Radioimmunotherapy of refractory or relapsed Hodgkin's lymphoma with ^{90}Y-labelled antiferritin antibody

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The aim of this study was to evaluate the safety and efficacy of radiolabelled rabbit polyclonal antiferritin antibody in relapsed or refractory Hodgkin's lymphoma. The protocol included a first intravenous injection of ^{111}In-labelled antiferritin antibody, followed by immunoscintigraphy at 4, 48 and 72 h, and an intravenous injection of ^{90}Y-labelled antiferritin antibody in the case of tumour targeting. Ten patients were included in the study: median number of chemotherapy regimens: 3; number of autografted patients: 8; number of previously irradiated patients: 9; response to last chemotherapy: six partial response and four progressions. All immunoscintigraphies showed tumour targeting. Nine patients were treated, as the last patient died from progressive Hodgkin's lymphoma before therapeutic injection. Median injected activity was 12 MBq/kg (0.32 mCi/kg). Among the 10 patients who were included in the study, one complete response and six partial responses were observed (overall response rate 70%) with a median duration of response of 8 months (range: 7–12 months). Toxicity was mainly haematological, with grade 1 or 2 neutropenia and anaemia, and grade 2 and 3 thrombocytopenia. The pharmacokinetic study showed that the half-lives of ^{111}In and ^{90}Y were almost identical. These results confirm those previously reported and show the therapeutic potential of rabbit polyclonal antiferritin antibody in relapsed or refractory Hodgkin's lymphoma. They therefore justify further multicentre prospective trials. *Anti-Cancer Drugs* **18:725–731 © 2007 Lippincott Williams & Wilkins.**

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Introduction

The treatment of Hodgkin's lymphoma (HL) constitutes one of the great successes of oncology in the last 40 years. This is because most patients with HL are cured by conventional treatment methods, i.e. chemotherapy (CT) and radiotherapy (RT) [1–3]. In particular, involved-field RT, combined with poly-chemotherapeutic regimens, constitutes one essential way to cure early stage I or II HL [4], whereas its role appears less important in advanced-stage HL [5]. Patients with refractory or relapsed lymphoma, however, have a much poorer prognosis [6]. Dose intensification with peripheral haematopoietic stem cell transplantation – the proposed treatment for these severe forms – has resulted in an improvement in survival rates compared with those in conventional salvage chemotherapies [7,8] and in a 25–50% probability of disease-free survival [9]. Similarly, bone marrow allografts have reduced the risk of relapse, although at the price of significant toxicity [10]. The important role of RT in the treatment of HL dates back to the beginning of the 20th century [11]. For cases of refractory or relapsed lymphoma, RT presents a number of theoretical advantages: (1) approximately one-half of the patients who are candidates for dose intensification have never undergone irradiation [12] and (2) almost one-third of the patients who relapse after CT achieve complete remission following a single session of salvage RT [13–16]. Some teams have therefore incorporated RT into the conditioning regimen for dose intensification, either in the form of total-body irradiation or in the form of 'radical' RT consisting of total-lymphoid irradiation that may then be extended to the other tumour sites [17]. Finally, 'involved-field' irradiation carried out before or after dose intensification improves the complete remission rate and reduces the risk of relapse in the initially involved field [18].

In this particular disease setting, radioimmunotherapy (RIT) can prove to be an innovative approach to treatment, as it presents the dual benefits of specific recognition of tumour sites by the antibody (Ab) used, and of selective irradiation of the bound cells and the adjoining cells by the radioisotope linked to the Ab. The first tests with radiolabelled antiferritin Abs developed in the US by Huib Vriesendorp and Syed Quadri, using diethylenetriamine pentaacetic acid (DTPA) as chelator,

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achieved promising results, justifying the setting up of therapeutic trials in patients with refractory or relapsed HL. On the basis of extracts from the spleens of patients with HL, a lymphoma-specific antigen was detected and was subsequently identified as ferritin [19,20]. Ferritin is a polymer consisting of 24 subunits. There are two types of subunit: subunit H (for heart or heavy) and subunit L (for liver or light). Various isoforms of ferritin have been isolated according to the relative proportions of subunits H and L that they contain. The ferritin present in the liver, spleen and bone marrow is predominantly composed of L subunits, and its functions include protecting organs from damage caused by free radicals. The ferritin present in the heart, kidneys, ovaries and pancreas is mainly composed of H subunits. The iron-depleted form of ferritin, known as apoferritin, is found in high serum and tumour tissue concentrations in certain types of cancer, such as cancer of the liver, pancreas and ovaries, head and neck cancers, neuroblastomas, and, of course, HL [21]. The increased ferritin ratio in tumour tissues is favourable to the development of RIT, specifically targeted against ferritin-positive cells.

