Radiotherapy for Stage I/II Follicular Lymphoma (FL): Is it Time for A Re-appraisal?

PATRIZIA MONDELLO[1], NORMANN STEINER[2], INES WASLE[3], VINCENZO PITINI[1] and MICHAEL MIAN[2,4]

[1]*Department of Human Pathology, University of Messina, Messina, Italy;*
[2]*Department of Hematology & Oncology, Medical University of Innsbruck, Innsbruck, Austria;*
[3]*Department of Internal Medicine, Hospital of Feldkirch, Feldkirch, Austria;*
[4]*Department of Hematology, Azienda Ospedaliera S. Maurizio, Bolzano, Italy*

Abstract. *Aim: Almost 30% of follicular lymphomas (FL) present with stage I-II disease. Although the standard-of-care consists of involved-field radiotherapy (IFRT), approximately half of patients relapse usually outside the primary irradiation field. Systemic immunotherapy with rituximab (R), with or without IFRT, could reduce distant recurrences leading to a better outcome. Therefore, we compared the efficacy of IFRT-alone or associated with R (R+IFRT) versus R-alone in stage I/II FL (grade 1-3A). Patients and Methods: From 1995 to September 2012, 108 early-stage FL patients were retrospectively assessed: 36 underwent IFRT, 38 R-alone and 34 R+IFRT. Results: Complete response rate was 84% in the IFRT-group, 87% in the R group and 97% in the R+IFRT-group. Median progression-free survival and time to next treatment were significantly higher in both rituximab arms compared to IFRT-alone. Conclusion: R or R+IFRT have demonstrated a better long-term control of the disease without significant additional toxicities.*

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) representing about 30% of all new diagnoses (1). Most patients present with advanced disease, while 30% have stage I-II (2). In the latter cases, due to the high percentage of complete remissions and the durable local response (3-5), the standard-of-care consists of involved-field radiation therapy (IFRT) (6). Nevertheless almost half of the patients relapse, leading to death in a substantial number of cases (7). Disease recurrence mostly occurs outside the primary irradiation field (8), suggesting the presence of a disseminated but yet undetectable disease already at the time of diagnosis. The addition of chemotherapy to radiotherapy (RT) provided controversial results. Chlorambucil plus RT did not improve disease-free survival (9), while the combination of RT with an anthracycline containing chemotherapy improved relapse-free survival (10-12). However, the latter was associated with significant acute toxicity as well as the development of secondary malignancies, which is why such treatment intensifications did not enter clinical routine (11, 12). Therefore, new and less toxic treatment approaches are needed. Rituximab (R), a chimeric monoclonal antibody against CD20, has demonstrated to be an effective treatment for patients with low–tumor burden FL and to eradicate minimal residual disease (MRD) in a part of patients with a favorable toxicity profile (13). In addition, Rituximab may improve the effect of radiotherapy due to its ability to enhance radiosensitivity of lymphoma cells (14). Therefore, the addition of R to IFRT could reduce the rate of distant recurrences, leading to a better outcome. Indeed, only recently Janifova *et al*. presented preliminary data of the Czech Lymphoma Group database suggesting that Rituximab alone or in combination with radiotherapy improves the outcome of stage I-II FL patients (15). However, the treatment arms were not well-balanced (65 patients treated with IFRT, 14 with R-alone and 14 with R+IFRT) and the median follow-up of 4.3 years was rather short. The positive impact of systemic treatment on localized FL was also observed by Friedberg *et al*. who retrospectively evaluated a large series of stage I FL (16). However, due to several limitations, inherent in the registry nature of the report, they did not provide any therapy recommendations. (16). Overall, the data available up to now suggests that systemic therapy might improve the outcome of patients with localized FL but both available analyses have important limitations and a rather short follow-up considering the usually indolent course of this disease. In order to evaluate the efficacy of IFRT alone, in association with R (R+IFRT) *versus* R-alone

Correspondence to: Patrizia Mondello, MD, Department of Human Pathology, University of Messina,Via Consolare Valeria, 98125 Messina, Italy. Tel: +39 0902212751, Fax: +39 0902213750, e-mail: patriziamondello@hotmail.it

Key Words: Early stage, follicular lymphoma, radiotherapy, rituximab.

