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Short duration immunochemotherapy followed by radioimmunotherapy consolidation is effective and well tolerated in relapsed follicular lymphoma: 5-year results from a UK National Cancer Research Institute Lymphoma Group study

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Summary

We report a phase II study to evaluate the efficacy and toxicity of abbreviated immunochemotherapy followed by ^{90}Y Ibritumomab tiuxetan (^{90}Y-IT) in patients with recurrent follicular lymphoma. Of the 52 patients enrolled, 50 were treated with three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone), followed by ^{90}Y-IT regimen (15 MBq/kg, maximum 1200 MBq) preceded by two infusions of 250 mg/m^2 rituximab. The overall response rate was 98% with complete response (CR) 30% and partial response (PR) 68%. 18 patients with a PR following chemotherapy improved to a CR following ^{90}Y-IT: a conversion rate of 40%. Seven patients with PR following ^{90}Y-IT subsequently improved to a CR 12–18 months later, leading to an overall CR rate of 44%. With a median follow-up of 5 years, median progression-free survival was 23·1 months and overall survival was 77·5% at 5 years. High trough serum rituximab levels (median 112 μg/ml; range 52–241) were attained after four doses of rituximab, prior to ^{90}Y-IT; this was not found to influence response rates. The treatment was well tolerated with few (13·5%) grade 3 or 4 infective episodes and manageable haematological toxicity. Abbreviated immunochemotherapy followed by ^{90}Y-IT is an effective and well-tolerated treatment in recurrent follicular lymphoma patients previously exposed to rituximab. Trial registration: clinicaltrials.gov identifier: NCT00637832.

Keywords: rituximab, follicular lymphoma, zevalin, ^{90}Y Ibritumomab, radioimmunotherapy.

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL), comprising around 70% of cases, the majority of whom present with advanced stage disease (The Non-Hodgkin's Lymphoma Classification Project 1997). The introduction of the anti-CD20 monoclonal antibody (mAb) rituximab for induction and as maintenance has improved clinical outcomes, with more than 70% of patients over the age of 60 years now surviving 10 years (Pulte *et al*, 2012). However current treatment approaches are not curative and the majority of patients relapse with lymphoma that eventually becomes refractory to treatment, and ultimately die as a consequence of their disease (Ansell & Armitage, 2005). The protracted duration of therapy over a period of years can be difficult to tolerate for many, particularly older patients, and increases the incidence of cumulative toxicities. Therefore novel treatment approaches with high efficacy and manageable toxicity delivered using abbreviated treatment regimens would provide attractive alternatives in the management of FL.

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One such convenient approach is ^{90}Y ibritumomab tiuxetan (^{90}Y-IT; Zevalin™) radioimmunotherapy (RIT) (Illidge & Morschhauser, 2011), which is delivered in just two outpatient visits. ^{90}Y-IT is highly active as a single agent in relapsed FL, demonstrating high overall response rates (ORR) of 47–83% and complete response (CR) rates of 15–51% in heavily pre-treated patients refractory to chemotherapy and/or rituximab, leading to approval by the United States Food and Drug Administration (FDA) in 2002 (Witzig *et al*, 1999, 2002a; Wiseman *et al*, 2002). However, there is little reported data on the efficacy in patients with relapsed FL when the initial treatment is rituximab-containing 'immunochemotherapy', with small numbers of patients in the registration studies being exposed to rituximab. Furthermore, concerns have emerged from preclinical work, suggesting that RIT may not work as well as a consolidation therapy after initial immunochemotherapy, as rituximab may block the CD20 target for subsequent anti-CD20 RIT (Golay *et al*, 2006). Although immunochemotherapy followed by consolidation RIT has been investigated in untreated FL (Jacobs *et al*, 2008; Zinzani *et al*, 2008, 2010; Hainsworth *et al*, 2009), this type of approach has not previously been investigated in relapsed FL patients who have received initial rituximab-containing chemotherapy.

In this Phase II study, we investigated the feasibility, safety and efficacy of ^{90}Y-IT consolidation following an abbreviated course of immunochemotherapy in relapsed FL and measured serum rituximab levels in relation to RIT administration to determine whether serum rituximab levels after initial immunochemotherapy and prior to RIT influence ^{90}Y-IT efficacy.

