

Review of ^{90}Y -ibritumomab tiuxetan as first-line consolidation radio-immunotherapy for B-cell follicular non-Hodgkin's lymphoma

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Abstract: Several studies have indicated that radioimmunotherapy is an effective and clinically relevant complementary therapeutic approach for patients with B-cell non-Hodgkin's lymphoma (NHL) and may convert partial to complete response when given as consolidation after induction chemotherapy. Yttrium-90(^{90}Y)-ibritumomab tiuxetan (^{90}Y -IT, Zevalin[®], Y2B8) has documented efficacy for both indolent and aggressive NHL. Patients considered eligible for ^{90}Y -IT treatment should satisfy several screening criteria. A recently completed randomized study for patients with follicular lymphoma has demonstrated that ^{90}Y -ibritumomab consolidation also produced a marked prolongation of the median time to progression from 13.5 to 37 months, while partial responders seem to derive relatively more benefit. Other published and ongoing studies explore a similar use for patients with aggressive lymphoma. Studies are comparing the use of ^{90}Y -IT consolidation with the anti-CD20 antibody rituximab maintenance, which is also gaining acceptance. In conclusion, the documented benefit of radioimmunotherapy should be viewed in the context of the goals of treatment and the changing standards of care for lymphoma.

Keywords: radioimmunotherapy, ^{90}Y -ibritumomab tiuxetan, follicular lymphoma, consolidation

Introduction

The therapeutic application of monoclonal antibodies has revolutionized the treatment of lymphoma.¹ Although engagement and direct interaction with surface proteins appear to be of therapeutic value, antibodies also constitute excellent targeting systems, marking selected cells for the interaction with innate immune effector mechanisms, or by conjugation with moieties of therapeutic value which are thus locally delivered. Because radioimmunotherapy (RIT) has been shown to be sufficiently effective, the US Food and Drug Administration approved the first ever radioimmunoconjugate (RIC) for the treatment of a malignancy in February of 2002, when ^{90}Y -ibritumomab tiuxetan (^{90}Y -IT; Zevalin[®]; RIT Oncology) was licensed for the treatment of indolent or transformed, relapsed or refractory B-cell lymphoma. Soon thereafter, a second anti-CD20 radioconjugate ^{131}I tositumomab (Bexxar[®]; GlaxoSmithKline) was also approved.^{2,3} In Europe, ^{90}Y -IT was subsequently approved for the treatment of follicular lymphoma, relapsed or refractory after prior rituximab-containing treatment. Ibritumomab (IDEC-2B8) is the murine anti-CD20 antibody developed by Biogen-IDEC (San Diego, CA, USA); its chimeric version, rituximab (Rituxan[®]; Genentech; Mabthera[®]; F. Hoffmann-La Roche Ltd), is also available and widely used. Tiuxetan connotes the linker used (MxDTPA) to conjugate ^{90}Y to the antibody.

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RIT offers several advantages over external beam irradiation. Normal tissues overlying the tumor mass are prevented from significant radiation exposure. Since the RIC is given intravenously, it provides systemic radiation treatment to known as well as unsuspected tumor cells. It should be noted that neither rituximab nor the RIC available or under development are truly tumor specific as they bind to a marker also present at the normal lymphocyte counterparts. However, mounting experience from trials and clinical practice suggests that prolonged normal B-cell depletion is not associated with significant sequelae.⁴ As a pure β emitter, ⁹⁰Y seems to offer theoretical and practical advantages, mainly simple handling practices.^{5,6} The lack of γ component simplifies radioprotection during handling and administration of the RIC.

⁹⁰Y-IT for the treatment of lymphoma

During the registrational clinical trials, a meticulous and thorough dosimetry procedure was performed, largely using data derived from indium-111 (¹¹¹In-IT) kinetics.^{7,8} The purpose of dosimetry was to eliminate the possibility of excessive radiation exposure of vital organs. Based on favorable observations on kinetics and safety, the requirement of imaging has been eliminated in most countries.⁹

Patients considered eligible for ⁹⁰Y-IT treatment should satisfy several screening criteria, including having less than 25% involvement of the bone marrow by disease determined by adequate core biopsy, absence of myelodysplasia, and satisfactory blood counts. In the phase I/II study, it became apparent that the major toxicity was reversible myelosuppression with median absolute neutrophil count (ANC) 1100/ μ L and median nadir thrombocytopenia of 49,500/ μ L.¹⁰ The extent of bone marrow involvement by lymphoma and the pre-treatment platelet counts correlate with the risk of myelosuppression. The remainder of the toxicity was mostly associated with the infusion of rituximab, with the possible exception of mild fatigue and mild nausea.