Various studies have tested antiferritin Abs linked to ^{90}Y using a DTPA chelator ([^{90}Y] DTPA–antiferritin Abs). Two dose-escalating studies were conducted in patients with HL. The first study showed an overall response rate (ORR) of 51% for doses between 10 and 50 mCi [22]; the second compared a single injection of 0.3, 0.4 or 0.5 mCi/kg, with ORRs of 22, 60 and 86% and complete response (CR) rates of 12, 26 and 43%, respectively [23]. Fractionated doses were also studied, specifically comparing an injection of 0.5 mCi/kg with two injections of 0.25 mCi/kg. The objective response and CR rates were 86 and 43% for the single injection compared with 45 and 3% for the fractionated dose [23]. No adverse effects were observed following injection of ^{111}In-labelled Abs [23]. Following the therapeutic injection of ^{90}Y-labelled Abs, one-half of the patients complained of tiredness and nausea for 3 days. The major toxicity was haematological as it mainly affected the platelet counts. It was observed within 2–3 weeks and usually resolved within a few weeks [22]. Exceptional cases of myelodysplasia were observed, although it was impossible to determine whether this was a complication of RIT or of the previous treatments received by these patients [23,24]. No nonhaematological toxicity was reported. Finally, fewer than 5% of patients developed human antibody rabbit antibody (HARA).

On the basis of these results, and after obtaining [^{90}Y] DTPA–antiferritin Abs from Huib Vriesendorp and Syed Quadri, several patients with refractory or relapsed HL were treated. In this study, we therefore present the results of this small cohort of patients with refractory or relapsed HL. These results support the initiation of clinical trials that were started in 2006 with newly produced 1,4,7,10-tetra-azacyclododecane-N, N′, N″ N‴-tetraacetic acid (DOTA)-conjugated polyclonal antiferritin Abs labelled with ^{111}In/^{90}Y radioelements.

Patients and methods

Patient selection

After obtaining informed consent from each patient, 10 patients with histologically proven HL were selected for antiferritin Ab RIT between October 1998 and December 2000. All data concerning the patients' histories and lymphomas were collected. We therefore determined all the treatments previously received by the patients, i.e. the number of CT regimens, the number of courses of irradiation and the histories of high-dose CT regimens followed by autologous stem cell transplantation. We also assessed the initial staging of the disease with determination of performance status according to the Eastern Cooperative Oncology Group classification [25], determination of B-symptoms, and nodal and/or extranodal sites. Staging of the disease was established according to the Ann Arbor classification for malignant lymphomas. Before RIT, the extent of the disease was determined by a standardized staging evaluation, including computed tomography of the chest and the abdomen. Bone marrow biopsy was not systematically performed before the radiolabelled Ab injections. Very few data are, therefore, available on cellularity and tumour infiltration.

Radioimmunoconjugates

Polyclonal rabbit antihuman ferritin Abs, provided by Huib Vriesendorp and Syed Quadri, were produced according to the previously reported protocol [24]. Immunoconjugates were prepared by reacting isothiocyanatobenzyl-DTPA chelators with lysine residues of the immunoglobulin [26]. Radiolabelling methods consisted of indirect conjugation between Ig protein and ^{111}In and ^{90}Y radiometals [24]. Between 148 and 370 MBq (4–10 mCi) of indium chloride or 7–15 MBq (0.19–0.40 mCi) of ^{90}Y per kg of body weight was linked to 2 mg of Ab with a radiolabelling yield ranging from 91 to 95%. Various control tests were performed after radiolabelling. These consisted of the Endotoxin Detection Kit based on the limulus amoebocyte lysate assay and instant thin layer chromatography. These tests established the endotoxin limits in radioimmunoconjugates and determined the radiochemical purity.