Patients and methods

Patients

Patients were eligible if over 18 years old, with histologically confirmed CD20-positive FL grade 1–3a and Ann-Arbour stage II–IV disease, requiring treatment according to at least one modified British National Lymphoma Investigators/Groupe d'Etude des Lymphomes de l'Adulte criterion (Brice *et al*, 1997), in first or second relapse with progressive disease (PD) after chemotherapy (plus or minus rituximab). Detailed inclusion and exclusion criteria are included in the online supplement. All patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Study design and treatment

This study was a multi-centre open labelled single arm, non-randomized prospective phase II study. Patients received three cycles of rituximab-chemotherapy, followed by ^{90}Y-IT consolidation at a dose of 14·8 MBq/kq (maximum 1184 MBq) if response evaluation with computerized tomography (CT) scan demonstrated at least a partial response (PR) or CR/unconfirmed CR (CRu) 2 weeks after chemotherapy. Stable disease (SD) resulted in withdrawal from the trial and no administration of ^{90}Y-IT. The regimen was R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone); the latter was given if the ejection fraction was <50%, previous anthracycline tolerance was reached, or the patient had known cardiac disease. Patients with >25% bone marrow involvement required repeat trephine biopsy 2–3 weeks after the last rituximab-chemotherapy cycle and were allowed to proceed with ^{90}Y-IT if marrow involvement was reduced to <25%. If the platelet count was >100 and $<150 \times 10^9$/l, the ^{90}Y-IT was dose reduced to 11·1 MBq/kg (maximum 888 MBq). ^{90}Y-IT was preceded in all cases by 2 doses of rituximab (250 mg/m^2) given 7-8 d apart, with the second dose given immediately before ^{90}Y-IT.

Measurement of serum rituximab levels

Pre-dose (trough) and post-dose (peak) serum rituximab levels were quantified at weeks 0, 3, 6, 9 and 10 by enzyme-linked immunosorbent assay (ELISA). A high affinity mAb (MB2A4) specific for the idiotype region of rituximab was developed by our group, produced by AbD Serotec (Kidlington, Oxfordshire, UK) and previously validated (Hampson *et al*, 2010). ELISAs utilizing this antibody detect rituximab in the presence or absence of high levels of human Immunoglobulin G, and are sensitive to serum rituximab levels of 1 μg/ml.

Study objectives, response and toxicity evaluation

The primary end-point was overall response rate (ORR) including combined CR (CR/CRu) and PR after three cycles of rituximab-chemotherapy, and subsequently 2 months after ^{90}Y-IT. Secondary end-points were overall survival (OS), progression-free survival (PFS), time to next treatment (TTNT) and safety. Response was evaluated according to standard international criteria (Cheson *et al*, 1999). Adverse events were classified according to the National Cancer Institute Common Toxicity Criteria version 3 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Statistical analysis

The sample size was calculated to ensure sufficient precision in the primary end point estimate of ORR and CR using a width of confidence interval (CI) approach. For 60 patients, if the observed overall response rate was 90%, the associated 95% CI would be 79·5–96·2%; if the observed CR rate was 60%, the associated 95% CI would be 46·5–72·4%; if the observed CR rate was 70%, the associated 95% CI would be

56·8–81·2% The secondary parameters, PFS and OS, were analysed with the Kaplan–Meier method. Patients who had not progressed at the time of analysis were censored at their date of last follow-up assessment (date last seen alive for OS). Sub-group comparisons utilized the log-rank test. Pre-cycle rituximab levels correlated to bulk and change in response before and after ^{90}Y-IT were compared using a box and whisker plot and the Mann-Whitney test. Responses by baseline characteristics were assessed using Chi-square tests of association. *P* values <0·05 were considered statistically significant.

Results

Patient characteristics

54 patients were recruited between May 2008 and August 2010. Two patients were excluded as they failed to meet the entry criteria on review: one for having greater than two documented relapses and the other for receiving immunochemotherapy within 6 months prior to study entry. Therefore the intention to treat (ITT) population included 52 participants (Fig 1). The median age was 62 years (range 31–87) [Table I], with 24 (46%) having a high Follicular Lymphoma International Prognostic Index (FLIPI) score at entry, 16 (31%) intermediate and 12 (23%) low. Trial entry was at first recurrence for 58% (30/52) of the patients and second recurrence for 42% (22/52) of the patients. The median duration of best prior response (either first or second remission) before study entry was 28 months (range, 7·5–188·4 months). 71% (37/52) of patients had previously received rituximab and 29% (15/52) had received an anthracycline-containing regimen. Nineteen patients (37%) had bone marrow infiltration, which was greater than 25% of interstitial space in four cases.