Studies of RIT as single agent indicate that the expected response rate for patients fulfilling the above criteria with relapsed or refractory indolent or transformed B-cell NHL is 74% to 80% and duration of response is approximately 1 year.^{4,11–13} Particularly longer remissions for several years were observed in subsets of patients.⁴ Importantly, in the 211 patients of the registrational studies, there was no difference in toxicity and efficacy of the treatment among the 113 patients less than 60 years old, the 58 patients of the age group between 60 and 70 and the 40 patients

over 70.¹⁴ For aggressive B-cell lymphoma, the activity of ⁹⁰Y-IT has been documented in the phase I/II study¹⁰ and it was confirmed in a multicenter prospective phase II study involving 102 evaluable patients;¹⁵ in the latter, an overall 44% response rate with 27% complete response (CR) rate was observed. The results were more favorable in rituximab naïve patients. In relapsed mantle cell lymphomas the activity of ⁹⁰Y-IT has been reported in the range of 30% to 40% but responses usually last a few months.¹⁶

Rationale for consolidation use of RIT

There are many reasons to consider the delivery of radiotherapy immediately after a course of chemotherapy, ie, as commonly referred to, as consolidation treatment. It is conceivable that induction chemotherapy may “prime” patients for an enhanced RIT effect. In multivariate analysis of 203 patients involved in the ⁹⁰Y-IT registrational studies, a factor that predicted for better response was tumor bulk;¹⁶ patients with nodal masses more than 5 cm had a 68% response rate, as opposed to 90% for patients with smaller tumors ($P < 0.001$). Thus, cytoreduction achieved by chemotherapy may render patients more amenable to RIT. In addition, chemotherapy treatment usually results in amelioration of bone marrow disease, so that the likelihood of considerable bone marrow involvement exceeding 25% is extremely low. This may translate in reduced bone marrow exposure to irradiation. Furthermore, the impact of RIT on measurable residual disease could be quantified, ie, one could know how many partial responses could be converted to complete ones.

Retrospective meta-analysis of the registrational trials indicate a considerably better outcome in patients treated with radiotherapy early in their disease course;¹⁷ for instance, in patients with follicular lymphoma receiving ⁹⁰Y-IT as second line treatment, the complete and overall response rate were 51% and 89% respectively. The complete response (CR) rate and time to progression (TTP) were statistically better compared to the group of patients with more prior treatments ($P < 0.05$). Patients who achieved a CR had a median 2-year TTP. Such data suggest that it may be preferable to move up ⁹⁰Y-IT treatment in the sequence of therapy for lymphoma, in order to take advantage of the high likelihood of achieving a CR, which confers a longer TTP. In fact, a response rate of 100% has been reported after first-line use of RIT in patients with follicular lymphoma.¹⁸ Late toxicity and particularly myelodysplasia seems not to be an issue, so that subsequent treatments upon relapse are possible.^{19,20}

All the above observations support the use of RIT as a practical and convenient consolidation treatment after induction chemotherapy as it may be associated with increased efficacy and lack of long-term toxicity.

