Introduction of Rituximab in Front-Line and Salvage Therapies Has Improved Outcome of Advanced-Stage Follicular Lymphoma Patients

Stefano Sacchi, MD[1]
Samantha Pozzi, MD[1]
Luigi Marcheselli, MS[1]
Alessia Bari, MD[1]
Stefano Luminari, MD[1]
Francesco Angrilli, MD[2]
Francesco Merli, MD[3]
Daniele Vallisa, MD[4]
Luca Baldini, MD[5]
Maura Brugiatelli, MD[6] on behalf of the Italian Lymphoma Study Group

[1] Department of Oncology and Hematology, University of Modena, Modena, Italy.

[2] Department of Oncology, Santo Spirito Hospital, Pescara, Italy.

[3] Department of Hematology, Santa Maria Nuova Hospital, Reggio Emilia, Italy.

[4] Department of Internal Medicine and Hematology, Piacenza Hospital, Piacenza, Italy.

[5] Department of Medical Science, University of Milan, Milan, Italy.

[6] Department of Hematology, Papardo Hospital, Messina, Italy.

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BACKGROUND. It is unclear whether new treatment modalities have improved the survival of follicular lymphoma patients. Some data show that there has been no improvement in survival in the last 3 decades of the 20th century, whereas the results of recent retrospective studies suggest that evolving therapy has improved the outcome for follicular lymphoma patients.

METHODS. To evaluate the impact of evolving therapies for follicular lymphoma, particularly the introduction of rituximab, the overall survival (OS), failure-free survival (FFS), and survival after recurrence (SAR) was analyzed in 438 advanced-stage follicular lymphoma patients enrolled in consecutive Gruppo Italiano Studio Linfomi (GISL) trials between 1988 and 2004.

RESULTS. A stepwise improvement in FFS and a significant reduction in the hazard ratio was observed with succeeding studies. Cox regression analysis showed an improvement over time for OS, with a decline in the hazard ratio particularly evident in the group treated with rituximab. Furthermore, the SAR significantly improved in the group of patients treated with chemotherapy + rituximab.

CONCLUSIONS. After adjusting for all parameters with an impact on FFS and OS, the results of multivariate analysis suggest that rituximab therapy has a favorable effect on the prognosis of follicular lymphoma. The data show that FFS and OS have significantly improved in advanced-stage follicular lymphoma patients treated on GISL protocols during the last 18 years. These improvements are related to evolving front-line and salvage therapies, particularly the introduction of rituximab in combination with chemotherapy. ***Cancer* 2007;109:2077–82.** © *2007 American Cancer Society.*

KEYWORDS: non-Hodgkin lymphoma, follicular lymphoma, chemotherapy, rituximab, treatment outcome.

Follicular lymphoma is the second most frequent form of non-Hodgkin lymphoma in the Western world, accounting for 22% of all cases.[1] Treatment options for treatment-naive or recurring follicular lymphoma patients are still controversial, ranging from "watch and wait" to hematopoietic stem-cell transplantation. However, none of these treatments has demonstrated the potential to cure follicular lymphoma patients. It is also unclear whether new treatment modalities have improved the survival of follicular lymphoma

Address for reprints: Sacchi Stefano, MD, Centro Oncologico Modenese, Policlinico, Largo del Pozzo 71, 4100 Modena, Italy; Fax: (011) 39.059.422.3707; E-mail: ssacchi@unimo.it

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patients. Some data show that there has been no improvement in survival in the last 3 decades of the 20th century,[2] whereas the results of recent retrospective studies[3–5] suggest that evolving therapy has improved the outcome for follicular lymphoma patients.

Over the past 18 years the Gruppo Italiano Studio Linfomi (GISL) has conducted a series of Phase II clinical trials in previously untreated or recurring follicular lymphoma patients. Patients enrolled in these trials received anthracycline- and/or fludarabine-based regimens. Recently, the introduction of rituximab has considerably modified treatment strategies. Since 1998 the GISL has performed a series of Phase II studies utilizing rituximab in combination with interferon (IFN) or chemotherapy. In the current study we analyzed the overall survival (OS), failure-free survival (FFS), and survival after recurrence (SAR) in various groups of patients to evaluate the impact of evolving therapy including the introduction of rituximab.