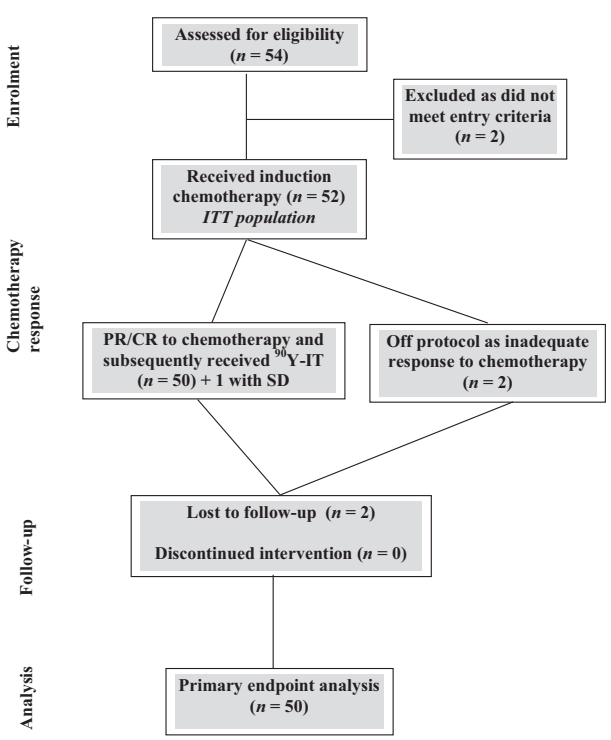

Fig 1. CONSORT diagram depicting flow of patients through the study.

Serum rituximab data

Figure 2 and Table SI show pre-cycle rituximab levels before rituximab-containing chemotherapy (at weeks 0, 3 and 6), before rituximab alone (at week 9) and before rituximab followed by ^{90}Y-IT administration (week 10) by change in response before and after ^{90}Y-IT. Median pre-administration rituximab levels increased with successive rituximab administration, with median levels of >100 μg/ml only reached at week 10. There were no statistical differences in median rituximab levels between the PR and CR/CRu group and the PR to PR group. There were no statistically significant differences in rituximab levels in those with or without bulky (>5 cm) disease.

Completion of treatment phase

Fifty-two patients received induction chemotherapy: R-CHOP in 71% (37/52) and R-CVP in 29% (15/52) of cases. Two patients were withdrawn as they had failed to achieve PR by objective criteria (Cheson *et al*, 1999) following immunochemotherapy, leaving 50 patients who subsequently received ^{90}Y-IT (Fig 1).

Safety and tolerability of abbreviated chemotherapy with consolidation ^{90}Y-IT

Haematological toxicity. Grade 3 or 4 thrombocytopenia occurred in 38·5% of the ITT population (20/52; Table II); in 5·8% (3/52) of patients following chemotherapy, increasing to 34% (17/50) of patients following consolidation with ^{90}Y-IT. The median time of onset was 28 d following administration (range 19–46). Grade 4 thrombocytopenia occurred in 1·9% following chemotherapy and increased to 8% (4/50) following ^{90}Y-IT. Grade 3 or 4 neutropenia occurred in 36·5% of the ITT population (19/52) and in 29% (15/52) of patients following immunochemotherapy. Similar rates of Grade 3 or 4 neutropenia were seen following ^{90}Y-IT, with 30% (15/50) occurring at a median of 39 d following administration (17–149 d). Of these, 93·3% (14/15) occurred within 53 d of ^{90}Y-IT. Grade 3 and 4 anaemia occurred in two patients, both within 43 d of ^{90}Y-IT. Blood product support was required in 11·5% of patients (6/52), all following ^{90}Y-IT. Four patients received red cell transfusions, with a median of 4·5 units (range 2–12), while five patients

Table I. Baseline characteristics of study population (Intent-to-treat population, $n = 52$).

