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Review Article

Radioimmunotherapy as a treatment modality for non-Hodgkin's lymphoma

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Abstract

Radioimmunotherapy (RIT) is a new treatment option for non-Hodgkin's lymphoma (NHL). In this approach, monoclonal antibodies directed against B-cell antigens are labeled with radionuclides, in order to irradiate the lymphoma from a short distance. Various monoclonal antibodies are used for this purpose, and are labeled with iodine-131, yttrium-90 and rhenium-186. Several combinations, their clinical efficacy, dosing and administration of radiolabeled antibodies, and pharmaceutical aspects of this treatment are discussed. It is concluded that RIT could be a safe and effective treatment, although its role when compared to other forms of treatments needs to be determined.

Introduction

Non-Hodgkin's lymphoma (NHL) is a malignancy of lymphocytes. Over 80% of NHLs are of B-cell origin. The incidence is 16–20 new cases per 100,000 inhabitants per year and still rising. The treatment and prognosis of B-cell NHL depend on the lymphoma type, grade and stage of the disease. Advanced stages are thought to be incurable, although patients with lymphomas of an indolent type can have prolonged periods without evidence of disease. Especially in patients with relapsed or refractory follicular lymphoma, which is a lymphoma of an indolent type, monoclonal antibodies (MAbs) such as rituximab are currently used for treatment, with an overall response rate of about 50% (1).

Monoclonal antibodies may not only be used for treatment, but also as selective carriers for cytotoxic agents or radioisotopes. For the latter therapy, called radioimmunotherapy (RIT), predominantly β-emitting isotopes are used. By these means, targeted anticancer therapy can take place in a selected cell type. The magic bullets used can increase the effectiveness of the therapy, whereas the side effects are reduced (2).

Patients with NHL appear to respond particularly well to treatment with RIT (3). Two products were approved for clinical use by the United States FDA in 2002 and 2003. Moreover, a phase III study was recently started utilizing yttrium-90 (^{90}Y)-labeled MAbs at several large medical centers thoughout Europe. Hence, in this review we would like to highlight the radiopharmaceutical aspects and clinical results of radioimmunotherapy as a new treatment modality.

Antibodies

Immunotherapy has rapidly evolved during the last decade, although the principle of labeling antibodies with

Table I: Radionuclides and monoclonal antibodies used for radioimmunotherapy.

Radiopharmaceutical	Emissions	Physical half-life (days)	Maximum range in tissue (mm)	Advantages/Disadvantages	
^{131}I-Lym-1	β/γ	8.0	2.9	Pro:	-Radionuclide widely available at low cost -Scintigraphy possible
^{131}I-Tositumomab				Contra	-Clinical application in most countries -Murine antibodies
^{90}Y-Ibritumomab				Pro:	-Easy and stabile labeling -Outpatient treatment
				Contra:	-No scintigraphy possible -Unlabeled ^{90}Y accumulates in bone
	β	2.7	11		-Murine antibody
^{90}Y-Epratuzumab				Pro:	-Easy and stabile labeling -Outpatient treatment -Humanized antibody
				Contra:	-No scintigraphy possible -Unlabeled ^{90}Y accumulates in bone
^{186}Re-Epratuzumab	β/γ	3.8	5.1	Pro:	-Scintigraphy possible -Outpatient treatment -Humanized antibody
				Contra:	-Laborious labeling procedure
^{67}Cu-Lym-1	β/γ	2.6	1.8	Pro:	-Scintigraphy possible -Outpatient teatment
				Contra:	-Low availability of the radionuclide -Murine antibody

radioisotopes and their administration to patients was already known 50 years ago. At that time, immunoglobulins were labeled with iodine-131 (^{131}I). The efficacy of this first RIT was very low. In the early years, polyclonal antibodies were used (4), but this was changed by the development of a technique for the production of MAbs by Köhler and Milstein in 1975 (5).

At first, unlabeled MAbs were used for the immunotherapy of patients with NHL. Rituximab, a chimeric anti-CD20 MAb, is the only licensed immunotherapeutic product for the treatment of relapsed follicular NHL. As stated earlier, the overall response rate in these patients is 50%: 6% complete responses (CR) and 44% partial responses (PR) after 4 weekly infusions of 375 mg/m^2 (1). In the near future, a humanized anti-CD22 MAb, epratuzumab, is expected to be available for the same kind of treatment. It is currently being studied in phase III clinical trials at a dose of 4 weekly infusions of 360 mg/m^2 (6).

