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Radioimmunotherapy (RIT) for Follicular Lymphoma achieves long term lymphoma control in first line and at relapse: 8-year follow-up data of 281 patients from the international RIT-registry

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Summary

To assess efficacy of radioimmunotherapy (RIT) in follicular lymphoma, data from 281 patients collected in the RIT Network, with a median follow-up of 8·2 years after RIT were analysed. RIT was given at first line in 18·5% and at relapse in 81·5%. Following first line therapy, 76·9% achieved complete remission (CR), 9·6% partial remission (PR), 1·9% stable disease (SD) and 1·9% had progressive disease (PD); response was not documented in 9·7%. At relapse, the rate of CR was 48·5% and that of PR was 16·6%, SD 2·6% and PD 10·5%; response was not documented in 21·8%. After median follow-up of 8·2 years, median progression-free survival (PFS) for all was 2·54 years, median overall survival (OS) was not reached. Median PFS and OS (both not reached) were significantly better in first line, compared to RIT at relapse (PFS, 2·11 years; OS, 10·8 years; $P = 0·0037$ and $P = 0·0021$, respectively). Overall 8-year PFS was 33·9%, 53·6% for first line and 29·6% for relapsed individuals. Overall 8-year OS was 58·8%, 78·1% for first line and 54·5% for relapsed patients. Thirty-five patients (12·5%) developed secondary malignancy and 16 patients (5·7%) experienced transformation into aggressive lymphoma. RIT is a safe and effective treatment option for follicular lymphoma, both at front line and relapse with an 8-year PFS of 53·6% and 29·6%, respectively.

Keywords: long-term follow-up, radioimmunotherapy, follicular lymphoma, first line treatment, late toxicity.

Follicular lymphoma (FL) is a radiosensitive disease and while external beam radiotherapy (EBRT) is commonly employed in stage I or II FL, only about 15–25% of cases are diagnosed at this stage (Mac Manus & Hoppe, 1996; Mondello *et al*, 2014). Patients with stage III or IV FL in need of therapy are commonly treated with six cycles of chemoimmunotherapy, i.e. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or bendamustine, combined with an anti-CD20 antibody, i.e. obinutuzumab or rituximab, followed by a maintenance therapy with an anti-CD20 antibody (Marcus *et al*, 2017; Hiddemann *et al*, 2018). For these patients, EBRT is not used upfront and is infrequently employed upon relapse, i.e. for palliative treatment of local symptoms. Antibodies against CD20 increase response rates

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and duration compared to chemotherapy alone (Hiddemann *et al*, 2005; Herold *et al*, 2007). In addition, rituximab monotherapy is capable of inducing remissions in front line treatment (Martinelli *et al*, 2010) and at relapse (Sehn *et al*, 2015). Radioimmunotherapy (RIT) with the radionucleotide Yttrium-90 (^{90}Y) linked to the anti-CD20 antibody ibritumomab through the linker tiuxetan combines the treatment modalities of immunotherapy and radiotherapy. Efficacy of ^{90}Y- ibritumomab-tiuxetan (^{90}Y-IT, Zevalin®), the only currently commercially available RIT, has been demonstrated in distinct clinical trials, e.g. as consolidation after first line chemo(immuno)therapy (Witzig *et al*, 2002; Morschhauser *et al*, 2008; Provencio *et al*, 2014; Casadei *et al*, 2016), at relapse (Witzig *et al*, 2002) and even as a monotherapy for first line treatment (Scholz *et al*, 2013; Ibatici *et al*, 2014). ^{90}Y-IT can be administered in an outpatient setting and its side effects, particularly cytopenia between week 6 and 9 after application, are manageable. However, if ^{90}Y-IT is employed in an early treatment line, infections are infrequent and the requirement for transfusions is low. While ^{90}Y-IT has been tested in prospective clinical trials, most studies only included relatively small patient numbers. Furthermore, longer follow-up data regarding progression-free survival (PFS), overall survival (OS), secondary malignancies and transformation into aggressive lymphoma is generally missing. The RIT network (RIT-NT), founded in 2006, is a large registry employing a web-based electronic data-capturing system to follow patients with non-Hodgkin lymphoma (NHL) that have been treated with ^{90}Y-IT. Here, we present results from patients with FL treated with ^{90}Y-IT and a median follow-up of 8 years.