Nevertheless, there are certain theoretical concerns for indiscrete consolidation treatment with RIT. The ratio of beneficial radiation vs radiation deposited to surrounding tissue depends on the size of the lymphomatous mass and the path length of the radioisotope used. Since most of the radiation energy is delivered within a sphere with a radius of a few millimeters, if one conceptualizes residual disease as a dispersion of single cells, most of the radiation emitted by the lymphoma-attached radioconjugate would be wasted. On the other hand, the definition of complete response is a convention, which almost certainly includes patients with small lymphomatous aggregates in "normal size" lymph nodes of less than 1.5 cm. Thus, complete responders may still derive benefit from the crossfire effect. This is more valid if the response to preceding chemotherapy was not complete; in such cases, RIT may be an ideal agent to treat the remaining involved nodes. Chemotherapy-resistant lymphoma cells may still be susceptible to radiation as significant activity of RIT in patients with chemotherapy refractoriness has been reported.^{12,21} Another concern about consolidation use is whether a bone marrow in the process of recovering and regenerating from the effects of recent myelotoxic chemotherapy can sustain safely the effect of RIT. Completed studies seem to indicate that an interval period of 4 to 6 weeks post-chemotherapy is sufficient for safe administration of RIT. The inclusion of the anti-CD20 antibody in the induction chemotherapy does not eliminate the benefit of anti-CD20-based RIT. The interaction of the antibody with its target should be viewed as a dynamic process of equilibrium with constant detachment of antibody molecules and replacement by others. In any case, RIT is known to be active even in the presence of measurable rituximab levels, as shown in the study in rituximab-refractory follicular B-cell lymphoma patients.¹⁰

Consolidation studies Indolent NHL

The proof of principle of radioimmunotherapy consolidation was first demonstrated by the Southwest Oncology Group (SWOG) phase II study in 90 patients with untreated follicular B-cell non-Hodgkin's lymphoma.²² After an initial full course CHOP (cyclophosphamide, doxorubicin, vincristin, prednisolone) chemotherapy, responding patients received the radioconjugated anti-CD20 antibody ¹³¹I-tositumomab (¹³¹I-T) as consolidation. The mean time between the end

of chemotherapy and the treatment with RIT was 35 days. RIT was well tolerated without excessive myelotoxicity, and 57% of the patients achieving less than a CR after chemotherapy, improved their remission with RIT. Thus the overall response rate was 90% including 67% complete responses, and the 2-year progression-free survival was estimated at 81%. The same radioimmunoconjugate was tested after an abbreviated 3-cycle course of fludarabine first-line treatment.²³ The sequence induced a complete response in 83% of the 35 evaluable patients. Grade 4 neutropenia or thrombocytopenia was noted in 34% and 29% respectively.

A number of studies have subsequently examined the role of ⁹⁰Y-IT as consolidation treatment in B-cell NHL. In the Sarah Cannon Cancer Center, an abbreviated 3-cycle regimen of CHOP-rituximab or CVP (cyclophosphamide, vincristine, prednisone)-rituximab was followed by ⁹⁰Y-IT, which is thus used as a chemotherapy sparing agent.²⁴ ⁹⁰Y-IT was given 5 to 7 weeks after the last chemotherapy cycle. All of the 22 reported patients resounded; there were 13 partial responders to chemotherapy, 10 of whom achieved a CR after ⁹⁰Y-IT, for an overall CR rate of 86%. Responses were long-lasting. Limited grade 4 neutropenia or thrombocytopenia was seen (18% and 0% respectively). This study preliminarily addressed the relevant question of whether ⁹⁰Y-IT consolidation would perform well after rituximab-containing induction regimens. Further evidence is provided by a phase 2 study of 3-cycle rituximab-CHOP induction chemotherapy given to patients with symptomatic or bulky untreated follicular NHL followed by ⁹⁰Y-IT consolidation supplemented by 4 additional rituximab infusions.²⁵ In that study involving 60 patients, the addition of RIT consolidation nearly doubled the PET-confirmed CR rate achieved by rituximab-CHOP, from 46% to 89%. After a median follow up of 19 months, 10 patients relapsed, an outcome better than expected.

Results of ⁹⁰Y-IT consolidation following alternative chemotherapy (fludarabine-mitoxantrone combination) are suggestive of similar efficacy. Applying ⁹⁰Y-IT consolidation to a group of 61 patients with follicular NHL after treatment with 6 cycles of oral fludarabine and mitoxantrone resulted in a 96% overall response rate.²⁶ Radioimmunotherapy converted 12 of the observed partial responses to complete ones. With a median observation time of 30 months, the 3-year actuarial progression-free and overall survival was 76% and 100% respectively. Grade 3 or 4 hematologic toxicity was noted in 36 of 57 evaluable patients, and blood or platelet transfusions were often required. The feasibility of the same strategy with analogous results has been reported by the same group in patients with non-follicular

indolent B-cell lymphoma.²⁷ Although direct comparisons are not possible, it is likely that the type of regimen as well as the number of chemotherapy cycles may have resulted in increased hematologic toxicity compared to the Sarah Cannon study.

