Annals of Oncology 22 (Supplement 4): iv51–iv53, 2011
doi:10.1093/annonc/mdr174

VIII. Radioimmunotherapy in malignant lymphoma: an underused tool?

A. Hagenbeek

Department of Hematology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

introduction

The radiosensitivity of malignant lymphomas as well as the local targeted delivery of high doses of radiation both make radioimmunotherapy (RIT) an attractive option to fully explore. Radioisotopes are linked to a monoclonal antibody and after intravenous infusion the complex binds to all cells expressing the respective antigen. In this way not only cells binding the radioimmunoconjugate are killed, but also surrounding cells in hundreds of cell layers (depending on the type of isotope used) through a crossfire/collateral damage effect. Obviously, RIT has more side-effects than treatment with cold antibodies like rituximab. However, no major damage to vital organs has been reported as local radiation doses stay (far) below acceptable dose limits. Tolerable, transient toxicity to the bone marrow, in terms of granulocytopenia and thrombocytopenia, is the most prominent feature and therefore so far in most studies only patients with <25% lymphoma cells in the marrow are eligible. On the other hand, RIT is the most effective (single) drug in the treatment of lymphoma, in particular follicular non-Hodgkin lymphoma (NHL), as will be reported below.

The two most commonly used radioimmunoconjugates are [^{90}Y]ibritumomab tiuxetan (zevalin) and [^{131}I]tositumomab (bexxar). Both are based on murine anti-CD20 antibodies. Their properties are summarized in Table 1.

[^{90}Y]ibritumomab tiuxetan (zevalin)

monotherapy in follicular NHL

The initial studies were performed in patients with relapsed or refractory low-grade NHL yielding overall response rates (ORRs) of 70%–80% including 15%–50% complete remission (CR)/CRru and significant progression-free survival (PFS) times [1–4]. It appeared that when zevalin is applied earlier in the course of the disease, higher ORRs and longer duration of remission (DR) were achieved [5]. Comparing results in patients with only one prior line of therapy ($n = 63$), with those in patients who received two or more treatment regimens ($n = 148$), the responses are 86% versus 72% ORR ($P = 0.051$) and 49% versus 28% CR/CRu ($P = 0.004$). Median time to progression (TTP) was 12.6 versus 7.9 months ($P = 0.038$), respectively. Furthermore, in the CR/CRu patients, the median TTP was significantly longer in the group of patients treated with only one prior regimen: 23.9 months versus 15.6 months ($P = 0.04$). In addition, zevalin appears to be effective in rituximab-refractory patients [4]. A randomized, controlled trial comparing zevalin with rituximab in patients with relapsed/refractory follicular NHL showed a higher ORR for zevalin (80% versus 56%) and an improved CR rate (30% versus 16%). The DR and TTP were not enhanced, but the study was not powered to show a possible difference [3].

Zevalin has also been applied as first-line treatment in patients with follicular NHL. Most recently the results of a study in 59 previously untreated patients were reported [6]. At 1 year after zevalin treatment ORR was 72% with 52% CR and 20% partial remission (PR). Among the 33 patients who reached a follow-up of >18 months, 52% continued to stay in CR. At a median follow-up of 23 months, the PFS is 17.9 months. The molecular remission rate (PCR negativity of the Bcl2–IgH translocation product in blood or bone marrow) in this study was 73%. It is concluded that these remission rates after just one injection of zevalin are similar to those achieved by six to eight courses of immunochemotherapy and that zevalin is certainly not more toxic.

zevalin consolidation after induction (immuno)chemotherapy

The FIT trial, initially published in 2008 [7] is so far the largest prospective, randomized trial in RIT, studying the role of zevalin consolidation after first-line remission-induction chemotherapy in follicular NHL. Patients in CR/PR were randomized between one infusion of zevalin ($n = 207$) and observation only ($n = 202$). Comparing the zevalin with the observation group in the updated analysis [8] yielded the following results: CR rates after randomization 87% versus 53%; conversion from PR to CR 78% versus 19%, median PFS at a median follow-up of 66.2 months, 49 months versus 15 months ($P < 0.001$); median PFS for patients in CR after induction >92 months versus 32 months. In the relatively small group of patients induced with rituximab chemotherapy ($n = 59$), the conversion from PR to CR was 71% after zevalin versus 42% in the control group; PFS: >67 months versus 59 months, respectively. These results, albeit from a small subgroup analysis, point to the fact that zevalin is active in patients pretreated with rituximab chemotherapy. This conclusion is further supported by several phase II studies where zevalin was given to patients after remission induction

Table 1. Properties of [^{90}Y]ibritumomab tiuxetan (zevalin) and [^{131}I]tositumomab (bexxar)