Patients and methods

The RIT-NT was active in 14 countries between December 2006 and November 2009, evolving from already existing national RIT registries in Austria, Germany, Switzerland and Spain. A web-based electronic data capturing (EDC) system was used for documentation by all participants. The core data set includes age, indication, lymphoma subtype, clinical course, and haematological side effects. For the purpose of specific evaluation projects, such as the one presented here, data sets from the national registries were merged with the international data base. Ethics Committee approval was obtained on a national basis by the respective national RIT registry chairs. Informed consent of patients was mandatory, mainly relating to the process of pseudonymized data collection and storage within the registry database. An Institutional Review Board vote was provided by the Ethics Committee of the University of Göttingen.

The web-based EDC system is managed by a professional clinical research organisation (Alcedis GmbH, Giessen, Germany), which ensures data privacy protection and quality assurance according to recognised guidelines and standards, such as the US Food and Drug Administration (FDA) regulation 'Guidance on Computerised Systems used in Clinical Trials' (FDA 1997; International Society for Pharmaceutical Engineering 2017). Access to the EDC systems follows the 'Principle of Least Privileges' realised through a role-based access control and corresponding process rights. Access authorisation to the software is granted individually by means of user accounts (user ID and password). Patients are recorded and saved pseudonymized in the EDC data base.

For the analysis presented here, all originally participating centres with documented FL patients in the RIT-NT were requested by mail to undertake an extended follow-up of all FL patients with the web- based EDC system.

Results

Six countries participated in the extended follow-up analysis (Argentina $n = 24$, Germany $n = 107$, Italy $n = 126$, Poland $n = 18$, South Korea $n = 4$ and Switzerland $n = 2$ patients), while seven countries chose not to participate for unknown reasons. The response rate to the extended follow-up request was 56%, providing data sets for 281 patients analysed in this study. Follow-up analysis included PFS, OS, relapse therapy, secondary neoplasia and FL transformation.

Of the 497 patients originally documented in the RIT-NT, 218 patients were lost to follow-up because they were from countries who did not participate in the extended follow-up analysis for unknown reasons.

Patient and disease characteristics

Between December 2006 and November 2009 data from 1105 lymphoma patients treated with radioimmunotherapy were collected in the RIT-NT, of which 497 were diagnosed with FL. Longer follow-up data could be obtained from 281 FL patients for this analysis. Median follow-up time after RIT was 8·2 years (range 0·2–13·6 years). Median age at diagnosis was 58 years (range 26–88 years), 44% of the patients were older than 60 years and 13% were aged over 70 years. Forty-eight percent of patients were male and 52% were female patients (Table I). Disease stage according to the Ann Arbor staging system was documented only at initial diagnosis: 58·4% of patients had stage IV, 25·4% stage III, 10·3% stage II and 4·9% stage I disease. Prior to treatment with RIT, 15·3% ($n = 43$) of the patients had bone marrow infiltration but only three patients had a bone marrow infiltration of more than 25% (Table I). The FL International Prognostic Index (FLIPI) score for these patients was not available as neither the score nor the variables were documented at the start of the RIT-NT in 2006 (Solal-Celigny *et al*, 2004; Federico *et al*, 2009).