Treatment protocol

The protocol included a first intravenous injection of 2 mg of antiferritin Ab, labelled with 112 MBq (3 mCi) of ^{111}In, followed by immunoscintigraphy at 4, 48 and 72 h to evaluate tumour targeting. In the presence of tumour targeting, an intravenous injection of ^{90}Y-labelled antiferritin Ab was administered at various activities. One patient received two sequential administrations of ^{90}Y-labelled antiferritin Ab at 15-day intervals. Several other patients for whom HL relapsed after the first polyclonal antiferritin Ab RIT were retreated with a total of one to

four administrations. Response to RIT was assessed according to standard recommendations [27].

Pharmacokinetics

To determine the pharmacokinetic (PK) profile of ^{111}In and ^{90}Y labelling, a limited five-time-point plasma sampling schedule was performed. Blood samples were drawn at 0 (baseline), 2, 24, 48 and 72 h after the start of the infusion. Urine samples were collected at 24, 48 and 72 h after the start of the infusion. The analytical method used to determine radioimmunoconjugate concentrations in human plasma and urine was based on a γ-counting method. This method consists of triplicate counting of each sample with a γ counter. Pharmacokinetic analysis was fitted to a biexponential function.

Results

Patient characteristics

Patient characteristics at initial diagnosis are presented in Table 1. Seven patients were in CR after the first CT/RT and relapsed after a median interval of 18 months (range: 5–26 months). The median number of CT regimens before RIT3 was three (range: 2–4); nine patients received high-dose CT followed by autologous stem cell transplantation and eight patients had been previously irradiated. The response to last CT before RIT was six partial responses (PRs) and four progressions. Nine patients had stage IV disease with a performance status between 1 and 3 before antiferritin Ab RIT (Table 2).

Treatment protocol

All the 10 patients who received ^{111}In-labelled antiferritin Ab showed tumour targeting on immunoscintigraphy. One patient is illustrated in Fig. 1. Immunoscintigraphies performed at 4, 48 and 72 h showed a slow vascular clearance of the radiolabelled Ab, and a specific mediastinal and liver uptake (arrows).

Nine patients were treated with ^{90}Y-labelled antiferritin Ab, while one patient did not receive RIT because of HL progression. Five patients received one injection, three patients received two injections (0.5, 5 and 14 months after the first injection) and one patient received four injections (3, 9 and 16 months after the first injection). The median injected activity of the first radiolabelled Ab administration was 12 MBq/kg (0.32 mCi/kg) (range: 7–15 MBq) (Table 3).

Safety and response assessment

Toxicity was mainly haematological, with grade 1 or 2 neutropenia and anaemia, and grade 2 and 3 thrombocytopenia; no grade 4 haematological toxicity was observed, except after repeated injections in one patient (Table 4). One patient experienced generalized convulsions 24 h after the therapeutic injection, for which no aetiology, in particular brain lymphomatous involvement, was demonstrated and which was not proved to have been induced by RIT (Table 4).

Among the 10 patients who were included in the study, we observed one CR (10%), six PRs, for an ORR of 70%, one stable disease and one tumour progression after the first therapeutic injection (one patient received two administrations at a 15-day interval and tumour response was then assessed after the two RIT injections) (Table 3). The median duration of response for the responding patients was 8 months after the first therapeutic injection (range: 7–12 months).

Table 2 Patient characteristics at the time of RIT

Patients	PS	Stage	Tumour targets	*N* lines of CT	Response to last CT
1	2	IV	Liver, lung	2	PR
2	3	IV	Nodes, lung	4	Refractory
3	1	IV	Nodes, lung	4	PR
4	2	IV	Nodes, lung	4	Refractory
5	3	IV	Nodes, lung	3	Refractory
6	2	IV	Nodes, lung	2	Refractory
7	2	III	Nodes	2	PR
8	3	IV	Nodes, lung	3	PR
9	3	IV	Bone, lung	4	PR
10	2	IV	Nodes, lung	4	PR

