ibritumomab tiuxetan highlighted within the study included the ability to increase the therapeutic exposure without causing significantly increased doses to the hospital personnel caring for the patient or the need for specialised facilities.

Escalated dose or myeloablative radioimmunoimmunotherapy alone

In addition to being investigated as an adjuvant to conventional conditioning regimens, ^{90}Y-ibritumomab tiuxetan has been investigated as a potential primary conditioning agent for effective myeloablation prior to ASCT. In order to determine the non-haematopoietic maximum tolerated dose (MTD), Flinn et al. conducted a dose-finding study of ^{90}Y-ibritumomab tiuxetan prior to ASCT.[45] Patients with relapsed or refractory low-grade, mantle cell or diffuse large cell NHL with platelet count ≥75,000/mm^3, white cell count ≥3,000/mm^3 and no greater than 35% bone marrow involvement were eligible.[45] Following an initial protocol that included weekly rituximab for 4 weeks and a single dose of cyclophosphamide, patients received ^{90}Y ibritumomab tiuxetan 15 days after stem cell collection; the total dose of 90Y ibritumomab tiuxetan administered ranged from 20.2 to 121.7 mCi. Of 6 patients evaluated at 60 days post-transplant, 4 patients achieved a complete response, 1 patient had a partial response and 1 patient had progressive disease. These results prompted the investigators to conclude that significant dose escalation could be achieved with ^{90}Y ibritumomab tiuxetan when used in conjunction with ASCT, although larger studies are required to confirm these findings.[42]

Devizzi et al. conducted a pilot study of high-dose ^{90}Y-ibritumomab tiuxetan with tandem stem-cell support among 13 patients unable to safely undergo BEAM.[46] Prior to ^{90}Y-ibritumomab tiuxetan administration, all patients received one cycle of high-dose cyclophosphamide plus rituximab and one cycle of high-dose cytarabine and rituximab at patient-adapted doses. Peripheral blood stem cell (PBSC) harvesting was conducted during the post-cyclophosphamide and/or the post-cytarabine recovery phase. ^{90}Y-ibritumomab tiuxetan was then administered at twice the MTD (0.8 mCi/kg) and followed by tandem autografting of CD34$^+$ at days 7 and 14. Supportive autografting was done in the presence of potentially myelotoxic doses of circulating radioactivity and was aimed to achieve an immediate yet transient haematopoietic recovery. After a mean follow-up period of 6 months, 11 patients remained alive, of which 10 patients were in continuous complete remission. These data suggested that high-dose ^{90}Y-ibritumomab tiuxetan with tandem stem-cell produced low toxicity in a heavily pretreated population and was therefore fully applicable in an outpatient setting. ^{90}Y-ibritu-

momab tiuxetan administration at 0.8 mCi/kg, and possibly up to 1.2 mCi/kg as a final consolidation step appears warranted and should be prospectively compared with conventional dose regimes.[46]

In another study to determine the feasibility and toxicity of myeloablative doses of ^{90}Y-ibritumomab tiuxetan (0.8, 1.2, 1.5 mCi/kg), 12 patients with resistant-refractory NHL were enrolled in a phase I/II study with PBSC support.[47] All patients engrafted promptly and 5 of 11 evaluable patients experienced a complete response. In addition, no significant differences in haematological toxicity were reported with higher doses of ^{90}Y-ibritumomab tiuxetan. Therefore, even at doses approximately four times that of the standard clinical dose, ^{90}Y-immunotherapy can be safely delivered with PBSC support to elderly and heavily pretreated patients. Such data suggest a possible new direction for treatment options available with ^{90}Y-ibritumomab tiuxetan for patients with resistant or refractory NHL.