Table I. *Clinical characteristics at time of diagnosis.*

Parameter	IFRT (n=36)		R (n=38)		R+IFRT (n=34)		*p*-Value
	N	%	n	%	n	%	
B-Symptoms	2	5.5	6	15.8	14	41.1	0.001
LDH>UNL	8	22.2	10	26.3	18	52.9	0.013
B2-microglobulin	12	33.3	18	47.3	21	62	0.059
FLIPI							0.015
0	28	77.8	20	52.6	16	47	
1	8	22.2	18	47.4	18	53	
Stage							0.715
I	19	52.7	17	44.7	15	44.1	
II	17	47.3	21	52.3	19	55.9	

LDH, Lactate dehydrogenase; UNL, upper normal limit; FLIPI, follicular lymphoma international prognostic index; IFRT, involved-field radiation therapy; R, rituximab.

in stage I/II FL grade 1-3. After a long term follow-up, and to provide a basis for a prospective trial, we retrospectively assessed consecutive patients in two cancer centers.

Patients and Methods

Patients. From 1995 to September 2012, 108 consecutive patients affected by FL were retrospectively assessed at the Medical University of Innsbruck and at the University Hospital "G. Martino" in Messina. Treatment response was evaluated 6-12 weeks after the end of treatment and consisted of a physical examination, blood testing and computed tomography (CT) scan. The ethical committee approved this analysis. Statistical analysis. Chi-square test was performed to assess the significance of differences between categorical variables. Overall survival (OS), progression- free survival (PFS) and time to next therapy (TTNT) were plotted as curves using the Kaplan-Meier method and were defined as time from diagnosis until death of any cause, as time from diagnosis until disease progression or death of any cause and as time from the achievement of a complete response (CR) to relapse or death as a result of lymphoma or acute toxicity of treatment, respectively. The log-rank test was employed to assess the impact on survival of categorical variables. A *p*-value of <0.05 was considered as statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA), MedCalc (version 8.0) software and the GraphPad Prism (version 5.0) package.

Results

A total of 108 patients with early stage FL (grade 1-3A) were identified. Overall, median age at time of diagnosis was 60 years (range=31-88 years). As requested by the inclusion criteria, all patients had stage I/II disease. The percentage of adverse prognostic factors was significantly higher in patients who underwent R or R+IFRT (Table I).

Thirty-six patients (33%) underwent IFRT, 38 R-alone (35%) and 34 (31%) both. Similarly to the previous report by Janikova *et al*. (15), radiation doses were ≥24Gy in all cases. R was administered weekly at the standard dose of 375 mg/m^2 for a median of 5 administrations (range=4-8) to those who underwent only immunotherapy and for 4 cycles after IFRT in the R+IFRT group. Among all three treatment groups no grade 3/4 toxicities were registered.

The percentage of CR varied, but not in a significant way, between the three cohorts, being 84% in the IFRT-group, 87% in the R group and 97% in the R+IFRT-group (p=0.1). During the whole observation period, 64 relapses were registered. Most of them occurred in the IFRT- group (27 patients, 75%), followed by 19 in the R-IFRT (55%) and 18 in the R-group (47%; p=0.03). After a median follow-up of 8 years (range=1-20), 42 patients were alive and in CR, 54 with disease and 12 died (8 for disease and 4 for non disease related causes). PFS and TTNT were significantly higher in both rituximab arms when compared to IFRT alone: median PFS was 5 and 6 years in the R and R+IFRT groups *vs*. 2.3 years in the IFRT one (p<0.001) (Figure 1) (Panel A), median TTNT was 5 and 6.6 years in the R and R+IFRT groups *vs*. 2 years in the IFRT one (p<0.001) (Figure 1) (Panel B). In the present analysis, patients treated with rituximab +/- IFRT showed a trend for a better OS without reaching statistical significance (p=0.059) despite the rather long follow-up (Figure 1, Panel C).

Discussion

Herein, we present the so far largest real-life analysis of patients affected by localized FL who underwent IFRT, R alone or in addition with IFRT. We were able to show that immunotherapy has a significant impact on the clinical course of these patients, providing the basis for a prospective clinical trial. The strengths of this analysis were the long-

term follow-up, which is nearly twice that of the previous reports (15, 16), the "real-life" nature and the homogeneous treatment, although these patients were treated outside a clinical trial. The main limit of this study was the retrospective data assessment.