Characteristic	Number (%)
Age, years: median (range)	62 (31 to 87)
Sex	
Male	29 (55·8%)
Female	23 (44·2%)
FLIPI	
Low	12 (23·1%)
Intermediate	16 (30·8%)
High	24 (46·2%)
Bone marrow involvement	
Not present	31 (59·6%)
Present	19 (36·5%)
<25%	15 (78·9%)
≥25%	4 (21·1%)
Unknown*	2 (3·9%)
Prior treatment with rituximab	
Yes	37 (71·2%)
No	15 (28·8%)
Prior treatment with anthracycline	
Yes	15 (28·8%)
No	37 (71·2%)
Recurrence at study entry	
First recurrence	30 (57·7%)
Second recurrence	22 (42·3%)
Initial treatment	
Chlorambucil	18 (34·6%)
Chlorambucil + Interferon	1 (1·9%)
R-CVP	16 (30·8%)
R-CHOP§	9 (17·3%)
FMD	1 (1·9%)
FMD + COP	1 (1·9%)
CHOP**	1 (1·9%)
CVP	1 (1·9%)
Other§§	4 (7·7%)
Treatment after 1st relapse prior to 2nd relapse††	
R-CVP	10 (45·5%)
R-CHOP	3 (13·6%)
Chlorambucil	1 (4·5%)
CVP	1 (4·5%)
FMD	1 (4·5%)
Rituximab	2 (9·1%)
Other***	4 (18·2%)
Maximum tumour diameter at week 8 (visit 6)‡‡	
≤5 cm	37 (71·2%)
>5 cm to ≤7·5 cm	10 (19·2%)
>7·5 cm to ≤10 cm	1 (1·9%)
>10 cm	2 (3·8%)
Unknown†	2 (3·8%)
Time from diagnosis to initial treatment, months: median (IQR) (range)‡	1·8 (0·7, 8·0) (0, 118·9)
Time from diagnosis to consent to study, months: median (IQR) (range)	42·8 (27·4, 97·4) (13·0, 226·6)

FLIPI, Follicular Lymphoma International Prognostic Index; (R)-CVP, (rituximab), cyclophosphamide, vincristine, prednislolone; (R)-CHOP, (rituximab), cyclophosphamide, doxorubicin; vincristine, prednisolone; FMD, fludarabine, mitozantrone, dexamethsone; COP, cyclophosphamide, Oncovin (vincristine), prednisolone; IQR, interquartile range.

*For two patients bone marrow biopsy was not done at baseline.

†For two patients maximum tumour diameter at week 8 is unknown.

‡If the exact day of date of first treatment or diagnosis is unknown then it is assumed the date was the 1st of the month. If, in addition, the month is missing, the 1st of January is assumed. For two patients the date of first treatment is assumed to be the same as the date of diagnosis.

§For two patients this is R-CVP + R-CHOP, counted under R-CHOP.

**This patient received CVP + CHOP, listed as CHOP.

††Percentages are based on the number of patients who had a second relapse before trial entry.

‡‡For lesions where the case report form (CRF) stated 'No longer apparent', 'Reduced in size – difficult to measure', 'Resolved', 'Too small to measure', 'Resolved', 'Small no measurements' or 'A number of sub 5 mm non-specific nodules' were counted in the ≤5 cm category. For lesions where the CRF stated 'Evaluable', 'Not assessed (No CT head)', 'Thickening (no measurement)', 'n/a' were assumed missing.

§§These patients had entries other than chemotherapy regimens entered as their initial treatment, as follows: 'Watch and wait'(1), 'Surgery + Watch and wait' (1) and 'Radiotherapy' (2).

***These patients had entries other than chemotherapy regimens entered as their treatment prior to second relapse, as follows: 'Steroids'(1), 'Unknown biopsy implied patient did not want further treatment' (1) and 'Radiotherapy' (2).

received platelet transfusions, with a median of 2 units (range 1–5).

Non-haematological toxicities. One grade 4 event was recorded; an episode of chest pain during chemotherapy. 27% of patients (14/52) experienced a grade 3 event, including eight grade 3 infective/febrile episodes in separate patients. Of these infective episodes, four (including one episode of neutropenic sepsis) occurred following chemotherapy and four (including one episode of neutropenic sepsis) occurred following ^{90}Y-IT, which was thought to be attributable to treatment. There were a further two events of grade 3 skin infection occurring more than 10 months after RIT in a patient who developed myelodysplastic syndrome (MDS). There were no grade 4 infective complications.