	[^{90}Y]Ibritumomab tiuxetan	[^{131}I]Tositumomab
Status	Commercial	Commercial (USA only)
Parent antibody	Ibritumomab (murine)	Tositumomab (murine)
Isotope	^{90}Y (tiuxetan)	^{131}I (covalent)
Emitter	β	β, γ
Imaging	– (^{111}In)	+ (dosimetry required)
β energy, MeV	2.3	0.8
Path length, mm	5.3	0.8
Half life	64 h	8 days
Outpatient treatment	+	Dependent on dose/ regulations

with R-CHOP [9, 10] or R-FND [11]. So far, in the FIT study overall survival (OS) is not different between the two groups. Secondary MDS/AML occurred in six patients in the zevalin group compared with one in the control group. However, given the cytogenetic abnormalities these are most likely due to preceding chemotherapy or to aggressive chemotherapy given after the patients left the FIT trial because of relapsing/ progressing lymphoma. In general, the annualized rate of secondary MDS/AML in patients treated with zevalin (0.55% in the FIT study; 1.0% in the Witzig studies) does not appear to be higher than that observed in patients treated for follicular lymphoma in general (1.03% according to the SEER data) [12].

[^{131}I]tositumomab (bexxar)

monotherapy in follicular NHL

The pivotal study of bexxar in chemotherapy-refractory low-grade NHL showed a 65% ORR, as compared with 28% ORR in the same patients after their last qualifying chemotherapy ($P < 0.001$) [13]. In this study bexxar also induced greatly superior relapse free survival as compared with that after the last chemotherapy. Like zevalin, bexxar shows significant activity in rituximab-refractory patients [14].

Bexxar monotherapy has also been studied in previously untreated patients with follicular lymphoma ($n = 76$): ORR 95% with 75% CR and median TTP of >5 years. It should be noted that most of the patients had a low tumor burden and a low Follicular Lymphoma International Prognostic Index (FLIPI) score [15]. A recent update of the study after a median follow-up of 8 years reported a 10-year OS of 83%, with a median PFS of 6.1 years for all patients and 9.1 years for complete responders [16]

bexxar consolidation after induction (immuno)chemotherapy

Bexxar proved to be highly active after induction of a first remission in patients with follicular NHL employing CVP, CHOP or fludarabine. CR rates of between 67% and 86% were achieved and after bexxar consolidation the conversion rates from PR to CR ranged from 49% to 84% [17–19]. PFS and OS rates were quite impressive, i.e. at 5 years 67% and 87%, respectively, and are thought to be higher than historical data from patients who had received induction chemotherapy alone. So far, not much is known as regards the efficacy of bexxar after remission induction with rituximab-containing regimens. Results of the US Intergroup Study randomizing follicular NHL patients between six cycles of R-CHOP and six cycles of CHOP followed by bexxar are eagerly awaited.

The incidence of 3.5% secondary MDS/AML after treatment with bexxar does not differ significantly from the observations after zevalin. Neither does it seem to be higher than rates described after extensive chemotherapy in these patients [20].

additional currently explored indications for RIT

Currently, there are accumulating data on the role of RIT in diffuse large B-cell lymphoma (DLBCL). During this conference, data on 232 patients with relapsed or refractory DLBCL who underwent RIT are presented [21]. The ORR was 60%; CR 50%, PR 10%. The CR rate for first-line patients was 75%, for relapse patients 37%. The median OS after RIT in first-line therapy was 788 days; for patients treated in relapse, 446 days. With all the data available on RIT in DLBCL, it can be concluded that RIT induces a significant response rate followed by meaningful PFS/OS.

Furthermore, RIT is explored as consolidation treatment after remission induction with R-CHOP in DLBCL. It was shown that zevalin increased CR rates from 75% after R-CHOP to 90%. Toxicity is acceptable and—in one series—at a median follow-up of 42.4 months, median PFS and OS were not reached [22].

Finally, adding RIT to marrow ablative chemotherapy regimens is currently also explored, in both follicular lymphoma and DLBCL. Data from phase II trials are encouraging, toxicity being within the limits of the acceptable. Comparing zevalin–BEAM (Z-BEAM) with a total body irradiation (TBI)-based conditioning regimen in 92 DLBCL patients showed a trend towards an improved 2-year PFS in the Z-BEAM RIT group (66% versus 50%; $P < 0.08$) and a better OS in favour of the Z-BEAM group as compared with TBI-controls (84% versus 59%; $P < 0.01$ [23]. A prospective, randomized trial comparing Z-BEAM with BEAM as conditioning prior to autologous stem cell transplantation in patients with DLBCL showed trends towards superior PFS and OS in particular in low-risk patients. However, due to the limited number of patients and follow-up, the analyses did not reach statistical significance [24].

conclusions

Given the above, RIT is indeed an underused tool. In follicular NHL, RIT represents one of the most effective single agents, in particular if applied as consolidation after remission-induction treatment. The two most frequently used radioimmunoconjugates, i.e. zevalin and bexxar, do not seem to differ in terms of efficacy or toxicity. In comparison with rituximab maintenance in first-remission follicular NHL, applying $4 \times 4 = 16$ infusions of rituximab given over 2 years

after induction with CVP chemotherapy (ECOG 1496 study) [25], just one infusion of zevalin consolidation in first remission [8] yielded a similar 3-year prolongation of median PFS. From a number of phase II studies it is clear that zevalin is active after induction with rituximab-containing regimens. Thus, there are sufficient arguments to move zevalin as consolidation treatment in follicular NHL to an earlier stage of disease, consolidating the remission.