The radioimmunotherapy of NHL patients can have two additional benefits over unlabeled antibody treatment: NHL is a radiosensitive malignancy, and adjacent lymphoma cells can be irradiated by labeled MAb bound to tumor cells nearby. Therefore, it is not necessary to target every individual cell with an MAb to cause cell death, which is the case in regular immunotherapy. This phenomenon is known as the bystander effect.

Radionuclides for RIT

One of the most common radionuclides utilized for therapy in nuclear medicine is ^{131}I. It emits electrons (β-radiation) from the atomic nucleus with a maximal range of 3 mm. Further specifications of the isotopes used are listed in Table I. Moreover, ^{131}I also emits γ-photons. This type of radiation can be visualized by a gamma camera, making this radionuclide suitable for imaging.

A disadvantage of the γ-radiation emitted by ^{131}I is its high energy, which could cause relatively high radiation doses to relatives and staff in the direct environment of the patient. Depending on national legislation, patients should stay on the nuclear medicine ward after treatment with high doses of ^{131}I.

Yttrium-90 (^{90}Y) is becoming a widely used isotope for RIT. This nuclide emits solely high-energy β-particles with a maximal range of 11 mm (Table I). Because it decays by β-emissions only, the dose rate after RIT is very low, even when high doses are given. Therefore, it would be possible to treat patients on an outpatient basis. The absence of γ-radiation makes imaging impossible.

Another nuclide utilized for RIT is rhenium-186 (^{186}Re, Table I). It is used for RIT of both hematological and solid tumors (7, 8). Rhenium-186 emits medium-energy β-radiation and low-energy γ-photons. The latter are emitted in only 10% of all disintegrations. Hence, scintigraphy and dosimetry are possible. Moreover, the dose rate after treatment (maximum of 5 μSv.m^2/h) is low enough to facilitate outpatient treatment.

Radiopharmacy

Isotope chemistry determines the way in which radiolabeling can take place. Metal isotopes like ^{90}Y and ^{111}In

are conjugated to MAbs using chelators. The most frequently utilized chelators are related to ethylenediamine tetraacetic acid (EDTA). A two-step preparation procedure is most common for experimental labeling of radioisotopes to MAbs. First, a chelator–isotope complex is produced, followed by conjugation to the MAb. Subsequently, this mixture is purified by, for instance, column chromatography. Before administration, quality control is assessed by chromatography, yielding the radiochemical purity of the compound.

The MAb ibritumomab, which is currently being tested in clinical trials for the treatment of NHL, is provided as a kit containing ibritumomab conjugated with the chelator tiuxetan. Using this radiopharmaceutical kit, ^{90}Y-chloride can be easily added to the MAb solution at an optimal pH. This mixture should be allowed to incubate during 5 min at room temperature. According to the manufacturer's specifications, a radiochemical purity of > 95% must be obtained.

Iodine-131 and other halogens are labeled to proteins by addition to aromatic structures using a catalysator like chloramine T. Thus, these isotopes are bound to tyrosine and histidine amino acid residues within the MAb. A disadvantage of the latter method is dehalogenation of the isotope *in vivo*, causing release of unbound radioactivity within the patient (9).

Another chelator which is used for the labeling of MAbs is mercaptoacetyltriglycine (MAG3). This chelator forms a complex with group VII elements, such as ^{186}Re and ^{99m}Tc (10). The latter production method yields a stable preparation, but has the disadvantage of being very laborious.

After preparation of the radiopharmaceutical, quality control should be assessed. For the determination of radiochemical purity, both thin-layer chromatography and high-pressure liquid chromatography (HPLC) are used. The type of assay used for the determination of radiochemical purity depends on the amount of experience available for the respective labeling method. The complexity of most labeling procedures requires an adequate validation before less accurate methods like thin-layer chromatography can be used. Therefore, HPLC combined with UV and radiochemical detection is often used to validate the preparation. Furthermore, the pH is determined as an indication of a proper preparation performance. Depending on the preparation method and the physical half-life of the isotope, additional quality control assays such as a pyrogen test can be performed. Monoclonal antibodies labeled with β-emitting isotopes may show radiolysis. Often, inline filters (0.22 m) are used to protect patients for degradation products of MAbs undergoing radiolysis.