Thirty serious adverse events (SAEs) were reported in 18 individuals, of which seven events were deemed to be related to ^{90}Y-IT. The majority (22 events, 14 patients) related to non-haematological toxicity. Serious haematological toxicity was reported in six patients (eight events), including four episodes of neutropenia and two episodes of febrile neutropenia. There

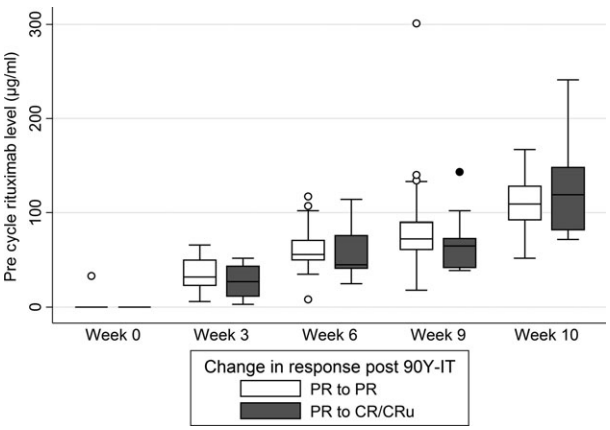

Fig 2. Box and whisker plot showing median (with range) of trough and peak rituximab levels before each cycle by change in response before and approximately 8 weeks after ^{90}Y-IT. ^{90}Y-IT was administered at week 10 (includes all eligible patients with rituximab level data available). ^{90}Y-IT, ^{90}Y-ibritumomab-tiuxetan; PR, partial response; CR, complete response; CRu, unconfirmed complete response

was one occurrence of pulmonary embolism, two of cardiac chest pain in the same patient and one patient affected by MDS. The latter occurred ten months following ^{90}Y-IT administration but there were no other reported second malignancies.

Clinical efficacy of abbreviated chemotherapy with consolidation ^{90}Y-IT

Following three cycles of immunochemotherapy the ORR was 94·2% (95% CI 84·1–98·8%), CR/CRu 7·7% (95% CI 2·1–18·5%) and PR 86·5% (95% CI 74·2–94·4%) (primary outcome data summarized in Tables III and IV). Three patients had SD and no patients had PD. Therefore 50 patients subsequently received ^{90}Y-IT, with one patient whose imaging did not show a PR receiving ^{90}Y-IT, with subsequent development of a CR. The final two-month response assessment post ^{90}Y-IT demonstrated an ORR of 98% (95% CI 89·4–99·9%) with CR/CRu of 30% (95% CI 17·9–44·6%) and PR of 68% (95% CI 53·3–80·5%). Seven patients who were in PR post ^{90}Y-IT subsequently demonstrated an improved CR/CRu response on subsequent CT (range 12–18 months post ^{90}Y-IT). The best CR/CRu rate was therefore 44% (95% CI 29·9, 58·7%). Of the 45 patients with PR post-chemotherapy, 18 demonstrated improved response to CR/CRu with a conversion rate from PR to CR of 40% (95% CI 25·7, 55·7%) post ^{90}Y-IT.

With median follow up of 5 years, the median PFS of the ITT (n = 52) population is 23·1 months (95% CI 17·9, 34·5), with estimated 1- and 3- and 5-year PFS of 94·1%, 34·0% and 21·9% respectively (Fig 3B; Table SII) and the estimated 5-year OS is 77·5%, median 75·2 months (95% CI

Table II. Haematological and non-haematological toxicity data during study (Grade 3 and 4 events). (Intent-to-treat population, n = 52).

Characteristic	Grade 3 or 4	Grade 3	Grade 4
Number of patients that experienced at least one adverse event	32 (61·5%)	20 (38·5%)	12 (23·1%)
Haematological:	25 (48·1%)	14 (26·9%)	11 (21·2%)
Neutropenia	19 (36·5%)	10 (19·2%)	9 (17·3%)
Anaemia	2 (3·9%)	1 (1·9%)	1 (1·9%)
Thrombocytopenia	20 (38·5%)	15 (28·9%)	5 (9·6%)
Myelodysplasia	1 (1·9%)	0	1 (1·9%)
Other	12 (23·1%)	10 (19·2%)	2 (3·8%)
Non-Haematological:	14 (26·9%)	13 (25·0%)	1 (1·9%)
Infections/pyrexia	7 (13·5%)	7 (13·5%)	0
Febrile Neutropenia	1 (1·9%)	1 (1·9%)	0
Dermatological	1 (1·9%)	1 (1·9%)	0
Cardiac	1 (1·9%)	0	1 (1·9%)
Gastrointestinal	2 (3·9%)	2 (3·9%)	0
Syncope	3 (5·8%)	3 (5·8%)	0
Other	6 (11·5%)	6 (11·5%)	0

Table III. Clinical response after 3-cycles of rituximab-chemotherapy.

