

Use of ^{18}F FDG PET and the short temporal response of Hodgkin's disease to RIT

ABSTRACT

Radioimmunotherapy (RIT) has been available for some time to treat patients with non-Hodgkin's lymphoma, but its use in Hodgkin's lymphoma has been less available, partly because of the need to find an appropriate antibody. A new radioiodinated chimeric antibody directed against the CD25 epitope (^{131}I basiliximab) seems promising, but assessment of response has been difficult. ^{18}F -fluorodeoxyglucose-positron emission tomography (^{18}F -FDG-PET) has become a standard method by which the response of Hodgkin's disease to chemotherapy is both predicted and assessed with well-understood criteria of response. The aim of this study is to determine ^{18}F -FDG-PET can be used to assess response to RIT. Pre- and post-treatment ^{18}F -FDG-PET imaging was performed in a series of 13 patients with advanced Hodgkin's disease who had failed conventional therapy and had been enrolled on a compassionate use program for treatment with ^{131}I basiliximab. The ^{131}I basiliximab was given at an activity of 1200MBq/m² with one patient receiving 2 cycles and the rest a single cycle. The ^{18}F -FDG-PET studies were compared using the "Deauville" criteria and by comparing the maximum standardized uptake value (SUVmax) of target tumors before and 4 and 8 weeks after treatment. All patients survived long enough for their initial ^{18}F -FDG-PET-computed tomography scan at 4 weeks after their ^{131}I basiliximab therapy. One out of ten patients with "Deauville" Grade 4 or 5 response died during the 6-month follow-up period. Two out of three patients with a "Deauville" Grade 2 or 3 response died in the follow-up period. The mean SUVmax pretreatment was 11.9 (± 4.7); at 4-week posttreatment, the mean SUVmax was significantly lower at 6.5 (± 5.8) ($P = 0.02$). At 8 weeks, the mean SUVmax was 8.8 (± 7.0), which was not significantly different from the pretreatment level. ^{18}F -FDG-PET imaging is able to predict the short-term response to treatment of Hodgkin's disease by RIT, and an initial poor response appears to predict poor outcome. Early changes in ^{18}F -FDG-PET uptake did not predict sustained response and by 8 weeks all but one patient had recurrent disease.

Keywords: ^{131}I basiliximab, ^{18}F -fluorodeoxyglucose-positron emission tomography, Hodgkin's disease, radioimmunotherapy, response

INTRODUCTION

Most types of lymphoma are radiosensitive and until recently radiotherapy offered the first effective form of treatment.^[1-3] Even today, external beam radiotherapy may be used in those patients with chemotherapy-resistant disease or in whom chemotherapy is not well tolerated especially if the disease is localized.^[3-5] However, generalized radiotherapy regimens such as mantle fields have become less popular partly due to the recognition of an increased probability of secondary malignancies and cardiovascular disease in long-term survivors.^[6-11]

Over the past 15 years, radioimmunotherapy (RIT) has been developed for the treatment of follicular non-Hodgkin's

lymphoma (NHL), based on antibodies targeted to the CD20 epitope. Two such products, ^{131}I tositumomab (Bexxar) and ^{90}Y ibritumomab tiuxetan (Zevalin), have been shown to more

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efficacious than immunotherapy alone.^[12-17] These products are now available and licensed but often not widely used.^[18]

Although now less common than NHL, Hodgkin's disease remains one of the major forms of hematological cancers seen in the developed world. At present, there have only been a few attempts at RIT.^[19,20] Part of the issue is that within a tumor mass, there may be very few tumor cells in Hodgkin's disease which is not the case with NHL.

However, our institution has been involved in the development of an anti-CD25 chimeric human/murine antibody which attaches to the interleukin-2 (IL-2) receptor which is overexpressed in many Hodgkin's lymphomas.^[21]

It is known that ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) is able to identify response to the treatment of Hodgkin's disease but also able to predict the outcome of treatment^[22-25] and is considered the standard of care when assessing response to chemotherapy in Hodgkin's disease.

A Phase I dose-ranging study was performed which demonstrated that the treatment could be well tolerated at activities of <1850 MBq/m² and some efficacy was demonstrated.^[21] During the study, the patient's progress was monitored by computed tomography (CT) and ¹⁸F-FDG imaging. It was found because of the problem of a residual mass seen on CT in a treated patient; ¹⁸F-FDG provided the most accurate imaging modality.