MATERIALS AND METHODS

Between 1988 and 2004, 691 patients with indolent lymphoma were enrolled in various GISL trials. To address a uniform patient population in this study, 189 patients with indolent non-follicular lymphoma were excluded. Furthermore, 64 patients with recurrence treated with rituximab + IFN were excluded from this analysis because they were entered into the M39008 Roche-sponsored trial (GISL FOLREC01) and follow-up data were not available.[6] Thus, for the purpose of this study we identified 438 advanced-stage (IIB, III, and IV) patients with a histologically confirmed diagnosis of follicular lymphoma (grades 1, 2, and 3) who had either previously untreated (307 patients) or recurring (131 patients) disease. The number of patients in each group, the regimens, and the time spans are summarized in Table 1. The baseline patient characteristics for each group are reported in Table 2. Briefly, naive patients were treated in groups 1–4 with 1 of following regimens: ProMECE-CytaBOM (methylprednisolone, cyclophosphadime, epidoxorubicin, etoposide, citarabine, bleomycin, vincristine, and methotrexate)[7]; BACOP (bleomycin, epidoxorubicin, cyclophosphamide, vincristine, and prednisone)[8]; BACOP+FND (BACOP plus fludarabine, mitoxantrone, and dexamethasone)[9]; or BACOP+FR (BACOP fludarabine + rituximab).[10] Patients who experienced recurrence were placed in groups 5 and 6 based on treatment with or without rituximab; specifically, with CHOP (cyclophosfamide, doxorubicine, vincristine, and prednisolone) or FC (fludarabine and cyclophosphamide), or with CHOP or FC in combination with rituximab.[11]

TABLE 1
Treatments Used in 6 Groups of Follicular Lymphoma Patients Between 1988 and 2004

Group	Treatment	Period	No. of patients	Status of patients
1	ProMECE-CytaBOM	1988–92	36	Previously untreated
2	BACOP	1993–97	66	Previously untreated
3	BACOP/FND	1997–02	144	Previously untreated
4	BACOP/FR	2003–04	61	Previously untreated
5	CHOP or FC	1992–02	52	Recurrence
6	CHOP+R or FC+R	2000–04	79	Recurrence

ProMECE-CytaBOM indicates methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, citarabin, bleomycin, vincristine, methotrexate; BACOP, bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone; BACOP+FND, BACOP plus fludarabine, mitoxantrone, dexamethasone; BACOP+FR, BACOP plus fludarabine+rituximab; CHOP: cyclophosfamide, doxorubicine, vincristine, prednisolone CHOP+R: CHOP plus rituximab; FC, fludarbine, cyclophosphamide; FC+R, FC plus rituximab.

At the end of chemotherapy, involved field radiotherapy (IF-RT) was allowed to treat residual masses or at the site of previous bulky or extranodal disease, in either treatment-naive or relapsed patients, at the treating physician's discretion.

Statistical Analysis

All eligible patients entered into each of the previously described treatment groups were included in the analysis. Clinical parameters were prospectively registered at the time of the patient's entry into each study. OS was measured from the date of registration until last follow-up or death from any cause. FFS was calculated from the date of registration until disease progression, relapse, or disease- or treatment-related death. SAR was measured from the time of first recurrence until the last follow-up, or death from any cause. Survival curves were estimated using the Kaplan-Meier method.[12] Fisher exact and chi-square tests were used to asses differences in the distribution of clinical features among the different treatment groups. To analyze the association between variables and OS, FFS, and SAR, Cox univariate and log rank tests were used. The Cox regression model[13] was utilized to determine the effect of multiple variables on OS and FFS. The proportionality of risk was checked in all Cox regression analyses.

We used 2-sided P-values $<.05$ as moderate evidence against the null hypothesis.

The Follicular Lymphoma International Prognostic Index (FLIPI)[14] was calculated for 281 (92%) of the 307 untreated follicular lymphoma patients.