Clinical studies

A variety of MAbs have been used in combination with the radionuclides ^{90}Y, ^{131}I and ^{186}Re in clinical trials. A breakthrough in this field was achieved by the group of DeNardo. In contrast to earlier studies in which MAbs directed against the lymphoma cells of every individual patient were used, this group was the first to use MAbs directed against a specific antigen that could universally be used for the treatment of B-cell NHL. Their MAb, Lym-1, directed against HLA-DR10, was used in combination with the radionuclides ^{131}I, ^{90}Y and copper-67 (^{67}Cu) (11).

An overview of radiopharmaceuticals for the RIT of NHL is given in Table I. Some of the products are described in detail in the section below, with results of their clinical application.

^{90}Y-Ibritumomab (Zevalin®)

Ibritumomab is the murine antibody that preceded the development of the chimeric MAb rituximab. This murine IgG_1 is directed against the B-cell antigen CD20. Labeled with ^{90}Y (Zevalin®), it was approved by the FDA for clinical use in 2002 (12). Administration of ^{90}Y-ibritumomab was preceded by infusions of various amounts of unlabeled rituximab in a clinical trial in 14 patients. A large quantity of unlabeled MAbs preceding the infusion of the labeled MAbs led to an improved biodistribution of the labeled product. Higher uptake in tumors and lower uptake in the spleen and spine were observed (13).

Since that trial, in all other clinical trials the infusion of ^{90}Y-labeled ibritumomab was preceded by 2 infusions of 250 mg/m^2 rituximab. The therapeutic effects shown in the first trials were promising. In a phase I/II trial, an overall response rate (ORR) as high as 68% was achieved. In 13 of the patients included (26%), CRs could be demonstrated (14). In a multicenter, prospective, randomized trial, treatment of patients with relapsed or refractory CD20-positive NHL with rituximab was compared with treatment of these patients with ^{90}Y-ibritumomab (15). Of the 143 patients included, 70 were treated with 4 weekly infusions of 375 mg/m^2 rituximab, *i.e.,* the standard treatment schedule of rituximab. The other 73 patients were given 2 infusions of 250 mg/m^2 rituximab at an interval of 2 weeks. The second rituximab administration was accompanied by an infusion of 15 MBq/kg ^{90}Y-ibritumomab. In the rituximab group, the ORR was 56% compared to 80% in the ^{90}Y-ibritumomab group (15). In particular, the percentages of CRs differred: 16% in the rituximab group *vs.* 30% in the ^{90}Y-ibritumomab group (15).

Last year, a multicenter phase III trial started in Europe and Canada, in which ^{90}Y-ibritumomab is given to patients with stage III or IV follicular lymphoma directly after first-line chemotherapy. Patients with a PR or CR after first-line treatment are eligible for randomization to a group that will be treated with 2 infusions of 250 mg/m^2 rituximab and a single infusion of ^{90}Y-ibritumomab, or a group that will not receive further treatment. The aim of the study is to determine the progression-free survival, change of response status (PR to CR) and overall survival.

^{131}I-Rituximab

In an increasing number of studies, the chimeric version of ibritumomab is used for radiolabeling and RIT. Behr *et al*. reported on the myeloablative use of ^{131}I-labeled rituximab instead of ibritumomab. In a study in 5 patients –2 with high-grade and 3 with low-grade NHL– who received myeloablative RIT followed by autologous stem cell support, a CR was achieved by 3 of these patients (16). This approach used in 7 patients with mantle cell lymphoma, an aggressive and prognostically unfavorable type of NHL, led to a CR in 6 cases and a PR in 1 patient (17). Another German group presented data on both myeloablative and nonmyeloablative RIT using ^{131}I-rituximab. An ORR of 54% was achieved in 26 patients with the latter procedure. Myeloablative RIT in 25 patients led to a CR in 48% and a PR in 28% of the treated patients.

In Australia, a phase II trial was conducted in 42 patients with relapsed or refractory NHL, using an individualized dosing regimen (18). First, an infusion of 375 mg/m^2 unlabeled rituximab was administered, followed by a tracer dose of 200 MBq ^{131}I-rituximab. Dosimetric analysis was used to determine the amount of radioiodine needed to deliver a whole-body dose of 0.75 Gy, comparable to the dosing scheme of ^{131}I-tositumomab. This calculated amount of ^{131}I-rituximab was administered a week after the tracer dose, again preceded by an infusion of 375 mg/m^2 unlabeled rituximab. This approach led to grade 4 hematological toxicity in 2 of 42 patients. Nineteen of 35 evaluable patients (54%) achieved a CR and 6 patients (17%) a PR to RIT. Iodinated rituximab is currently being used in German, Australian and U.K. RIT trials.