A Phase II study was being planned and funding sought, but in the meanwhile, the trial sponsor Cancer Research UK agreed to a limited access compassionate use program in which patients would be studied less intensely than in a trial setting but monitored by ¹⁸F-FDG-positron emission tomography (PET)-CT.

Therefore, the aim of this study was to establish whether ¹⁸F-FDG could be used to assess and monitor response to the treatment of patients treated with RIT for Hodgkin's disease.

METHODS

General

This prospective study was part of an open-label compassionate use pre-Stage II program as approved by Cancer Research UK, the Drug and Therapeutic Committee, the Ethics Committee of the Royal Free Hospital, and the Lymphoma Board of the North London Cancer Network. All patients had to read a patient information leaflet which detailed the experimental nature of the treatment and then sign their written informed consent.

Patients

All patients considered for this trial had failed or were unable to tolerate conventional treatment for their Hodgkin's disease. A total of 13 patients were treated within this program. All had been heavily pretreated, for example, patients had received between 3 and 6 courses of chemotherapy. There were nine patients who had received prior radiotherapy and six patients had failed bone marrow transplantation, one of these patients having failed two such transplantations [Table 1]. The mean age of the patients was 37 with a range of 25–71, with 5/13 patients being under. There were six female patients. In the ten patients where precise data were available on the date of diagnosis, the time interval between diagnosis and treatment with ¹³¹I basiliximab was 52 months.

Each patient had to have histologically proven Hodgkin's disease and also to be shown to have positivity for the IL-2a receptors also known as CD25.

The general inclusion and exclusion criteria were the same as, in the Phase I trial,^[21] the most essential exclusion criteria being involvement of more than 25% of the bone marrow with Hodgkin's disease, radiotherapy to an area of viable bone marrow, or chemotherapy within 4 weeks of the ¹³¹I basiliximab therapy. In addition, any female who could be pregnant or in whom the pregnancy status could not be determined was excluded from the study. Furthermore, patients with known human anti-mouse antibody or systemic illness which could reduce life expectancy to <12 weeks were eliminated from analysis. Finally, those individuals who were suffering from intercurrent infection were also ruled out from the study.

Table 1: Demographic details of patients and previous treatments

Patient	Age	Male/ female	B	PS	Stage	Tumor sites	Chemotherapy (n)	RT	ASCT
1	25	Female	Yes	2	IV	N, L, K, B, GI	3	Yes	No
2	34	Female	Yes	1	IV	N, L, B	6	Yes	No
3	31	Female	Yes	1	IV	N, L	3	No	Yes
4	57	Male	Yes	0	IV	N, B	5	No	Yes x2
5	28	Male	Yes	0	IV	N, L, B	4	Yes	No
6	29	Female	Yes	1	IIIb	N	5	No	No
7	26	Male	Yes	0	IV	N, L	3	No	No
8	39	Female	Yes	0	IV	N, L, B	6	Yes	Yes
9	28	Male	Yes	1	IV	N, H	6	Yes	Yes
10	38	Female	Yes	1	IV	N, L	4	No	Yes
11	47	Male	No	1	IV	N, L, S	4	No	No
12	33	Female	No	0	IV	L, S	4	Yes	Yes
13	71	Male	No	1	IV	N, L	3	Yes	No

B: Presence of B symptoms; PS: Performance status as defined by the World Health Organization (reference); RT: External radiotherapy; ASCT: Allogeneic stem cell transplantation; N: Lymph nodes; L: Liver; K: Kidney; B: Bone; GI: Gastrointestinal tract; S: Spleen

¹³¹I basiliximab

The basiliximab was provided from a commercial source (Novartis, Basel, Switzerland) as a sterile lyophilisate containing 10 mg of active agent. This was then labeled with ¹³¹I using the N-bromosuccinimide/L-tyrosine method.^[27] The product was assessed for labeling efficiency/radiochemical purity (RCP) using thin layer chromatography, and any batch with >95% labeling efficiency/RCP was released for use for therapy.