TABLE 2
Baseline Patient Characteristics for Previously Untreated Follicular Lymphoma Patients Treated With 1 of 4 Regimens

	Percentage of patients					
Variable	All Patients (N = 307)	ProMECE-CytaBOM (N = 36)	BACOP (N = 66)	BACOP/FND (N = 144)	BACOP/FR (N = 61)	*P*
Sex, male	47	31	44	50	52	.142
Age >60	31	8	26	37	34	.004
LDH >IUNL	17	15	18	19	15	>.50
Nodal sites >4	32	3	32	32	48	<.001
Stage III–IV	83	97	82	78	88	.017
Hb <12 g/dL	23	19	30	23	16	.328
Albumin <3.5 g/dL	13	11	14	15	10	>.50
B2microglobulin >IUNL	38	22	36	38	42	>.50
ESR >30/h	21	18	17	26	15	.332
Bulky disease*	14	6	6	17	21	.025
B symptoms	17	31	21	13	15	.076
Extranodal sites >1	20	0	30	24	10	<.001
IF-RT	16	14	26	16	8	.066
FLIPI						.021
0–1	42	73	42	39	33	
2	32	15	35	34	35	
3–5	26	12	23	27	32	

ProMECE-CytaBOM indicates methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, citarabin, bleomycin, vincristine, methotrexate; BACOP, bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone; BACOP+FND, BACOP plus fludarabine, mitoxantrone, dexamethasone; BACOP+FR, BACOP plus fludarabine + rituximab; CHOP: cyclophosfamide, doxorubicine, vincristine, prednisolone CHOP + R: CHOP plus rituximab; FC, fludarbine, cyclophosphamide; FC + R, FC plus rituximab. FLIPI, Follicular Lymphoma Prognostic Index; LDH, lactate dehydrogenase; IULN, institutional upper limit of normal; ESR: erythrocyte sedimentation rate; IF-RT: involved fields radiotherapy.
* Lymph node mass with maximum diameter greater than 5 cm.

RESULTS

A total of 438 previously untreated (n = 307) or relapsed (n = 131) follicular lymphoma patients who met the defined eligibility criteria were included in this analysis. Parameters with significant differences among groups were age >60 years, clinical stage III-IV, >4 nodal sites, FLIPI score, bulky disease (lymph node mass with a maximum diameter >5 cm), and extranodal sites >1 (Table 2). By univariate analysis, we observed a significant negative impact ($P < .05$) on FFS and OS for age >60 years, elevated lactate dehydrogenase level, >4 nodal sites, and clinical stage III-IV that is consistent with the FLIPI model. We also observed a significant negative impact for B symptoms, elevated erythrocyte sedimentation rate, and low albumin levels. More than 1 extranodal site affected only FFS, whereas elevated beta-2 microglobulin only affected OS. All of these parameters, which are not included in the FLIPI model, are strictly associated with FLIPI score (ρ between 0.24 and 0.30, $P < .002$). Furthermore, we observed a significant positive impact ($P = .007$) on FFS for IF-RT treatment. Thus, to evaluate the effect of variables with a significant impact on FFS we performed a Cox regression analysis adjusting for the FLIPI model and IF-RT treatment. To evaluate the effects on OS, we adjusted only for the FLIPI model.

FFS According to Treatment Program

The median FFS among the 307 untreated patients was 60 months (Fig. 1). Median FFS times for patients in groups 1, 2, and 3 were 40, 64, and 58 months, respectively. The median FFS for patients in group 4, which included rituximab, has not yet been reached after a median follow-up of 25 months (range, 4 months to 46 months).

FFS curves according to treatment regimen are shown in Figure 2. The curves for groups 2 and 3 overlap substantially after 36 months with a 4-year FFS of 55% and 59%, respectively. The 4-year FFS for groups 1 and 4 was 42% and 80%, respectively. The FFS improved from group 1 to group 4 with evolving treatment, and the overall *P*-value was <.05 for all curves. After adjusting for FLIPI score and IF-RT treatment, Cox regression analysis confirmed a sequential improvement over time as demonstrated by a statistically significant decline in the hazard ratio from group 1 to group 4 (Table 3).

OS According to Treatment Group

After a median follow-up of 58 months, the median survival among all 307 previously untreated patients has not been reached (Fig. 1). The 4-year estimates of OS were 76%, 87%, 82%, and 97% in groups 1, 2,

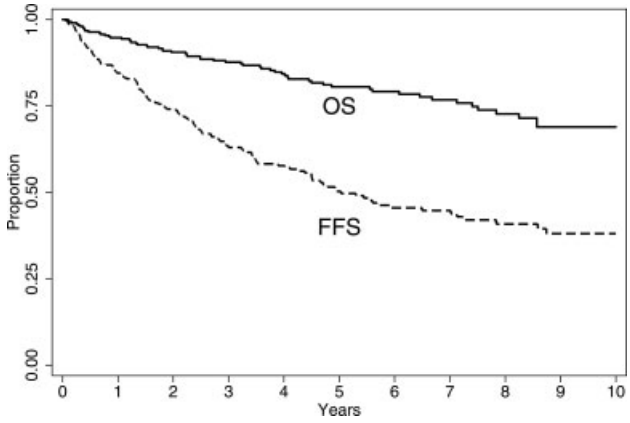

FIGURE 1. Overall survival and failure-free survival in 307 treatment-naive, advanced-stage follicular lymphoma patients enrolled in 4 consecutive GISL trials.