Response at week 8 post 3-cycles of rituximab-chemotherapy	Patients, n (%)	RR (95% confidence interval)	ORR (95% confidence interval)
Complete response	3 (5·8%)	7·7% (2·1%, 18·5%)	
Unconfirmed complete response	1 (1·9%)		94·2% (84·1%, 98·8%)
Partial response	45 (86·5%)	86·5% (74·2%, 94·4%)	
Stable disease	3 (5·8%)	–	–
Total	52		

RR, relative risk; ORR, overall response rate.

Table IV. Clinical response after treatment by ^{90}Y- ibritumomab-tiuxetan (^{90}Y-IT).

Response at week 18, approximately 8 weeks post ^{90}Y-IT	Patients, *n* (%)	RR (95% confidence interval)	ORR (95% confidence interval)
Complete response	12 (24·0%)	30·0% (17·9, 44·6%)	
Unconfirmed complete response	3 (6·0%)		98·0% (89·4– 99·9%)
Partial response	34 (68·0%)	68·0% (53·3%, 80·5%)	
Stable disease	1 (2·0%)	–	–
Total	50		

RR, relative risk; ORR, overall response rate.

65·1, not reached; Table SIII) with 40 patients having experienced PD. Subgroup analysis of PFS based upon attainment of either CR/CRu *versus* PR approximately 8 weeks post ^{90}Y-IT revealed respective 2, 3 and 4 year PFS rates of 80%, 60% and 53·3% vs. 36·5%, 24·3% and 12·2% (Fig 4) (P = 0·008). There was no significant difference in PFS when stratified according to FLIPI risk category (Fig S1). A review of response rates according to baseline clinical characteristics revealed no apparent correlation to ORR or CR rate except for maximum tumour diameter, where CR rate was 36·1% for maximum tumour ≤5 cm and just 8·3% for patients with maximum tumour diameter at week 8 of >5 cm (P-value 0·067, Table SIV).

Discussion

In this phase II study using an abbreviated course of 3 cycles of immunochemotherapy followed by consolidation ^{90}Y-IT in relapsed FL, the following observations were made. Firstly, high response rates were observed in a high/intermediate risk FLIPI (77%) group of relapsed FL patients. The ORR was 98% and the best CR/CRu 44%, with a median PFS of 23·1 months, estimated 5-year PFS of 21·9% and OS of 77·5%. Secondly we have evaluated the serum rituximab levels pre- and post- each cycle and immunochemotherapy and prior to ^{90}Y-IT and demonstrated that only after four infusions of rituximab are the median levels greater than 100 μg/ml. The pre-levels prior to ^{90}Y-IT are not significantly different based on response or bulk of disease. Finally the regime was very well tolerated, with few serious adverse events and manageable haematological toxicity.