^{131}I-Tositumomab (Bexxar®)

Tositumomab is another murine anti-CD20 MAb that is currently approved for radiolabeled clinical use. In June 2003, the FDA approved Bexxar® for the treatment of patients with CD20-positive follicular NHL, with and without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy. Tositumomab is a murine IgG2a that is labeled with ^{131}I. Several RIT approaches have been described for this radiopharmaceutical.

1. Nonmyeloablative radioimmunotherapy

For RIT using ^{131}I-tositumomab, a personalized radioactive dose is determined after a dosimetric study using a tracer dose of ^{131}I-tositumomab. In a dose-escalation phase I trial, a maximum tolerated whole-body dose of 0.75 Gy was found (19). Optimal tumor targeting was observed when unlabeled tositumomab was administered prior to infusion of radioiodinated tositumomab. In a subsequent multicenter phase II trial, all patients received a dosimetric dose of 185 MBq ^{131}I-labeled to 35 mg tositumomab, preceded by an infusion of 450 mg unlabeled antibody (20). After 1-2 weeks, the therapeutic dose of ^{131}I-tositumomab was administered, again preceded by 450 mg unlabeled tositumomab. Of 47 patients, 6 experienced a CR and 16 a PR.

Finally, a multicenter, open-label, randomized study was conducted comparing the efficacy and safety of ^{131}I-labeled tositumomab to unlabeled tositumomab in patients with relapsed or refractory CD20-positive NHL (21). Seventy-eight patients were enrolled. The original NHL was follicular in 97% of patients, with 17% having experienced transformation to an aggressive histology. Patients receiving ^{131}I-tositumomab therapy were dosed as mentioned above. The patients randomized to unlabeled tositumomab received 2 doses of 485 mg, *i.e.,* the same antibody dose that is given to patients treated with ^{131}I-tositumomab. A confirmed response was documented in 23 of 42 (55%; CR 33%, PR 21%) patients who received tositumomab RIT, and 6 of 36 (17%; CR 8%, PR 8%) patients who received tositumomab. The median duration of confirmed responses for Bexxar®-treated patients has not been reached, and for unlabeled tositumomab-treated patients it was 18 months. This study documents that the radioiodine component of RIT using ^{131}I-tositumomab provides significant therapeutic effect over and above that provided by unlabeled tositumomab, with an acceptable toxicity profile (21).

2. Myeloablative RIT

Another approach to the treatment of lymphoma patients is being applied by a group from Seattle. In their trials, a myeloablative dose of ^{131}I-tositumomab is chosen. Stem cells are harvested before RIT and reinfused to the patients after RIT. This approach demands an optimal condition of the patient population, since the patients will receive an autologous stem cell transplantation.

Results of myeloablative RIT trials cannot be easily compared with the results achieved with nonmyeloablative RIT trials. With myeloablative RIT, impressive results were obtained: CRs in over 80%, with a median disease-free survival of over 3 years (22). Prospective randomized trials should establish the role of myeloablative RIT compared to high-dose chemotherapy, with or without total-body irradiation, followed by autologous stem cell transplantation. These data suggest that at least toxic total-body irradiation could be replaced by RIT (23).

3. First-line RIT

Radioimmunotherapy could be a potential first-line treatment for NHL. Data on first-line RIT with ^{131}I-tositumomab in 76 patients with stage III or IV follicular lymphoma were presented by Kaminski in 2000 (24). Response rates were high: an ORR of 97% was achieved, and 63% of all patients experienced a CR. After

a period of 3 years, 68% of these patients remained progression-free. The same radiopharmaceutical is currently used in combination with chemotherapy.

Epratuzumab (LymphoCide™)