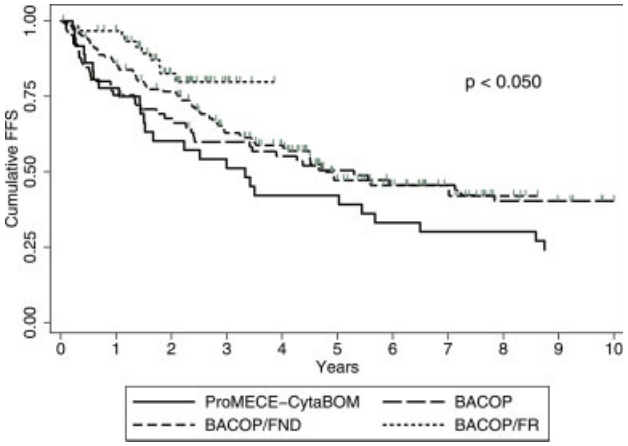

FIGURE 2. Failure-free survival in previously untreated follicular lymphoma patients according to treatment regimen. The overall *P*-value for all curves is $P < .05$. ProMECE-CytaBOM (methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, citarabine, bleomycin, vincristine, methotrexate); BACOP (bleomycin, epidoxorubicin, cyclophosphamide, vincristine, and prednisone); BACOP+FND (BACOP plus fludarabine, mitoxantrone, and dexamethasone); BACOP+FR (BACOP plus fludarabine + rituximab). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

3, and 4, respectively. The overall *P*-value is not statistically significant.

However, after adjusting for the FLIPI score Cox regression analysis showed a statistically significant reduction in the hazard ratio from group 1 to group 4 (Table 3).

TABLE 3
Cox Regression Analysis of Treatment Effect on FFS in Follicular Lymphoma Patients Adjusted for FLIPI Score and IF-RT, and on OS Adjusted for FLIPI Score

	FFS			OS		
Variable	**HR**	**CI 95%**	***P***	**HR**	**CI 95%**	***P***
ProMECE-CytaBOM	1.00	—	—	1.00	—	—
BACOP	.513	.296–.886	.017	.420	.200–900	.026
BACOP/FND	.509	.306–.844	.009	.712	.337–1.50	.374
BACOP/FR	.236	.108–.514	<.001	.087	.020–.699	.022
BACOP/ProMECE-CytaBOM	.513	.296–.886	.017	.420	.200–.900	.026
BACOP/FND vs BACOP	.992	.646–1.52	.971	1.70	.875–3.29	.118
BACOP/FR vs BACOP/FND	.464	.235–.915	.027	.122	.016–.905	.040

FFS indicates failure-free survival; OS, overall survival; ProMECE-CytaBOM, methylprednisolone, cyclophosphamide, epidoxorubicin, etoposide, citarabin, bleomycin, vincristine, methotrexate; BACOP, bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone; BACOP+FND, BACOP plus fludarabine, mitoxantrone, dexamethasone; BACOP+FR, BACOP plus fludarabine + rituximab; HR, hazard ratio; CI, confidence intervals, FLIPI, Follicular Lymphoma Prognostic Index; IF-RT: involved fields radiotherapy.

Survival After Recurrence According to Treatment Program

The median SAR for the 118 patients for whom front-line therapy failed was 113 months. The median SAR time for patients treated in group 1 was 42 months. To date, the median SAR for patients in groups 2, 3, and 4 has not been reached. The overall *P*-value for all SAR curves was not statistically significant.