Previous therapies

For this analysis, RIT first line therapy was defined as primary treatment (monotherapy) or consolidation after first

Table I. Patient characteristics and indications for radioimmunotherapy (RIT).

	n		%	
Patients	281			
Male/female	124/147		48%/52%	
Age, years; median (range)	58		(26–88)	
>60 years	128		44%	
>70 years	36		13%	
Stage				
IV	164		58.4%	
III	72		25.4%	
II	29		10.3%	
I	14		4.9%	
Missing	2		1.0%	
Previous therapies				
Prior Rituximab	*First line*		*Relapse*	
Rituximab	41	(78.8%)	191	(83.4%)
No Rituximab	11	(21.2%)	38	(16.6%)
Chemotherapy				
0	19		6.8%	
1	93		33.1%	
2	73		25.9%	
3	43		15.3%	
≥4	53		18.9%	
Radiotherapy				
0	235		83.6%	
1	30		10.7%	
2	13		4.6%	
≥3	3		1.1%	
Autologous stem cell transplantation				
1	38		13.52%	
Bone marrow infiltration prior to RIT				
Infiltration	43		15.3%	
<25%	40		14.2%	
>25%	3		1%	
No infiltration	229		81.5%	
Not done	9		3%	
RIT used, line of therapy				
1	52		19%	
2	94		33%	
3	57		20%	
4	78		15%	
≥5	36		13%	
Indication for RIT				
First line therapy	52		18.5%	
Primary therapy (RIT monotherapy)	10		19.2%	
Consolidation after first line therapy	41		80.8%	
Relapse	229		81.5%	
RIT monotherapy	172		61.2%	
Disease recurrence	131		46.6%	
Refractory disease	41		14.9%	
Conditioning	2		0.7%	
Consolidation	49		17.4%	
Other	6		1.1%	

line treatment with chemo- or chemoimmunotherapy. RIT at relapse was defined as ^{90}Y-IT applied for relapsed or refractory FL, as monotherapy, consolidation after chemo (immuno)therapy, and as part of a conditioning regimen prior to autologous stem cell transplantation [only 2 (0·7%) cases]. RIT was given as first line therapy in 52 patients

(18·5%) and for relapse in 229 individuals (81·5%). At relapse, the largest group, i.e. 172 patients (61·2%), received RIT as monotherapy for relapsing or refractory disease (Table I). Use of radiotherapy before RIT was infrequent, i.e. only 46 (16·4%) patients received conventional radiotherapy prior to RIT. In patients from the RIT-NT, ^{90}Y-IT was most frequently employed as second (33%, 93/281 patients) and third (20%, 57/281 patients) line treatment. A small population (13%) had more than five previous lines of chemotherapy (Table I). Stem cell transplantation had been performed in 38 patients prior to RIT. Regarding RIT in first line therapy, 42 patients (80·8%) received RIT as consolidation after chemo(immuno)therapy and 10 patients (19·2%) were treated with RIT monotherapy in first line. In first line therapy, 70% of patients received rituximab prior to RIT whilst 56% of relapsed patients had received rituximab treatment prior to RIT.

Response rates, response duration and overall survival

In the first line group, 76·9% of the patients achieved a complete remission (CR), 9·2% a partial remission (PR), 1·9% a stable disease (SD), 1·9% had progressive disease (PD) and response was not documented for 9·7%. For patients treated at relapse, the rate of CR was 48·5% and that of PR was 16·6%, SD 2·6% and PD 10·5%; response was not documented in 21·8%. (Table II). With a median follow-up of 8·2 years (range 0·2–13·6 years), the median PFS for all patients was 2·54 years [95% confidence interval (CI) 1·9–3·34] whilst median OS was not reached (95% CI 8·27-not reached) (Fig 1). As expected, median PFS and OS was significantly better for patients treated with RIT in first line (median PFS: not reached; (95%CI 1·66-not reached); median OS: not reached), compared to patients who received RIT at relapse [median PFS: 2·11 years (95% CI 1·68–2·95) and median OS: 10·8 years (95% CI 7·56 - not reached); $P = 0·0037$ and $P = 0·0021$, respectively] (Fig 2). Eight-year PFS was 33·9% (95% CI 28·1–39·7%) for all patients, 53·6% (95% CI 38·8–66·3%) for first line and 29·6% (95% CI 23·5–35·8%) for relapsed patients. Eight-year OS for all patients was 58·8% (95% CI 52·2–64·8%), 78·1% (95% CI 57·2–89·6%) for first and 54·5% (95% CI 47·3–61·1%) for relapsed patients. There was no significant difference regarding 3- and 8-year PFS and OS in the relapsed group for patients who had received previous rituximab and those who did not (data not shown).