Patient preparation

In the 2 weeks before treatment with ¹³¹I basiliximab, all patients were staged with an ¹⁸F-FDG-PET-CT study. These PET-CT images were acquired 60 min after injection of 310–405 MBq ¹⁸F-FDG on a GE Discovery ST 16-slice PET-CT machine (GE, Milwaukee, WI, USA) in three-dimensional mode with 4 min per bed position, the number of bed positions being dependent on the patient's height. Imaging was performed from the vertex of the skull to mid-thigh in an "arm-elevated" position. A low-dose CT (120 kVp, 80 mA) was performed in addition for purposes of attenuation correction and localization. Imaging was then transferred by disc to a Hermes viewing station for reading and analysis (Hermes Medical, Stockholm, Sweden). In four patients, different PET-CTs were used because of the patient's distance from the treatment site, but in these cases, the data were transferred by encrypted CD and uploaded onto the Hermes computer system. All imaging for a single patient was performed on the same system.

For 5 days before the treatment until 7 days after treatment, the patient was also given 50–60 mg potassium iodide t.d.s as thyroïdal protection.

Administration of ¹³¹I basiliximab

The parameters for administration were determined by Cancer Research UK after reviewing the data from the Phase I trial.^[21] The activity that could be administered was limited to 1200 MBq/m² with the time for administration of the antibody being 45–60 min by infusion pump. All administrations were performed in a special room designated for radionuclide therapy in which the patient stayed until they could be discharged, normally at 5–7 days' posttreatment. Despite there being no problems during the Phase I study, an emergency drug pack for anaphylaxis was also available during the administration.

Patient monitoring posttherapy

During the inpatient stay, the patient underwent daily monitoring of vital signs. For reasons of radiation protection, blood was not drawn until close to discharge. As this was a companionate use program, the imaging required

for dosimetry was not approved. A full blood count was performed on a weekly basis for evidence of bone marrow toxicity, and this was graded using the WHO grading system.

Positron emission tomography imaging for assessment of efficacy

The primary imaging method to assess response was by ¹⁸F-FDG-PET-CT. These were performed 4 and 8 weeks' posttreatment. The hematological oncologist also performed a series of clinical examinations at these time points. The criteria used for response were the "Deauville" criteria which have been accepted as standard practice in the UK^[28] and were applied only to the 4-week posttreatment study. These measurements of response were compared to clinical outcomes. This was applied to the scans performed at 4 and 8 weeks after treatment when compared to the pretreatment study. Due to the unreliability of CT imaging in Hodgkin's disease, CT criteria of response were not used.

Further follow-up

Patients continued to be followed up for a period of up to 6 months after treatment.

Data analysis

The site of disease with the most intense uptake of activity in the pretreatment scan was considered the "index" lesion. Using a 25-pixel region of interest and scrolling through the images of the index lesion, the maximum standardized uptake value (SUVmax) was calculated. The SUVmax and change in SUVmax were then compared using a paired "t" test (Microsoft Excel 1997–2003) where the index lesion had no uptake of ¹⁸F-FDG posttherapy; it was assigned a SUVmax of 1.0

RESULTS

General

All 14 treatments in 13 patients were successfully undertaken. The treatment was well tolerated in all patients and the single patient in whom a second treatment was performed had no additional problems with the second infusion of the ¹³¹I basiliximab. There were five patients who suffered a Grade 4 toxicity in platelet count requiring support with platelet transfusions. No Grade 3 toxicity in platelets was recorded. One patient had suffered a Grade 3 toxicity in leukocyte count and another single patient with a Grade 4 toxicity. For red cells, there were no Grade 3 or 4 toxicities.

Qualitative response 4 weeks

All patients were alive for their 4-week posttreatment ¹⁸F-FDG-PET-CT scan including the patient in whom two treatments were given who had a 4-week posttreatment

scan after both treatments. One patient did not survive long enough for a second ¹⁸F-FDG-PET-CT at 8 weeks having died of progressive lymphoma despite an initial partial metabolic response. There were no patients who had a complete metabolic response, but ten patients had a partial metabolic response. The patient who had two treatments had a partial metabolic response to both treatments. Recurrence of lymphoma was normally at the site of initial disease [Figure 1], but in some patients, the disease returned at a different site [Figure 2]. This would impact in the use of the same index lesion for quantitative comparison.