Radiolabeled immunotherapy in allograft conditioning regimens

Although allogeneic stem cell transplantation (SCT) may offer the additional advantage of graft-versus lymphoma effect when compared with ASCT, the outcome continues to remain poor in refractory NHL. The use of ^{90}Y-ibritumomab tiuxetan in conditioning regimens administered prior to ASCT and reduced-intensity allogeneic SCT in patients with refractory NHL has been studied by Shimoni et al.[48] In this study 7 patients (of 21 patients who had received a median of 3 prior therapies) received rituximab 250 mg/m^2 followed by ^{90}Y-ibritumomab tiuxetan 0.4mCi/kg 2 weeks prior to allogenic SCT (fludarabine + busulfan were also given as prior therapy in these patients). All patients engrafted in a median of 13 days following allogeneic SCT and the estimated 1-year survival rate was 44% after allogeneic SCT (75% for ASCT, *p*=NS) estimated from a median follow-up period of 8 months. The 1-year DFS was 44% for both ASCT and allogeneic SCT. These preliminary data indicate that ^{90}Y-ibritumomab tiuxetan may reduce the risk of post-transplant relapse and improve the poor outcome of patients with chemorefractory lymphoma after transplant with standard regimens. As with the use of 90Y-ibritumomab tiuxetan in escalated and myeloablative dose strategies, further larger scale comparative studies are warranted.

Discussion

Among patients with relapsed or refractory NHL, ^{90}Y-ibritumomab tiuxetan has been demonstrated to have high efficacy and a favourable safety profile.[27–30] On the basis of a number of phase II and III trials showing durable high response rates, ^{90}Y-ibritumomab tiuxetan has been approved for the treatment of CD20$^+$ follicular lymphoma refractory to or relapsed after rituximab.[30] However, further studies (including comparative trials with standard chemotherapy options) are required to properly determine the therapeutic role of ^{90}Y-ibritumomab tiuxetan. Current evidence suggests that ^{90}Y-ibritumomab tiuxetan is effective and, importantly, is not associated with the typical non-haematological adverse effects seen with chemotherapy.[30] Instead, myelosuppression is the major dose-limiting toxicity seen with ^{90}Y-ibritumomab tiuxetan, an expected finding that stem cell support may alleviate.[43]

There are several lines of argument supporting the use of ^{90}Y-ibritumomab tiuxetan as part of myeloablative conditioning regimen prior to ASCT. These include greater efficacy without the toxicity of TBI and high-dose chemothera-

py schedules as well as beneficial effects that can occur independent of tumour cell binding by monoclonal antibodies. Fractionated radiolabeled immunotherapy achieves more uniform distribution of the radiation dose throughout the tumour, reduces toxicity and extends the MTD.[25]

Trials of conventional-dose ^{90}Y-ibritumomab tiuxetan in combination with HDT have shown that this approach offers minimal additional toxicity compared with chemotherapy alone.[40,41] Despite this, additional studies are required before this strategy is applied in the general clinical setting. The advantages of this approach are the fact that conventional doses do not require specialised facilities for administration and that only universal safety precautions are necessary post-therapy. Hence, conventional dosing regimens can be a relatively simple and cost-effective approach. On the other hand, while escalated dosing of ^{90}Y-ibritumomab tiuxetan beyond the 0.4 mCi/kg dose is likely to be possible, this approach should only be conducted in the context of careful dosimetry to ascertain the expected radiation exposure to the critical organs. Trials of escalated dose regimens conducted to date reveal that this approach is feasible from the perspective of toxicity and has also yielded good efficacy.[43,44] The optimal dosing of ^{90}Y-ibritumomab tiuxetan in this situation is yet to be determined. Finally, preliminary research suggests that, in addition to having potential as an adjuvant to conventional conditioning regimens, ^{90}Y-ibritumomab tiuxetan may also be useful as a primary conditioning agent for effective myeloablation prior to ASCT, helping to avoid considerable non-haematological toxicity associated with high-dose chemotherapy.[45-47]

In summary, use of ^{90}Y-ibritumomab tiuxetan provides an effective option for enhancing clinical outcomes when combined with HDT followed by ASCT and can potentially spare patients the significant toxicity associated with TBI. The optimal dosing regimen for ^{90}Y-ibritumomab tiuxetan remains elusive although ongoing clinical trials aim to define this. However, it is already clear that a number of schedules based on conventional and escalated/myeloablative doses are feasible, with the therapeutic importance of these different approaches likely to depend on both disease and patient characteristics.

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