Survival After Recurrence According to Salvage Treatment

For the purpose of this analysis, which aimed to evaluate the impact of rituximab on salvage therapy, we identified 131 relapsed patients (Table 1). Fifty-two patients in group 5 were treated with chemotherapy alone, whereas 79 patients in group 6 were treated with chemotherapy in combination with rituximab. At the time of recurrence the available patient characteristics were age >60 years, sex, duration of previous remission, clinical stage, and performance status. The distribution of these characteristics between the groups was not statistically different ($P > .05$). The median SAR for patients in group 5 was 103 months after a median follow-up of 38 months (range, 2–162). The median SAR has not been reached for patients in group 6 who were treated with chemotherapy in combination with rituximab after a median follow-up of 39 months (range, 1–125). The 5-year estimate of SAR (Fig. 3) was 57% for group 5 and 74% for group 6 ($P = .032$). The statistically significant difference in SAR between the 2 groups is retained after adjusting for age >60 years and duration of the previous remission ($P = .014$).

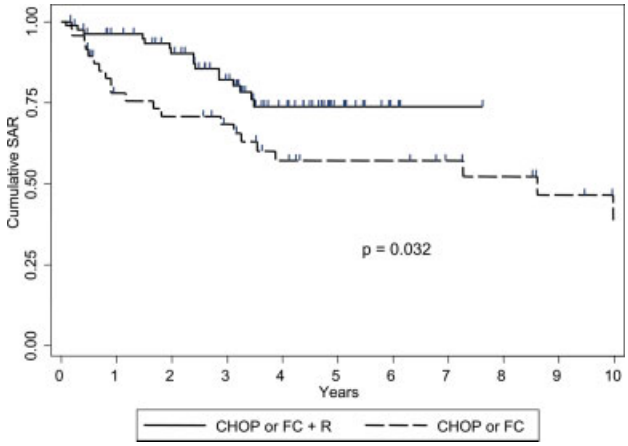

FIGURE 3. Survival of follicular lymphoma patients after relapse by salvage treatment. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone); CHOP + R (CHOP plus rituximab); FC (fludarbine and cyclophosphamide); FC + R (FC plus rituximab). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

Until a few years ago, there was a general consensus that the outcome of low-grade lymphoma has not changed over the last 30 years. For example, the analysis of 25 years experience at Stanford University in managing follicular lymphoma demonstrated no survival improvement.[2] However, this review ended in 1992, before treatment with the anti-CD20 monoclonal antibody rituximab became available. Contrasting experiences were recently reported[3–5] suggesting a stepwise improvement in FFS and OS with the introduction of new treatment options over the past few years.

The results of these studies prompted the current analysis to assess the outcome of follicular lymphoma patients entered into GISL trials. The results reported here summarize and update previous treatment strategies utilized at GISL between 1988 and 2004. We observed a stepwise improvement of FFS, with the 4-year FFS estimate increasing from 42% to 82% from groups 1 to 4, respectively, and a significant reduction in the hazard ratio over succeeding studies. After adjusting for the FLIPI score, the Cox regression analysis showed an improvement over time for OS, with a decline in the hazard ratio from group 1 to group 4, demonstrating that the outcome improvement is related to treatment and not confounded by a different distribution of clinical parameters among groups.

It is worth noting that in the group 4 patients treated with rituximab, improvements in FFS and OS were particularly evident, with reductions in the hazard ratio for FFS and OS of 76% and 91%, respectively, in comparison with the ProMECE-CytaBOM group, and of 51% and 71%, respectively, in comparison with the BACOP/FND group (Table 3). The difference for group 4 was statistically significant (except for OS in group 2) in comparison with groups 1, 2, and 3 treated with chemotherapy alone. Furthermore, the SAR according to salvage treatment showed a statistically significant improvement in the group of patients treated with chemotherapy + rituximab in comparison with chemotherapy alone (Fig. 3). These data suggest that survival improvement is due, at least in part, to an improvement in salvage therapy, and in particular to the introduction of rituximab in combination with chemotherapy.

Further, the results of recently reported controlled studies in either previously untreated[15–17] or recurring[18,19] follicular lymphoma patients demonstrated that the addition of rituximab to several different chemotherapies induces an improvement in survival.

Finally, although conclusions between nonrandomized groups may depend on differences in observed and unobserved prognostic features, we believe that the results of the multivariate analysis, after adjusting for all parameters with an impact on FFS and OS, suggest that rituximab therapy has a favorable effect on the prognosis of follicular lymphoma

In summary, our data show that FFS and OS have significantly improved in advanced-stage follicular lymphoma patients treated in GISL protocols over the past 18 years. These improvements are related to evolving front-line and salvage therapies, and in particular to the introduction of rituximab in combination with chemotherapy.

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