The three remaining patients had progressive disease of which two died in the follow-up period.

Response at 4 weeks after ¹⁸F-fluorodeoxyglucose-positron emission tomography-computed tomography – “Deauville”

All patients survived long enough for their initial ¹⁸F-FDG-PET-CT scan at 4 weeks after their ¹³¹I basiliximab therapy. There were nine patients who had a “Deauville” Grade 4 or 5 response, of which a single male patient with lung and nodal disease died during the follow-up period. Of the three patients who had a “Deauville” Grade 2 or 3 response, two died in the follow-up period.^[16] The single

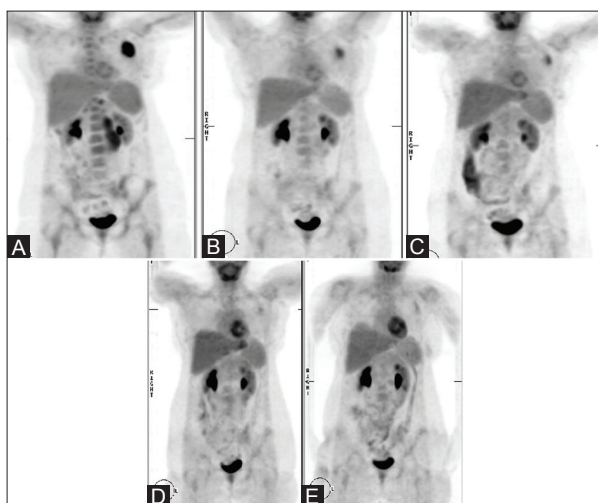


Figure 1: (A, B, C) Pre-therapy and Post-therapy images in 31 year old male with nodular sclerosing HL. (A) Pre-therapy images showed intense metabolic activity within left superolateral chest wall mass, retroperitoneal nodes and left para-aortic nodes. Low grade activity is present throughout the marrow and left sacroiliac joint. (B) Post-therapy image (4 weeks post first dose of RIT) showed residual disease in the chest wall. (C) Post-therapy image (8 weeks post first dose of RIT) showed metabolic response with only a small volume of residual disease in chest wall and left sacroiliac joint. (D,E) Further metabolic response seen on the following the second cycle of RIT (Patient 3). (D) The post-therapy MIP image performed 4 weeks following the second dose of RIT showed further marked improvement in the lateral chest wall. Low grade uptake seen within the left sacroiliac joint has not changed when compared to the previous scan. (E) The post-therapy images performed 4 weeks following the second dose of RIT has not changed when compared to previous study

patient who had two treatments had a “Deauville” Grade 5 response to the first treatment but only a Grade 2 response to the second treatment [Table 2].

Qualitative response 8 weeks

Of the remaining 12 patients who survived to have the 8-week ¹⁸F-FDG-PET-CT scan, 11 showed progressive disease when compared with the scan performed at 4 weeks [Figure 3]. Interestingly, the only patient to show a sustained partial metabolic response was the patient who had two cycles of ¹³¹I basiliximab.

Quantitative response

When comparing the SUVmax in the pretreatment ¹⁸F-FDG-PET-CT with the posttreatment studies, the mean SUVmax pretreatment was 11.9 (± 4.7), at 4-week posttreatment, the mean SUVmax was significantly lower at 6.5 (± 5.8) ($P = 0.02$), but by 8 weeks, the mean SUVmax was 8.8 (± 7.0), which was not significantly different from the pretreatment level [Table 3 and Figure 4]. There was no significant difference between the SUVmax at 4 and 8 weeks. Between the pretreatment scan and the scan 4-week posttherapy, there was one patient with an increase in SUVmax, whom was one of the three patients who died in the study period. When comparing the pretreatment scan with the scan at 8 weeks in the 12 patients who had survived, the patient in whom there had been an increase in SUVmax from 6.3–10.1 after 4 weeks dropped back down to 6.2 at 8 weeks. In two patients, the SUVmax of the index lesion was greater at the 8-week posttreatment scan than the baseline scan. When comparing the 4- and 8-week scans, there were six patients in whom there had been an increase in SUVmax in the index lesion. However, in the two patients who died