In our study the dosages of IFRT and immunotherapy were comparable to previous reports (15, 13). The different treatment groups were well-balanced in terms of patient numbers and in terms of clinical characteristics, except for a higher prevalence of adverse prognostic factors in those who underwent immunotherapy. Unlike the combination of chemotherapy and radiotherapy (11, 12), both IFRT and R proved to be well-tolerated. Of course, the limited radiotherapy-related toxicity could be attributed to the restriction of the irradiation field and to the technical improvements in these past years (17). Difference in CR-rate was not statistically significant among the treatment groups, despite the percentage of CR being ≥10% higher in those who underwent IFRT+R. However, this study was not powered for such analysis and in a larger patient series the difference would probably achieve statistical significance. Nevertheless, similar results were described in the Czech retrospective analysis, which presented the highest percentage of CR in the combined modality treatment group (14 patients, 100%) (15). It is noteworthy that the administration of immunotherapy translated into a significantly lower relapse rate (≥20% less) suggesting an important role in the elimination of persistent occult MRD. These results are in line with previous observations that R is able to eradicate MRD in patients with low tumor burden FL (13). Moreover, rituximab may improve the effect of radiotherapy due to its ability to enhance radiosensitivity of lymphoma cells. (14) In both previous similar reports the relapse rate was not mentioned (15, 16) but the herein observed percentages were similar to those described in other trials (18, 19). Also PFS and TTNT were significantly higher in both rituximab arms when compared to IFRT-alone, similarly as previously observed by Janikov *et al*. (15) who reported a significant difference in median event-free survival between the three treatment modalities. As expected, no difference in OS was observed. This because FL usually have an indolent course of disease and nowadays there exist efficient salvage treatments.

In conclusion, this analysis, the largest so far, showed that among stage I/II FL patients who underwent IFRT, R or R+IFRT with a median follow-up of 8 years, those who underwent immunotherapy had a clearly better long-term disease control despite a significantly poorer prognostic profile at time of diagnosis. In the R+IFRT group results were even better than in the R group. Our results findings justify the realization of a prospective, randomized clinical trial in order to confirm the superiority of R+IFRT in comparison to the current standard-of-care.

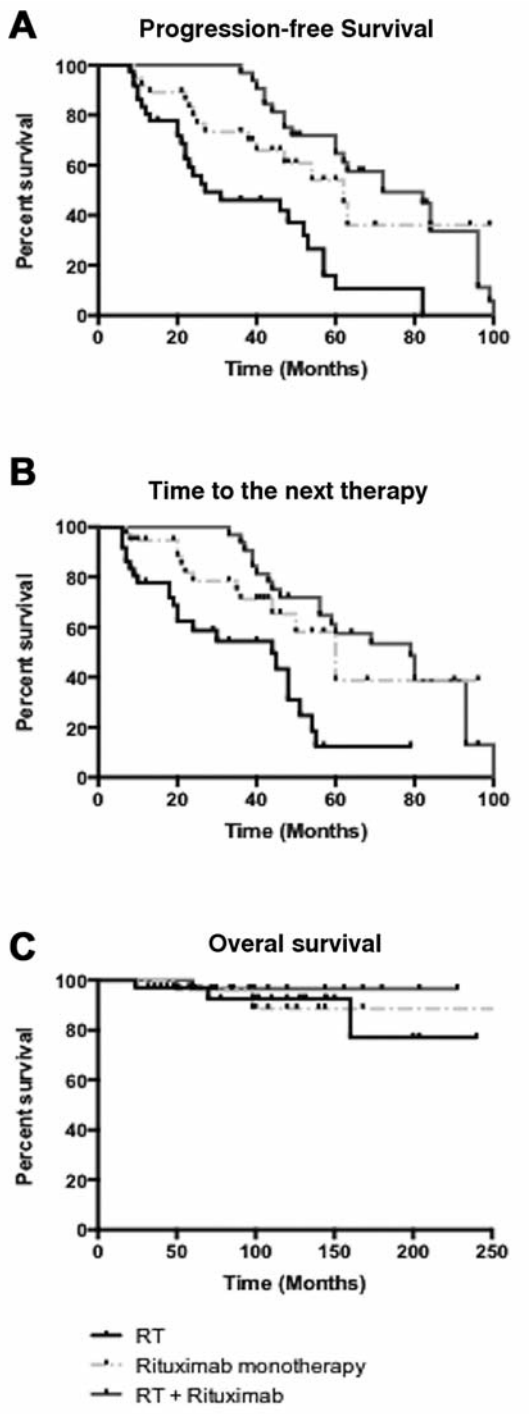

Figure 1. *Kaplan–Meier curves for the three-arms study. (A) Progression-free survival (PFS), (B) Time to the Next Therapy (TTNT) and (C) Overall survival (OS).*

Conflicts of Interest

The Authors declare no conflicts of interest.

References

1 The Non-Hodgkin's Lymphoma Classification Project: A clinical evaluation of the International Lymphoma Study Group Classification of non-Hodgkin's Lymphoma. Blood *89*: 3909-3918, 1997.