Fewer data are available for RIT in the treatment of DLBCL or as an integral part of marrow ablative conditioning regimens prior to autologous stem cell transplantation. However, results emerging are promising and randomized trials are ongoing.

In this era of targeted treatment RIT, given its impressive therapeutic index, deserves wider application to the benefit of patients with NHL.

references

1. Witzig TE, White CA, Wiseman GA et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 3793–3803.
2. Wiseman GA, Gordon LI, Multani PS et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. Blood 2002; 99: 4336–4342.
3. Witzig TE, Gordon LI, Cabanillas F et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 2453–2463.
4. Witzig TE, Flinn IW, Gordon LI et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 3262–3269.
5. Gordon LI, Molina A, Witzig TE et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. Blood 2004; 103: 4429–4431.
6. Scholz CW, Pinto A, Linkesch W et al. ^{90}Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. First results from an international phase II clinical trial. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 593.
7. Morschhauser F, Radford J, Van Hoof A et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008; 26: 5156–5164.
8. Hagenbeek A, Radford J, Van Hoof A et al. ^{90}Y-Ibritumomab tiuxetan (zevalin) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: updated results after a median follow-up of 66.2 months from the international, randomized phase III First-line Indolent Trial (FIT) in 414 patients. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 594.
9. Jacobs SA, Swerdlow SH, Kant J et al. Phase II trial of short-course CHOP-R followed by ^{90}Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008; 14: 7088–7094.
10. McLaughlin P, Neelapu S, Fanale M et al. R-FND followed by radioimmunotherapy for high-risk follicular lymphoma. 2008 ASH Annual Meeting Abstracts. Blood 2008; 112(11): Abstract 3056a.
11. Hainsworth JD, Spiegel DR, Markus TM et al. Rituximab plus short-duration chemotherapy followed by yttrium-90 ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clin Lymphoma Myeloma 2009; 9: 223–228.
12. Morton LM, Curtis RE, Linet MS et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. J Clin Oncol 2010; 28: 4935–4944.
13. Kaminski MS, Zelenetz AD, Press OW et al. Pivotal study of iodine-131-tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001; 19: 3918–3928.
14. Horning SJ, Younes A, Jain V et al. Efficacy and safety of tositumomab and iodine-131-tositumomab (bexxar) in B-cell lymphoma progressive after rituximab. J Clin Oncol 2005; 23: 712–719.
15. Kaminski MS, Tuck M, Estes J et al. 131-Tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352: 441–449.
16. Kaminski M. I-131-tositumomab monotherapy as frontline treatment for follicular lymphoma: updated results after a median follow-up of 8 years. ASCO Annual Meeting Abstracts. J Clin Oncol 2007; 25(18S): Abstract 8033.
17. Leonard JP, Coleman M, Kostakoglu L et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005; 23: 5696–5704.
18. Press OW, Unger JM, Braziel RM et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: 5-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006; 24: 4143–4149.
19. Link BK, Martin P, Kaminski MS et al. Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: 8-year follow-up in a multicenter phase II study. J Clin Oncol 2010; 28: 3035–3041.
20. Bennett JM, Kaminski MS, Leonard JP et al. Assessment of treatment-related myelodysplastic syndromes and acute myelogenous leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine 131 tositumomab. Blood 2005; 105: 4576–4582.
21. Hohloch K, Lankeit HK, Zinzani PL et al. Radioimmunotherapy for consolidation and relapse treatment of aggressive B-cell non-Hodgkins lymphoma: an updated analysis of the international RIT-network. 11th International Conference on Malignant Lymphoma, Lugano 2011; Abstract 97.
22. Karmali R, Manson A, Bueschel K et al. Phase II study of 2-weekly CHOP + rituximab followed by yttrium-90 ibritumomab tiuxetan (zevalin) in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): final analysis. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 3947.
23. Krishnan A, Palmer J, Nademanee A et al. Comparative analysis of autologous hematopoietic cell transplantation with radioimmunotherapy (RIT) based conditioning versus total body irradiation (TBI) for high-risk diffuse large B-cell lymphoma (DLBCL): toxicity and efficacy. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 32.
24. Shimoni A, Avivi I, Rowe JM et al. A multi-center prospective randomized study comparing ibritumomab tiuxetan (zevalin) and high-dose BEAM chemotherapy (Z-BEAM) vs BEAM alone as the conditioning regimen prior to autologous stem cell transplantation in patients with aggressive lymphoma: possible advantage for Z-BEAM in low-risk patients. 2010 ASH Annual Meeting Abstracts. Blood 2010; 116(21): Abstract 686.
25. Hochster H, Weller E, Gascoyne RD et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG 1496 study. J Clin Oncol 2009; 27: 1607–1614.