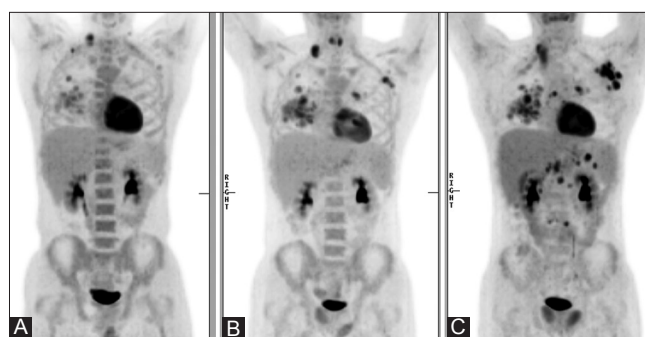


Figure 2: Pre and post therapy maximum intensity projection images showing disease progression following 1 cycle of RIT seen (Patient 10). (A) Pre-therapy image showed metabolically active disease in right supraclavicular fossa, left axilla and right lung. (B) Post-therapy image (4 weeks following first dose of RIT) showed disease progression in the right lung, mediastinum, left axilla, and right supraclavicular fossa. (C) Post-therapy image (8 weeks following first dose of RIT) showed progression of the disease in the right lung, mediastinum, left axilla, and right supraclavicular fossa with new disease in the abdomen



Figure 3: Pre and post therapy maximum intensity projection images showing initial response (4 weeks post RIT) followed by disease progression (8 weeks post RIT. (A) The pre-therapy MIP images showed an area of metabolically active disease in the right axilla, mediastinum, and bilateral retrocrural regions. Pra-aortic coeliac axis, portahepatis, right common and external iliac nodes were also demonstrated. (B) The post-therapy MIP image performed 4 weeks following first dose of RIT showed resolution of the majority of the disease above the diaphragm with low grade uptake in the right axillary node. (C) The post-therapy MIP image performed 8 weeks following first dose of RIT showed progression of the disease involving the abdominal

after the 8-week scan but within the study period, the 8-week SUVmax was <4-week SUVmax.

DISCUSSION

¹⁸F-FDG-PET-CT imaging has become the standard of care in assessment of response in Hodgkin's disease when treated with chemotherapy.^[22-25,28] This study suggests that it is possible to use ¹⁸F-FDG-PET-CT in monitoring the tumor's response to RIT. However, the conclusions that can be reached concerning the prognostication available with ¹⁸F-FDG-PET-CT are limited as none of the patients achieved a complete response during treatment with ¹³¹I basiliximab on either the 4-week or 8-week posttherapy image. It would appear that as seen in many other studies where there is residual activity of ¹⁸F-FDG, there is often rapid recurrence of disease. This was observed in this study. In our original Phase 1 trial, many patients received higher activities of ¹³¹I basiliximab than we were allowed to give in this study. In addition, a repeat treatment was given normally about 6 weeks after the first and this seemed to consolidate the initial response.^[21] A repeat treatment was sanctioned in one patient who had an initial partial response, but even then, there was some residual ¹⁸F-FDG activity post-2nd treatment and again by 8-week evidence of active disease recurring.

One reason for the response to RIT being only transient could be related to the effect of radiation on the target tissue. Within a Hodgkin's tumor mass, there are often only sparse tumor cells, but these are supported by a much more abundant lymphocytic stroma.^[29] It may be these lymphocytes which are not in themselves malignant, take up ¹⁸F-FDG, and may be the more radiosensitive cells so

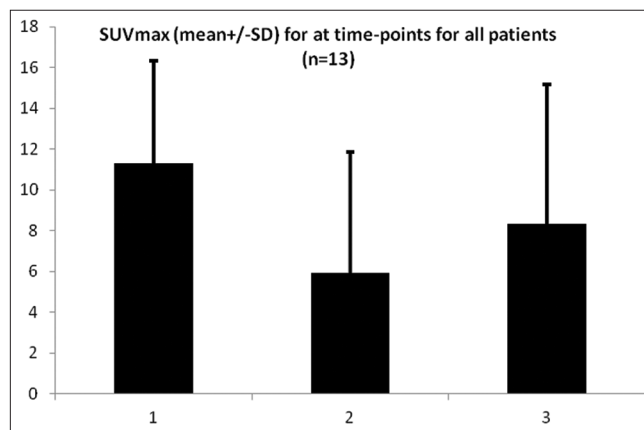


Figure 4: Plot of standardized uptake value (dot and whisker showing mean ± 1 standard deviation) before and at 4- and 8-week posttherapy