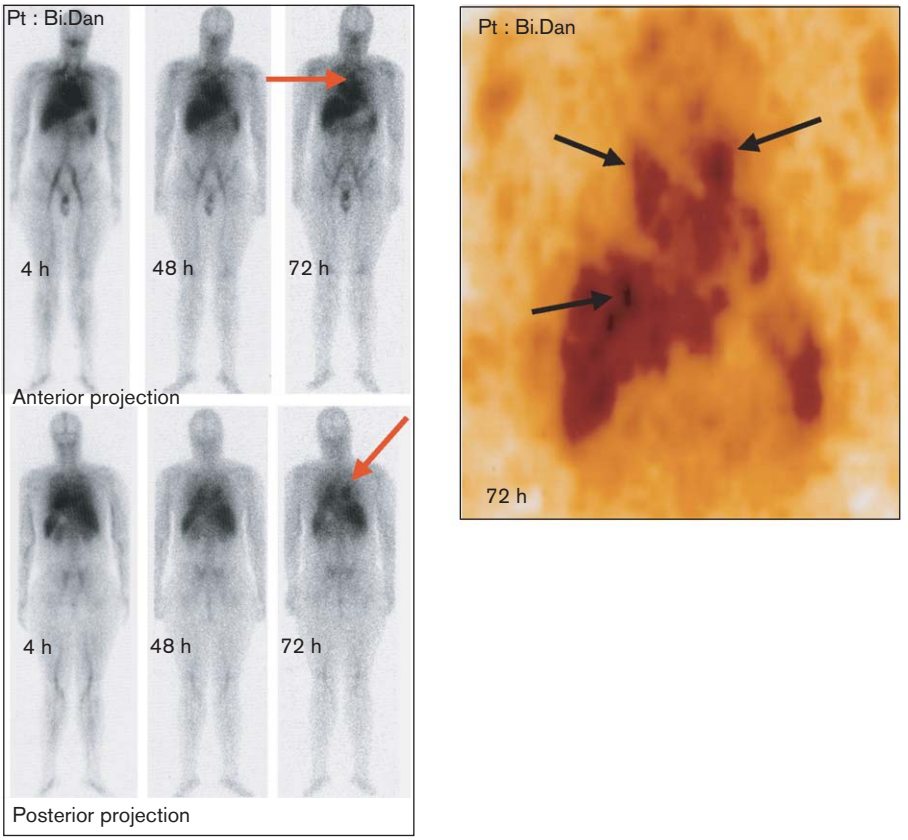
CR, complete response; CT, chemotherapy; PR, partial response; PS, performance status; RIT, radioimmunotherapy.

Table 1 Initial patient characteristics and outcome

Patients	Age	Sex	Histology	B	PS	Stage	Response to first CT	Time to first relapse (months)	RT	ASCT
1	28	M	NS	B	2	IV	CR	18	Yes	Yes
2	25	M	NS	B	2	II	CR	5	Yes	Yes
3	32	F	NS	A	0	II	Prog.	–	Yes	Yes
4	43	M	NS	B	1	IV	PR	6	No	Yes
5	18	M	MC	B	2	II	CR	18	Yes	Yes
6	36	M	NS	B	2	III	CR	26	No	Yes
7	29	M	NS	A	1	IV	CR	18	Yes	Yes
8	43	M	NS	B	2	II	Prog.	–	Yes	No
9	35	M	MC	A	1	IV	CR	7	Yes	Yes
10	32	M	NS	A	1	III	CR	9	Yes	Yes

ASCT, autologous stem cell transplantation; B, B-symptoms; CR, complete response; CT, chemotherapy; F, female; M, male; MC, mixed cellularity Hodgkin's lymphoma; NS, nodular sclerosis Hodgkin's lymphoma; PR, partial response; Prog., progression; PS, performance status; RT, radiotherapy.

Fig. 1



^{111}In-labelled antiferritin antibody (Ab) immunoscintigraphy. Immunoscintigraphy using polyclonal rabbit antihuman ferritin Abs radiolabelled with ^{111}In was performed at times 4, 48 and 72 h. The arrows indicate lymphomatous sites fixations in the sites of residual disease detected with computed tomography scan confirming the specific tumour targeting before therapeutic administration of ^{90}Y-labelled antiferritin Ab.