2 Armitage J and Weisenburger D: New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. J Clin Oncol *16*: 2780-2795, 1998.

3 Petersen PM, Gospodarowicz R, Tsang R, Pintilie M, Wells W, Hodgson D, Sun A, Crump M, Patterson B and Bailey D: Long term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. J Clin Oncol *22*: 6521, 2004.

4 Vaughan Hudson B, Vaughan Hudson G, MacLennan KA, Anderson L and Linch DC: Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer *69*: 1088-1093, 1994.

5 Guadagnolo BA, Li S, Neuberg D, Ng A, Hua L, Silver B, Stevenson MA and Mauch P: Long term outcome and mortality trends in early stage, grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys *64*: 928-934, 2006.

6 NCC Network: Non-Hodgkin's Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2011). Follicular Lymphoma (Grade 1-2) Guidelines, p. 27. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf. Accessed August 25, 2011.

7 Fuks Z, Glatstein E and Kaplan HS: Patterns of presentation and relapse in the non-Hodgkin's lymphomata. Br J Cancer Suppl *2*: 286-297, 1975.

8 Advani R, Rosenberg SA and Horning SJ: Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol *22*: 1454-1459, 2004.

9 Kelsey SM, Newland AC, Hudson GV and Jelliffe AM: A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy *versus* radiotherapy alone in low grade, localised non- Hodgkins lymphoma. Med Oncol *11*: 19-25, 1994.

10 Yahalom J, Varsos G, Fuks Z, Myers J, Clarkson BD and Straus DJ: Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer *71*: 2342-2350, 1993.

11 McLaughlin P, Fuller L, Redman J, Hagemeister F, Durr E, Allen P, Holmes L, Velasquez W, Swan F and Cabanillas F: Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and radiotherapy. Ann Oncol *2*: 137-140, 1991.

12 Seymour JF, Pro B, Fuller LM, Mannin JT, Hagemeister FB, Romaguera J, Rodriguez MA, Smith TL, Ayala A, Hess M, Cox JD, Cabanillas D and McLaughlin P: Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol *21*: 2115-2122, 2003.

13 Colombat P, Brousse N, Salles G, Morschhauser F, Brice P, Soubeyran P, Delwail V, Deconinck E, Haioun C, Foussard C, Sebban C, Tilly H, Thieblemont C, Bergougnoux L, Lazreg F and Solal-Celigny P: Rituximab induction immunotherapy for first-line low-tumor-burden follicular lymphoma: survival analyses with 7-year follow-up. Ann Oncol *23*: 2380-2385, 2012.

14 Skvortsova I, Popper BA, Skvortsov S, Saurer M, Auer T, Moser R, Kamleitner H, Zwierzina H and Lukas P: Pretreatment with rituximab enhances radiosensitivity of non-Hodgkin's lymphoma cells. J Radiat Res (Tokyo) *46*: 241-248, 2005.

15 Janikova A, Benesova K, Bortlicek Z, Campr V, Kopalova N, Belada D, Prochazka V, Pytlik R, Vokurka S, Pirnos J, Matuska M, Mocikova H, Mayer J and Trneny M: Radiotherapy With Rituximab Is Better than Radiotherapy alone In First Line Treatment Of Localized Follicular Lymphoma. Time To Change a Standard Strategy? Blood *122*: a4388, 2013.

16 Friedberg JW, Byrtek M, Link BK, Flowers C, Taylor M, Hainsworth J, Cerhan JR, Zelenetz AD, Hirata J and Miller TP: Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol *30*: 3368-75, 2012.

17 Engelhard M, Unterhalt M, Hansmann M and Stuschke M: Follicular lymphoma: Curability by radiotherapy in limited stage nodal disease? Updated results of a randomized trial. Ann Oncol *22*: iv90-iv91, 2011.

18 Michallet AS, Lebras LL, Bauwens DD, Bouafia-Sauvy FF, Berger FF, Tychyj-Pinel CC, D'Hombres AA, Salles GG and Coiffier BB: Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol *6*: 45, 2013.

19 Ruella M, Filippi A, DI Russo A, Caracciolo D, Matteucci P, Magni M, Di Nicola M, Ricardi U, Montefusco V, Parvis G, Tarella C, Gianni AM and Devizzi L: Rituximab Followed by Involved Fields Radiotherapy (IF-RT) in Stage I-II Follicular Lymphoma (FL): Long Term Results. Blood *118*: a369, 2011.

Received June 12, 2014
Revised July 31, 2014
Accepted August 5, 2014