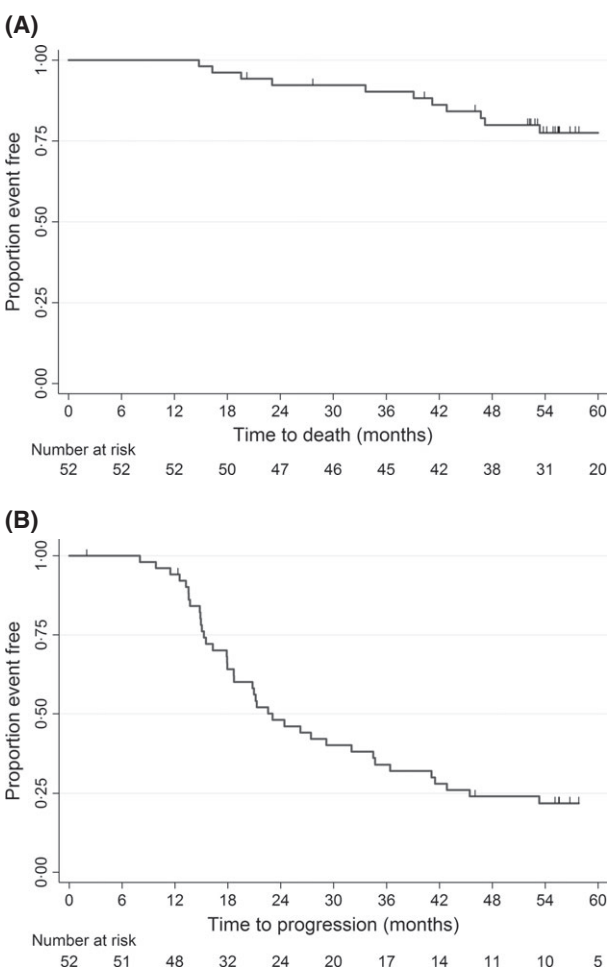

Fig 3. (A) Overall (time from consent to death from any cause or censored at date of last follow up if patient alive) and (B) Progression-free (time from consent to disease progression or censored at date of last follow up if patient did not progress) survival curves (Intent-to treat population, n = 52).

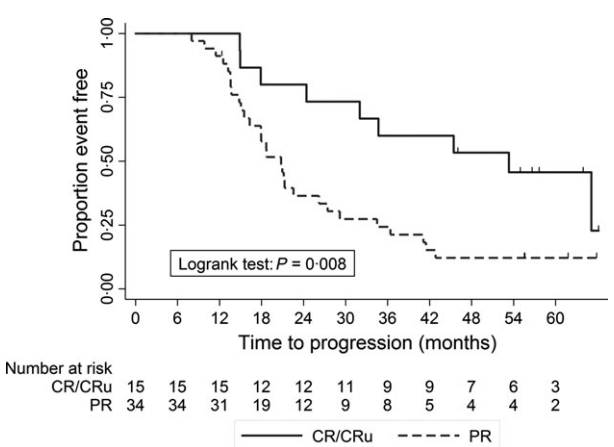

Fig 4. Kaplan–Meier plot showing progression-free survival in patients (A) achieving a CR/CRu versus PR shortly after ^{90}Y-IT (visit 16) (all responding patients, n = 49) ^{90}Y-IT, ^{90}Y-ibritumomab-tiuxetan; PR, partial response; CR, complete response; CRu, unconfirmed complete response

^{90}Y-IT has been extensively studied prior to rituximab being routinely used in the initial treatment of FL (Witzig *et al*, 2002b; Gordon *et al*, 2004; Fisher *et al*, 2005). In a randomized phase II trial, consolidation with ^{90}Y-IT was compared to rituximab maintenance in the upfront setting following response to R-CHOP, with an improved PFS at 36 months for rituximab (86% vs 64%) and no difference in OS (Lopez-Guillermo *et al*, 2013). There are no previously reported trials in relapsed FL investigating an induction immunochemotherapy and ^{90}Y-IT consolidation strategy. In the initial registration studies (Witzig *et al*, 2007), earlier treatment with RIT after first or second relapse was shown to correspond with better outcome. In a meta-analysis of the registration trials, patients with FL receiving ^{90}Y-IT as a second line treatment had CR rates of 51%, compared to 28% for those who had two or more previous treatments (Witzig *et al*, 2007). The time to progression was 15·4 months in the group treated after first relapse, compared to 9·2 months in the previously treated group. Emmanouilides (2009) reported improved ORR using ^{90}Y-IT as a single agent with CR rates of 51% vs 28% for FL patients treated at first relapse rather than subsequent relapses. The only negative predictor of response appeared to be bulky disease, with nodal masses >5 cm having a 68% response rate, compared to an ORR of 90% for patients who had no masses >5 cm (Emmanouilides *et al*, 2006). Our results were in keeping with this analysis, albeit that all of our patients had received an abbreviated course of immunochemotherapy so that the ORR was 100%, but those with nodal masses >5 cm had a CR rate of 8·3%, compared to 36·1% in those without bulky disease ($P = 0{\cdot}067$). Of note, there was no significant difference in median pre-dose rituximab levels between these two groups.