Table 3 First [^{111}In] and [^{90}Y] DTPA–antiferritin Ab injection

Patients	[^{111}In] DTPA–antiferritin Ab		[^{90}Y] DTPA–antiferritin Ab injection			
	Activity [MBq (mCi)]	Result	Activity/kg [MBq (mCi)]	Total activity [MBq (mCi)]	Response	Response duration (months)
1	198 (5.28)	+	7.5 (0.2)	712 (19)	CR	8
2	232 (6.18)	+	12.4 (0.33)	806 (21.49)	PR	12
3	109 (2.9)	+	12 (0.32)	504 (13.45)	PR	8
4	141 (3.76)	+	15 (0.4)	1080 (28.8)	PR	8
5[a]	197 (5.25)	+	–	–	–	–
6	239 (6.38)	+	12 (0.32)	1033 (27.55)	SD	6
7	191 (5.1)	+	7 (0.19)	703 (18.75)	PR	8
8	133 (3.54)	+	15 (0.4)	1230 (32.8)	PR	8
9	237 (6.33)	+	13 (0.35)	881 (23.5)	Progression	/
10	145 (3.88)	+	8.6 (0.23)	786 (20.97)	PR	7
Median	194 (5.2)	/	12 (0.32)	806 (21.49)	ORR 78% (CR 11%)	8

Ab, antibody; CR, complete response; DTPA, diethylenetriamine pentaacetic acid; ORR, overall response rate; PR, partial response.
[a]Patient 5 was not treated with [^{90}Y] DTPA–antiferritin Ab because of Hodgkin's lymphoma progression.

Pharmacokinetics

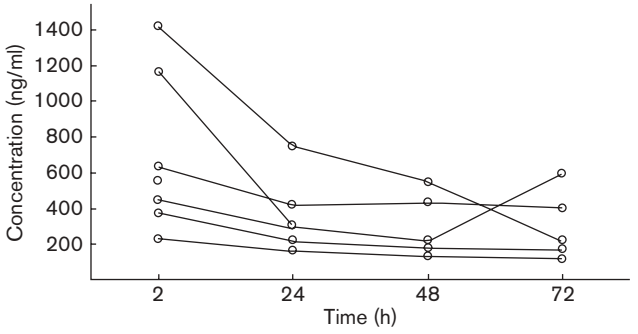
Aliquots of the ^{90}Y- or ^{111}In-labelled antiferritin Ab solutions were counted, and the count values have served for the calculation of the Ab-equivalent plasma concentrations and the Ab-equivalent amount in urine. Mean ^{90}Y- or ^{111}In-labelled antiferritin Ab concentration–time profiles are shown in Fig. 2. A summary of plasma pharmacokinetic parameters is presented in Table 5. The mean C_{max} of ^{90}Y and ^{111}In-labelled antiferritin Abs were 690 and 887 ng/ml, respectively. The mean $AUC_{0-\infty}$

Table 4 Haematological and nonhaematological toxicity of RIT

Patients	Haematological toxicity (grade)			Nonhaematological toxicity	Death-related to RIT
	Neutrophils	Hb	Platelets		
1	2	1	2	No	No
2	2	1	2	No	No
3	1	1	2	No	No
	NA	NA	NA	No	No
4	2	1	2	No	No
5	–	–	–	–	–
6	1	1	2	No	No
7	2	2	3	No	No
	3	4	3	No	No
	3	3	3	No	No
	3	4	4	No	No
8	2	2	3	No	No
9	1	1	2	No	No
10	2	2	2	Yes[a]	No
	NA	NA	NA	No	No

Hb, Haemoglobin; NA, not available; RIT, radioimmunotherapy.
[a]Generalized convulsions 24 h after the therapeutic injection, with no demonstrated aetiology.

Fig. 2



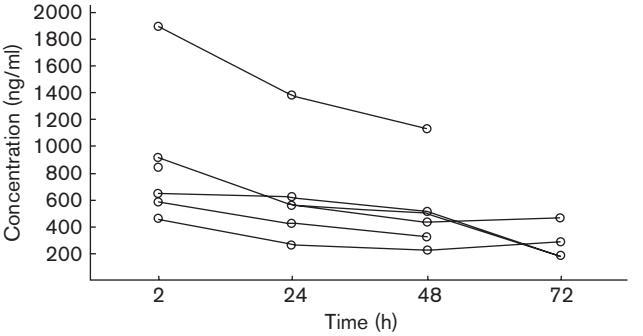
Mean ^{90}Y-labelled antiferritin antibody concentration–time profile.