Second malignancies and transformation

After a median follow-up of 8·2 years (range 0·2–13·6 years), 35 (12·5%) of the 281 patients developed a secondary malignancy and 16 (5·7%) experienced histological transformation into aggressive lymphoma. Of the 35 patients with secondary malignancies, three were diagnosed with myelodysplastic syndrome (MDS), five had acute myeloid leukaemia (AML), four patients developed NHL and one had Hodgkin lymphoma. The remaining 22 patients presented with solid tumours, including four patients with basal cell carcinoma (Table II).

Table II. Response to RIT and details of secondary malignancies.

	All		First line		Relapse	
Best response	*n*	%	*n*	%	*n*	%
CR	151	53.7	40	76.9	111	48.5
PR	43	15.3	5	9.6	38	16.6
SD	7	2.9	1	1.9	6	2.6
PD	25	8.9	1	1.9	24	10.5
ND	3	1.1	0	0	3	1.3
Missing	52	18.1	5	9.7	47	20.5
Secondary malignancies						
None	200	71.1				
Yes	35	12.4				
Unknown	46	16.4				
Solid tumours	22	7.8				
Breast cancer/NSCLC	6	2.1				
Basal cell carcinoma	4	1.4				
Prostate cancer	2	0.7				
Kidney cancer	1	0.35				
Lymphangioleiomyomatosis	1	0.35				
Lung cancer	1	0.35				
Pancreatic cancer	1	0.35				
Neuroendocrine carcinoma	1	0.35				
Cerebral neoplasia	1	0.35				
Colorectal cancer	1	0.35				
Endometrial cancer	1	0.35				
Meningioma	1	0.35				
Mesothelioma	1	0.35				
Haematological disease	13	4.6				
Acute myeloid leukaemia	5	1.8				
Myelodysplastic syndrome	3	1.1				
Diffuse large B-cell lymphoma	2	0.7				
Mantle cell lymphoma	2	0.7				
Hodgkin lymphoma	1	0.35				

CR, complete remission; ND, not documented; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial remission; SD, stable disease.

Discussion

Although clinical trials have repeatedly shown that ^{90}Y-IT is active and has, at least when employed in an earlier line of therapy, few and well manageable side effects, its usage has been in decline. In the pivotal phase III first line indolent trial (FIT), consolidation with ^{90}Y-IT significantly increased PFS as compared to observation only, i.e. 8-year PFS amounted to 48% and 32%, respectively (Morschhauser *et al*, 2013). However, most of the patients (87%) had received chemo- and not chemoimmunotherapy prior to consolidation in this trial (Marcus *et al*, 2017), and therefore this trial could not determine whether RIT improves the outcome of