Our data compares very favourably to this analysis of FL patients treated in first relapse and suggests that abbreviated immunochemotherapy followed by ^{90}Y-IT may provide longer PFS of 23·1 months than the median TTP of 15·4 months with a single infusion of ^{90}Y-IT seen in these four trials (Emmanouilides *et al*, 2006). Importantly this strategy of abbreviated immunochemotherapy followed by ^{90}Y-IT is applicable to a more general population and does not, for example, exclude patients with bone marrow infiltration >25% from commencing immunochemotherapy before having their bone marrow re-evaluated. It is interesting to note that our results also compare well with the phase II study of ^{90}Y-IT in 59 previously untreated FL patients (Scholz *et al*, 2013), with an 87% ORR, 56% CR/CRu and median PFS of 25·9 months with favourable baseline characteristics (27% high risk FLIPI in comparison to 46% in this study).

Patients achieving a CR (around one-third) following ^{90}Y-IT showed improved PFS compared to partial responders. The 3-year PFS for those achieving CR/CRu is 60% compared to 24·3% for PR, with some responses appearing to be more durable. In other studies, approximately one-third of patients treated with ^{90}Y-IT (37% in one integrated analysis (Wiseman & Witzig, 2005) experience a long term remission (LTR). A CR/CRu strongly predicts for a LTR (in two-thirds of such patients), which may be durable and last for years (Fisher *et al*, 2005; Wiseman & Witzig, 2005; Witzig *et al*, 2007).

We have previously performed a detailed pharmacokinetic analysis of the relationship between serum rituximab level, tumour bulk and half-life of the radioimmunoconjugate to address concerns that induction therapy with rituximab might compromise the clinical efficacy of RIT (Illidge *et al*, 2008). The data in the present study appears to confirm that subsequent response to ^{90}Y-IT is not impaired by rituximab pre-dosing, with 40% of patients in a PR following chemotherapy converting to a CR following ^{90}Y-IT. After four infusions of rituximab, the trough serum rituximab level reached a median of 112 μg/ml and there was no correlation between rituximab levels and subsequent response assessment after ^{90}Y-IT. This is potentially an important observation and suggests that, even in the presence of high serum rituximab, ^{90}Y-IT is effective in binding to CD20 tumour target and leads to high responses. The regime was tolerated well, with minimal toxicities, despite some patients having received heavy pre-treatment. This study demonstrates the excellent tolerability of an abbreviated course of just three cycles of immunochemotherapy followed by ^{90}Y-IT, with the most significant clinical toxicity being seen after the immunochemotherapy rather than following the ^{90}Y-IT. At the time of data analysis one patient has developed MDS.

The landscape for treatment of relapsed FL has changed since this study was designed, with increasing usage of two approved drugs, bendamustine and more recently, idelalisib (Gopal *et al*, 2014). Bendamustine was reported to lead to an ORR of 75% (a 14% CR rate, and a 58% PR rate), with a PFS of 9·3 months following 6–8 cycles with 12–14 hospital visits (Kahl *et al*, 2010). The results reported in the present study do not appear significantly different, but the duration of the therapy is considerably less.

In conclusion, we have demonstrated that multiple doses of rituximab as part of three weekly immunochemotherapy do not appear to compromise the clinical efficacy or increase the toxicity of subsequent RIT. In the presence of high serum rituximab levels, impressive clinical responses were obtained. This abbreviated regimen has the potential to reduce toxicity and provide a more convenient treatment approach for older and co-morbid previously treated patients and is worthy of further study.

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Author contributions

Tim M. Illidge: designed the study, recruited patients, analysed the results, wrote the manuscript; Hayley S. McKenzie, Ruth Pettengell, Louise Stanton, Kelly Cozens, Sam Mayes: analysed the results, wrote the manuscript; Andrew Bates, Eve Gallop-Evans, John A. Radford, Peter W.M. Johnson: recruited patients, analysed the results, wrote the manuscript; Andrew J. Davies: recruited patients, data management, analysed the results, wrote the manuscript; Grace Hampson, Caroline Dive, Maureen Zivanovic, Jill Tipping: developed results, analysed the results, wrote the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Progression free survival by FLIPI score at study entry (ITT population).

Table SI. (associated with Fig 1) – Rituximab levels over time by change in response before and 8 weeks after ^{90}Y-IT (all eligible patients with rituximab level data available).

Table SII. (associated with Fig 2B) – PFS summary statistics – ITT population.

Table SIII. (associated with Fig 2A) – Overall survival summary statistics – ITT population.

Table SIV. Response at visit 16 post ^{90}Y-IT by baseline characteristics of study population (all eligible patients who received ^{90}Y-IT, $n = 50$).

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