Phase 3 study of ⁹⁰Y-IT consolidation

The remarkable and consistent observation across these phase 2 studies of the capacity of ⁹⁰Y-IT to further enhance the response obtained by chemotherapy led the design of a multicenter phase 3 study known with the acronym FIT.²⁸ In order to overcome difference of opinions among various lymphoma specialists regarding the optimal first line regimen, the study randomized 409 patients with stage III and IV follicular NHL after they had achieved a response to a first-line induction regimen of the choice of the site investigators. Patients were assigned to either receive ⁹⁰Y-IT consolidation or just be observed, with progression-free survival being the primary end-point. Nearly all patients had stage 3 or 4 disease and were roughly equally divided between partial and complete responders. The majority of patients had received alkylator-based regimens, predominately CHOP. Fludarabine combination was given to 5.4% and 15% had been exposed to rituximab.

The administration of ⁹⁰Y-IT, as expected, increased the complete response rate, which at the end of the treatment was 87% in the radioimmunotherapy group and 53% in the control group. This resulted in a remarkable prolongation of the progression-free survival from a median of 13.5 months in the control group to 37 months ($P < 0.0001$). In the subset of patients with partial response who entered the randomization, the difference was even more pronounced (6.3 months vs 29.7 months, $P < 0.0001$). The benefit in complete response and prolongation of the time to treatment failure was seen in all treatment groups, regardless of the intensity of the induction regimen. However, because of the small size of the subset of patients who had received rituximab-based treatment, the difference in this group did not reach statistical significance (CR rate of 71% vs 93%, overlapping 95% confidence intervals). Overall survival data are premature, but given the likelihood of crossover and multiple lines of subsequent treatments, it is doubtful that an improvement in overall survival can be demonstrated from this study. Nevertheless, updated results confirm the long term safety of RIT consolidation, as well as the feasibility of subsequent treatments, as expected.²⁹ The rates of grade 3–4 thrombocytopenia, neutropenia and anemia in the ⁹⁰Y-IT group was 61%, 67% and 3% respectively. Despite that, grade 4 infections were observed

in only 8% of the patients. Platelet transfusions were given at the discretion of the investigators to 42 patients (20%), and leukocyte growth factor support to 36 patients.

This randomized study confirmed the value of radioimmunotherapy given as supplement to chemotherapy and has led to the approval of ⁹⁰Y-IT as consolidation after induction chemotherapy for follicular lymphoma. However this study leaves several unanswered questions. For instance, it leaves unsettled the question of whether reserving radioimmunotherapy delivery as treatment upon progression would benefit the patient at the same extent. On the other hand it is possible that the temporal proximity of radioimmunotherapy to lymphoma cells recently exposed to chemotherapy may make them more susceptible to apoptosis and thus enhance cell killing conferred by irradiation (chemosensitization). Another somewhat unclear issue is the exact magnitude of benefit from ⁹⁰Y-IT consolidation after rituximab-containing induction chemotherapy. Along those lines, as rituximab maintenance is gaining acceptance, a subsequent multicenter randomized study is underway, comparing RIT consolidation to rituximab maintenance, or assessing the benefit of the addition of ⁹⁰Y-IT consolidation on chemoimmunotherapy followed by rituximab maintenance backbone. It is noteworthy that the magnitude of the benefit of ⁹⁰Y-IT consolidation seems to be in the same range of that conferred by rituximab maintenance; for the sake of comparison, adding 4 weekly rituximab infusions every 6 months for 2 years after CVP–rituximab induction chemotherapy for follicular lymphoma increased the 3-year disease-free survival from 33% to 68%.³⁰ Notwithstanding the above reservations, the FIT trial has demonstrated beyond doubt the value of radioimmunotherapy consolidation in the first-line treatment of patients with follicular indolent lymphoma.