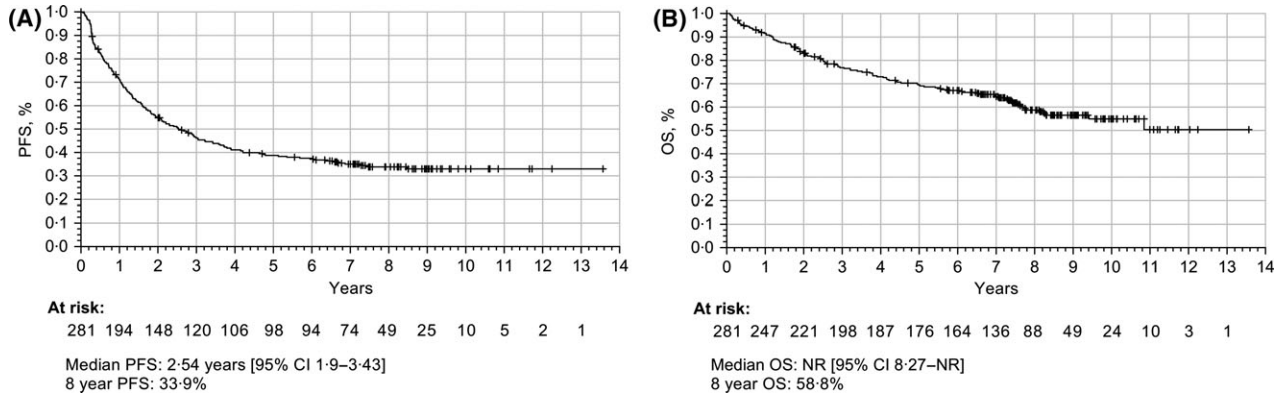

Fig. 1. (**A**) PFS and (**B**) OS for all patients. CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival.

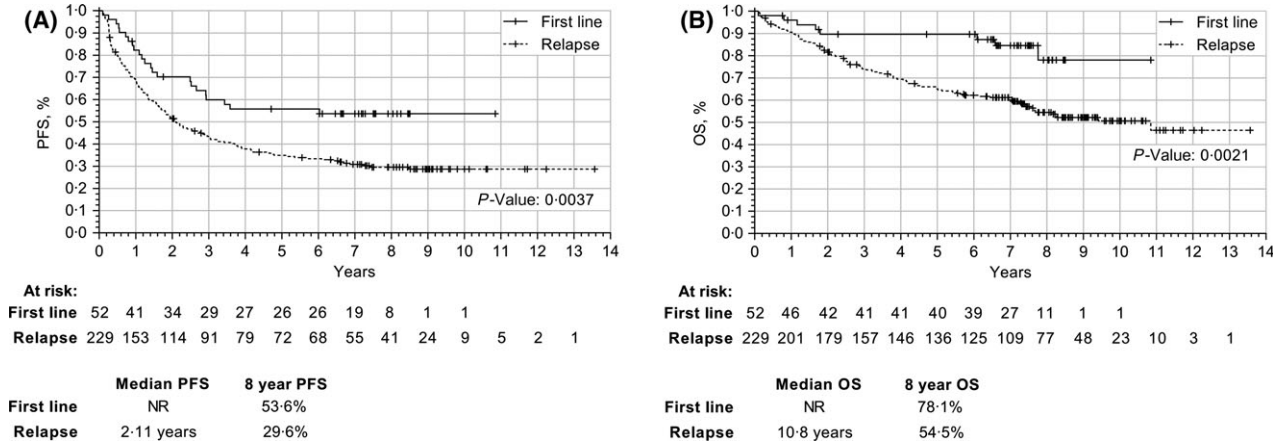

Fig. 2. (**A**) PFS and (**B**) OS according to disease status. NR, not reached; OS, overall survival; PFS, progression-free survival.