Table 2: Comparison of activity administered the response as measured by the "Deauville" criteria and outcome

Patient number	Activity of ¹³¹ I basiliximab administered	Deauville score	Final outcome
1	1820 MBq	4	Alive
2	2100 MBq	4	Alive
3	2260 MBq	4	Alive
	2080 MBq*	2	Alive
4	2380 MBq	2	Dead
5	2020 MBq	5	Alive
6	2400 MBq	3	Alive
7	2250 MBq	5	Dead
8	1990 MBq	4	Alive
9	2360 MBq	2	Dead
10	1910 MBq	5	Alive
11	2540 MBq	4	Alive
12	2050 MBq	4	Alive
13	2230 MBq	4	Alive

*2nd administration. The Deauville score looks at the residual activity 3-6 weeks after treatment; **Score 1 is no uptake; 2 is uptake of 18 female FDG at site of known tumor but less than mediastinum; 3 is uptake more than mediastinum but less than L; 4 is greater than L at any site; 5 uptake at new sites of disease, Grade 1 and 2 only are considered a treatment response. FDG: Fluorodeoxyglucose; L: Liver

that the more malignant Hodgkin and Reed–Sternberg cells remain unaffected by RIT and once they are no longer in a toxic environment start to regrow and result in reactivation of the Hodgkin mass.

Unlike NHL, it would appear the only certain way to secure any lasting remission in Hodgkin's lymphoma is to perform a bone marrow transplantation.^[26,30] Therefore, the next stage of this compassionate use program would be to use RIT with ¹³¹I basiliximab as induction therapy in those patients resistant to or unable to have chemotherapy. In this case, high activities could be used as bone marrow toxicity is less of an issue, and the Phase I trial did show some correlation between tumor radiation dose and eventual response.^[21] Although it is unclear from this study, how

Table 3: ¹⁸F-fluorodeoxyglucose maximum standardized uptake value before, 4 weeks, and 8 weeks after treatment compared to clinical outcome

Patient number	Target lesion site	SUV _{max}			Clinical outcome
		Study 1	Study 2	Study 3	
1	Right chest	14.2	12.2	11.6	Alive
2	Left pelvis	10.1	4.6	7.8	Alive
3	Left chest	15.5	4.4	3.5	Alive
	Left chest*	3.5	1.9	1.8	
4	Lumbar spine	8.2	2.0	Not done	Died
5	Upper abdomen	6.3	Neg	Neg	Alive
6	Middle abdomen	12.7	Neg	3.8	Alive
7	Right neck	6.3	10.1	6.2	Died
8	Upper chest	13.7	12.0	18.3	Alive
9	Left axilla	14.6	1.7	1.0	Died
10	Neck	4.3	Neg	6.0	Alive
11	Chest	12.0	3.0	10.7	Alive
12	Chest	15.3	13	16.8	Alive
13	Left chest	21.3	18.0	20.7	Alive

Study 1: Pretreatment; Study 2: 4-week posttreatment; Study 3: 8-week posttreatment; Neg: Negative, i.e., no uptake of ¹⁸F-FDG. SUV_{max}: Maximum standardized uptake value; ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose

useful ¹⁸F-FDG-PET-CT would be in this scenario as there was a good reduction in the SUV_{max} in the index lesion of those patients who died as well as those still alive at the end of the 6-month follow-up period.

CONCLUSION

This study confirms that ¹⁸F-FDG is sensitive in predicting treatment failure in patients treated with RIT for Hodgkin's disease, and in particular, residual ¹⁸F-FDG uptake was useful in demonstrating the short time to treatment failure in these patients. The place of 4-week post-RIT ¹⁸F-FDG in identifying long-term response is less clear. However, ¹⁸F-FDG should become the imaging test of choice if any study designed to improve the efficacy of RIT such as multiple dosing or sequential treatment of RIT followed by bone marrow transplantation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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