⁹⁰Y-IT consolidation use for aggressive NHL

The documentation of considerable activity of ⁹⁰Y-IT in patients with relapsed or refractory diffuse large B-cell lymphoma^{10,15} as well as the desire for further improvement of the overall survival in such group of patients led to the initiation of consolidation studies, most of which are still in progress. A phase 2 study describing the administration of ⁹⁰Y-IT as consolidation after full course of CHOP chemotherapy in patients over the age of 60 has been published and documents again the feasibility of this strategy, resulting in a 100% overall response rate and an actuarial 2-year disease-free survival of 2 years.³¹ Ongoing studies aim at reproducing these results. Consolidation with ⁹⁰Y-IT has also

been studied in patients with stage I-II diffuse large B-cell lymphoma of relatively high risk who were treated with CHOP for 3 cycles and involved field irradiation; ⁹⁰Y-IT consolidation was added to this standard regimen.³² The 2-year disease-free survival was estimated to be 91%, an encouraging outcome. A randomized study assessing the role of Zevalin[®] as consolidation after completion of full course R-CHOP in patients with aggressive lymphoma is underway. The goal of treatment of patients with aggressive lymphoma is to produce cures and, albeit somewhat ambitiously, such studies intend to explore a possible increase in overall survival.

In mantle cell lymphoma, the sequence CHOP-rituximab followed by ⁹⁰Y-IT consolidation has been tested as first-line treatment in 56 patients by the Eastern Cooperative Oncology Group (ECOG).³³ After 4 cycles of R-CHOP, the overall response rate and the complete response rate were 72% and 14% respectively. Similar to other consolidation studies, after administration of ⁹⁰Y-IT the responses increased respectively to 84% and 45%. A similar approach employing the combination of fludarabine, mitoxantrone, cyclophosphamide and rituximab (FCM-R) as induction regimen followed by ⁹⁰Y-IT consolidation was reported to induce CR in 19 out of 20 patients with untreated mantle cell lymphoma and with an excellent so far freedom from progression.³⁴ However, for relapsed mantle cell lymphoma, the same regimen was less efficacious; it induced a 40% CR and a TTP of 7 months in a small group of patients. Similar strategies are pursued by other groups. It emerges from the above studies, that ⁹⁰Y-IT may be particularly helpful in the treatment of mantle cell lymphoma as consolidation after first-line chemotherapy, but its usefulness in relapsed disease, either as monotherapy or as consolidation is limited.

Conclusion

The clinical evidence discussed above supports the role of ⁹⁰Y-IT as a useful consolidation agent after induction chemotherapy for lymphoma. In particular, the randomized phase 3 study (FIT) has demonstrated a remarkable prolongation of time to disease progression conferred by ⁹⁰Y-IT consolidation after induction chemotherapy in patients with follicular non-Hodgkin's B-cell lymphoma and therefore has produced an unequivocal clinical paradigm. This use can be supported by the feasibility of subsequent chemotherapy treatments, the apparent lack of long-term toxicity and the low infectious risk. Such application should be considered in patients with follicular lymphoma when prolongation of remission is desired. This concept is particularly useful for patients with less than complete response to chemotherapy.

The clinical merits of such consolidation use should be carefully weighed in each individual patient case taking into account the goals of treatment and the willingness to incur the risk of radioimmunotherapy-related toxicity. Whether the pre-emptive treatment with RIT of the residual disease may be more beneficial in terms of overall survival compared to reserving RIT for the inevitable progression of the indolent lymphoma will remain an important question to be answered in the subsequent years. If the hypothesis of "temporal synergy", as hypothesized above, is true, then consolidation use ought to be more beneficial than RIT treatment upon progression.

The conclusions of the FIT study allow the incorporation of RIT consolidation in an overall treatment strategy for follicular lymphoma, that may also include protracted maintenance such as rituximab long-term use. Accordingly, it is conceivable that a successful future strategy for follicular NHL may include an induction chemotherapy regimen followed by ⁹⁰Y-IT consolidation, to be followed by rituximab maintenance; this remains an intriguing research question for the future. Presently, radioimmunotherapy consolidation with ⁹⁰Y-IT represents an attractive and relatively brief consolidation treatment option, associated with prolongation of remission, a particularly desired outcome for most patients with follicular lymphoma. Ongoing randomized studies may further elucidate its role as consolidation agent for aggressive lymphoma and within the framework of an ever-changing lymphoma standard of care.

Disclosure

The author declares no conflicts of interest.

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