Table 5 Plasma pharmacokinetic parameters

	C_{max} (ng/ml) (mean ± SD)	AUC (ng/ml h) (mean ± SD)	Clearance (ml/h) (mean ± SD)	$T_{1/2}$ (h) (mean ± SD)
^{111}In	690 ± 437	78 010 ± 55 300	0.038 ± 0.021	94.4 ± 38.4
^{90}Y	887 ± 518	59 930 ± 52 620	0.084 ± 0.053	52.9 ± 29.3

values were 59 930 and 78 010 ng/ml h in plasma for ^{90}Y- and ^{111}In-labelled antiferritin Abs, respectively. The mean terminal phase elimination half-lives ($T_{1/2}$) were 69.9 ± 29 and 94.4 ± 38 h for the ^{90}Y- and ^{111}In-labelled antiferritin Abs, respectively. The mean total body clearances for ^{90}Y- and ^{111}In-labelled antiferritin Abs were 0.084 and 0.038 ml/h, respectively. Mean ^{90}Y- and ^{111}In-labelled antiferritin Ab concentration–time profiles are shown in Fig. 3. The average quantity in urine over the first 24 h for the tracer (^{111}In) was 66.2 ± 36.5 µg compared with 106.4 ± 75.9 for the therapeutic infusion (^{90}Y).

Fig. 3



Mean ^{111}In-labelled antiferritin antibody concentration–time profile.

Discussion

This small series of patients with relapsed or refractory disseminated HL treated by radiolabelled rabbit polyclonal antiferritin Ab confirms the results previously reported by Vriesendorp and Quadri. It showed an ORR of 70% among the nine patients evaluated after the first injection of ^{90}Y-labelled antiferritin Ab. Among the 134 patients with recurrent HL treated in five consecutive studies with intravenous ^{131}I- or ^{111}In-labelled antiferritin Abs for diagnostic purposes and ^{90}Y-labelled antiferritin Ab for therapeutic purposes, an ORR of 60% had been observed with a median duration of response of 8 months [28]. The authors had also reported a correlation between the total injected activity and the response rate, although such a correlation was not observed in our very small patient series. Finally, as corroborated in our series, the main reported toxicity was haematological, and consisted of reversible granulocytopenia and thrombocytopenia, with no significant nonhaematological toxicity. The generalized convulsions observed in one patient could not be formally attributed to the radiolabelled antiferritin Ab, as had been reported in previous studies. The reversible haematological toxicity of the antiferritin RIT, observed later than after conventional CT, is similar to that observed after [^{90}Y]ibritumomab tiuxetan (Zevalin) RIT [29] and requires the cautious follow-up of treated patients.

Very few other clinical trials of radioimmunotargeting have been performed in patients with HL. Immunoscintigraphies in HL and anaplastic large-cell lymphomas have been performed using ^{131}I-labelled HRS-3 Hodgkin-associated monoclonal Ab in 17 evaluable HL patients, showing 14 true-positive cases (82%), two true-negative cases and one false-negative case [30]. A recent study using murine ^{131}I-labelled anti-CD30 monoclonal Ab reported an ORR of 27% with one CR and five

PRs among the 22 evaluable patients [31]. This relatively disappointing result can be explained by the fact that eight patients had primary progressive disease and another eight patients had developed an early relapse within 12 months of the initial treatment. Whole-body scintigraphy performed after therapeutic injection, however, demonstrated the localization of the involved areas, each measuring 5 cm or more in diameter in four patients and 2.5 cm in one patient (23%). This observation contrasts with our immunoscintigraphy findings, and shows specific tumour targeting in all the selected patients, and with the same results as those reported by Vriesendorp and Quadri, who had observed tumour targeting in more than 90% of patients.

The pharmacokinetic study did not reveal any significant differences between the blood $T_{1/2}$ values obtained either by using tracer infusion of ^{111}In and or by using therapeutic infusion of ^{90}Y. The extremely long and highly variable biological half-life of ^{111}In and ^{90}Y is consistent with their quantities in urine up to 72 h after the start of infusions, and can be due to the fact that the effective and physical half-lives of these agents are nearly identical, reflecting the very long retention time of radiometals in the body after catabolism of the conjugated antiferritin Ab [23]. Body clearance was also similar with the two agents, as reported previously.

In conclusion, our results confirm those reported by Vriesendorp and Quadri, and show that rabbit polyclonal antiferritin Ab targets HL tumour sites and has a major therapeutic potential in this situation. We have consequently initiated a multicentre prospective trial to start in 2006, in patients with relapsed or refractory HL using newly produced DOTA-conjugated polyclonal antiferritin Abs labelled with ^{111}In/^{90}Y radioelements.

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