patients treated with the current standard of anti-CD20 antibody and chemotherapy, followed by anti-CD20 antibody maintenance. Nevertheless, several smaller phase II trials have shown an increased CR rate after ^{90}Y-IT consolidation (Provencio *et al*, 2014; Pisani *et al*, 2015; Casadei *et al*, 2016; Puvvada *et al*, 2018) following induction with CHOP and rituximab (R-CHOP) as compared to R-CHOP induction alone. However, a 2-year maintenance with rituximab or obinutuzumab (Salles *et al*, 2011; Marcus *et al*, 2017), instead of ^{90}Y-IT consolidation, is currently common practice after first line chemotherapy. This is supported to some extent by a small, albeit not yet fully published trial of 146 patients, that compared ^{90}Y-IT with rituximab maintenance after six cycles of R-CHOP and demonstrated a 3-year PFS of 63% and 77%, respectively [P = 0·044; hazard ratio=0·517 (95%CI: 0·269–0·996)] (Lopez-Guillermo *et al*, 2013). While this suggests an additional benefit for rituximab maintenance, patients may still prefer ^{90}Y-IT as this is a single treatment as compared to 12 cycles of rituximab maintenance, with frequent visits and possible side effects, e.g. an increased rate of infections. Our long-term follow-up data from the RIT-NT underscore the fact that ^{90}Y-IT is a very efficient consolidation after immunochemotherapy induction. First line treatment with ^{90}Y-IT resulted in a 3- and 8-year PFS of 59·9% (95% CI: 45–72%) and 53·6% (38·8–66·3), respectively. This compares well to the 3- and 8-year PFS of 45% and 41% reported in the FIT trial (Morschhauser *et al*, 2013) and to the 3- and 8-year PFS of 74·9% and approximately 60% observed after chemoimmunotherapy and rituximab maintenance in the PRIMA trial (Salles *et al*, 2011). Of note, only 70% of the first line patients from the RIT-NT received rituximab as part of their treatment and 19% (10 of 52 patients) were treated with ^{90}Y-IT monotherapy without any prior chemo(immuno)therapy at all. 65·9% of all relapsed patients received ^{90}Y-IT monotherapy as second- or third-line therapy. The median PFS and OS for all patients in relapse w to 2·1 and 10·8 years, respectively, which compares very well with data from monotherapy with rituximab (Sehn *et al*, 2015) or rituximab-bendamustine (Robinson *et al*, 2008) at relapse, which resulted in a median PFS of 25 and 23 months, respectively. Of note, data from different phase II trials of relapsing FL patients are difficult to put into context as it is frequently unclear whether patients had a treatment indication, e.g. according to the Groupe d'Etude des

Lymphomes Folliculaires criteria (Robinson *et al*, 2008; Fowler *et al*, 2011). Furthermore, a mixture of relapsed and chemo-refractory patients and of different subtypes of indolent B cell lymphomas may be included in these trials. Our data, however, demonstrate that ^{90}Y-IT is very effective in terms of the overall response rate, the PFS and the treatment side effects. One major concern with the combination of RIT and ^{90}Y-IT had been the possibility of an excess number of secondary cancers and histological transformations into high grade lymphoma. These long-term follow-up data from the RIT-NT address this question. During the follow-up of a median 8 years, we observed 35 secondary malignancies in 281 patients, including eight patients with MDS or AML. This amounts to an overall rate of 12·5% for all secondary malignancies and of 2·8% for MDS and AML, and results in an annual rate of 1·56% and 0·35%, respectively. This compares well with data from the 7·1-year follow-up from FIT where the annual rate for AML or MDS was 0·5% (Morschhauser *et al*, 2013). The observed frequency was similar to the annual 0·34% incidence of MDS reported in the Swiss Group for Clinical Cancer Research trial (SAKK35/98) after a follow-up of a median 9·5 years. In this trial, patients received immunotherapy and chemotherapy (Martinelli *et al*, 2010). Regarding transformation into aggressive lymphoma, we observed an incidence of 5·7%, which translates into an annual rate of 0·71%. This is well in line with reports from other analyses (Al-Tourah *et al*, 2008; Link *et al*, 2013; Wagner-Johnston *et al*, 2015; Sarkozy *et al*, 2016) in FL. Therefore, RIT does not lead to a significant increase either in secondary malignancies or transformations into aggressive lymphomas in comparison to the current standard treatment of immunochemotherapy followed by immunotherapy maintenance.

Conclusion

In conclusion, these data from the RIT-NT registry, with a median follow-up of 8 years, demonstrate that ^{90}Y-IT is an effective treatment in first line and relapsed disease in FL. There is no increased risk for the development of secondary malignancies or transformation into aggressive lymphoma after ^{90}Y-IT therapy. ^{90}Y-IT therapy consists of a single shot treatment of radioactively-labelled monoclonal antibodies. Treatment duration, side effects and cost compare favourably with current standard treatments, including phosphatidylinositide 3-kinase inhibitors. In our opinion, ^{90}Y-IT is underused in the treatment of FL patients. The RIT-NT data favour its inclusion in trials and treatment algorithms of FL patients.

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Conflict of interest

The authors have declared no conflicts of interest.

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