The only humanized MAb for the RIT of NHL patients is epratuzumab, which targets CD22. Predosing with large quantities of unlabeled MAbs to improve biodistribution appears to be unnecessary when using epratuzumab. This antibody was used for RIT with both ^{131}I and ^{90}Y. The pharmacokinetics, dosimetry and initial therapeutic results of both radiolabels were compared in a clinical trial (25). Doses were calculated applying an estimated red marrow dose of 1 Gy, or 0.5 Gy in the case of prior high-dose chemotherapy, as determined after administration of a tracer dose of 222 MBq ^{131}I- or ^{111}In-epratuzumab. The protein dose in all infusions was 0.75 mg epratuzumab/kg. In the ^{131}I-epratuzumab treatment group (n=13), 1 CR and 1 PR were obtained. In the ^{90}Y-epratuzumab group (n=7), 2 PRs were seen. Treatment with both radiolabels was equally safe and pharmacokinetics and dosimetry were similar, but the tumor dosimetry of ^{90}Y-epratuzumab appeared to be more favorable as compared to ^{131}I-epratuzumab, probably because the CD22 antigen is internalized by B-cells and ^{90}Y is retained by the cell after internalization of the radioimmunoconjugate. Recently, the results of a dose-escalation study were published, revealing that doses of 0.74 GBq/m^2 ^{90}Y-epratuzumab were well tolerated by lymphoma patients who had not had prior high-dose chemotherapy (26). At this dose level, no dose-limiting toxicity was observed. In a group of lymphoma patients with high-dose chemotherapy prior to RIT, a dose of 0.37 GBq/m^2 ^{90}Y-epratuzumab did not lead to dose-limiting toxicity.

Objective responses have been seen even at low doses of ^{90}Y-epratuzumab. A group at the University Hospital in Lund, Sweden, gave patients 2 or 3 injections of only 185 MBq ^{90}Y-epratuzumab/m^2. Patients with prior high-dose chemotherapy and stem cell rescue received only 92.5 MBq ^{90}Y-epratuzumab/m^2. Partial or complete responses were observed in 5 of 8 patients (27).

A nonmyeloablative dose-escalation study with ^{186}Re-labeled epratuzumab was conducted in our hospital (7). Eighteen patients were included in this trial, 15 of whom were treated with ^{186}Re-epratuzumab. Patients with relapsed or refractory CD22-positive NHL were eligible for inclusion. After inclusion, a tracer dose of 750 MBq ^{99m}Tc-epratuzumab was infused. Directly after infusion and 1 day after infusion, scintigraphic images were recorded. In the case of unfavorable biodistribution, *i.e.,* predominant uptake in bone marrow and spleen, no RIT was given. This was the case in 2 patients. If normal biodistribution was seen, the patients were treated 1 week after the diagnostic procedure with ^{186}Re-epratuzumab at a dose ranging from 0.5 to 2.0 GBq/m^2. A CR was obtained in 1 of the 15 patients treated, 4 patients had a PR lasting several months and 4 patients had stable disease following RIT with ^{186}Re-epratuzumab.

Adverse reactions and side effects

The major and dose-limiting toxicity of nonmyeloablative RIT is myelotoxicity: a transient decrease in platelet and white blood cell counts is observed 4–6 weeks following treatment. In the case of myeloablative RIT, cardiopulmonary toxicity is dose-limiting (28).

During or after infusion of labeled MAbs, the same infusion-related adverse reactions can be observed as following infusion of unlabeled MAbs like rituximab: fever, chills, hypotension, bronchospasm and allergic symptoms. Therefore, it is advised that patients to be treated with (labeled) MAbs be premedicated with paracetamol and an antihistaminic. Special attention should be paid to the equipment present in the administration room. Emergency medication such as antihistaminic drugs, prednisolone and epinephrine should be ready for use.

Dosimetry

The role of dosimetry depends on the radiopharmaceutical used. All trials so far used tracer doses to visualize the biodistribution of the radiolabeled MAbs prior to actual treatment. These data were also used for dosimetric analysis. Radioimmunotherapy trials using ^{131}I-labeled MAbs need dosimetric analysis prior to RIT in order to establish the radioactive dose to be given. Most studies using other radionuclides for RIT used tracer doses of ^{111}In- or ^{99m}Tc-labeled MAbs to acquire scintigraphy and dosimetry prior to RIT. ^{90}Y-Ibritumomab is the first radiopharmaceutical for which it is claimed that dosing can be safely done without dosimetric analysis, being based solely on the patient's weight (29).

The role of tumor dosimetry is of limited value. The low estimated absorbed doses to lymphomas are striking in light of the objective responses observed (30). No correlation between doses and responses could be found in a recent study (26). Although it is hard to estimate the absorbed doses, especially to small lymphomas that are hardly visible on scintigraphy, we can conclude that responses not only depend on the absorbed dose of radiation, but also on the antitumor activity of the monoclonal antibodies (13, 26).

Conclusions

Based on the data presented in this paper, we may conclude that RIT is an effective treatment modality for patients with NHL with limited toxicity. The efficacy of RIT in comparison with conventional treatment needs to be established, as well as the optimal timing of this novel treatment.

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