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ORIGINAL REPORT

Improvement of Overall and Failure-Free Survival in Stage IV Follicular Lymphoma: 25 Years of Treatment Experience at The University of Texas M.D. Anderson Cancer Center

Qi Liu, Luis Fayad, Fernando Cabanillas, Fredrick B. Hagemeister, Gregory D. Ayers, Mark Hess, Jorge Romaguera, M. Alma Rodriguez, Apostolia M. Tsimberidou, Srdan Verstovsek, Anas Younes, Barbara Pro, Ming-Sheng Lee, Ana Ayala, and Peter McLaughlin

From the Departments of Lymphoma/Myeloma, Biostatistics and Applied Mathematics, and Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

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Address reprint requests to Peter McLaughlin, MD, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 429, Houston, TX 77030; e-mail: pmclaugh@mdanderson.org.

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ABSTRACT

Purpose
Advanced-stage follicular lymphoma is considered incurable. The pace of improvements in treatment has been slow. This article analyzes five sequential cohorts of patients with stage IV follicular lymphoma treated between 1972 and 2002.

Methods
Five consecutive studies (two were randomized trials) involving 580 patients were analyzed for overall survival (OS), failure-free survival (FFS), and survival after first relapse. A proportional hazards analysis, and subset analyses using the follicular lymphoma international prognostic index (FLIPI) score were performed. Treatment regimens included: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin (CHOP-Bleo); CHOP-Bleo followed by interferon alfa (IFN-α); a rotation of three regimens (alternating triple therapy), followed by IFN-α; fludarabine, mitoxantrone, dexamethasone (FND) followed by IFN-α; and FND plus delayed versus concurrent rituximab followed by IFN-α.

Results
Improvements in 5-year OS (from 64% to 95%) and FFS (from 29% to 60%) indicate steady progress, perhaps partly due to more effective salvage therapies, but the FFS data also indicate improved front-line therapies; these observations held true after controlling for differences in prognostic factors among the cohorts. The FLIPI model adds rigor to and facilitates comparisons among the different cohorts. An unexpected finding in this study was a trend toward an apparent FFS plateau.

Conclusion
Evolving therapy, including the incorporation of biologic agents, has led to stepwise significant outcome improvements for patients with advanced-stage follicular lymphoma. The apparent plateau in the FFS curve, starting approximately 8 to 10 years from the beginning of treatment, raises the issue of the potential curability of these patients.

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INTRODUCTION

Patients with follicular lymphoma typically have indolent courses and relatively long median survival rates. The management approach for advanced-stage follicular lymphoma can include observation without therapy ("watchful waiting") for selected patients, and various therapies, including alkylating agent–based regimens, fludarabine-based regimens, dose intensification with transplantation, biologic therapies such as interferon (IFN-α), and therapy that targets the CD20 antigen.[1-10] Controversy about treatment options derives in part from the observation that despite the wide range of treatment approaches and initial responses, most patients with advanced-stage follicular lymphoma ultimately suffer relapse. Some data suggest that there has been no improvement in survival for follicular lymphoma patients in the last three decades of the 20th century.[11]

Since 1972, five consecutive studies (two of which were randomized trials) have been conducted at The University of Texas M.D. Anderson Cancer Center in 580 previously untreated patients with stage IV follicular lymphoma. Treatment regimens included: cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin (CHOP-Bleo) from 1972 to 1982[12]; CHOP-Bleo with IFN-α maintenance from 1982 to 1988[13]; alternating triple therapy (ATT) with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin

Table 1. Patient Characteristics

Patient Features	% of Patients						
	1972-1982: CHOP-Bleo (N = 94)	1982-1988: CHOP-Bleo → IFN (N = 112)	1988-1992: ATT → IFN (N = 111)	1992-1997: ATT → IFN *v* FND → IFN (N = 112)	1997-2002: FND + R → IFN *v* FND → R → IFN (N = 151)	All Patients (N = 580)	*P**
Sex							
Male	54	53	51	51	48	51	.88
Female	46	47	49	49	52	49	
Age, years							
≥ 60	33	34	31	23	24	28	.202
< 60	67	66	69	77	76	72	
Hemoglobin level, g/dL†							
≥ 12	76	86	83	88	81	83	
< 12	24	14	17	12	19	17	.125
Lactate dehydrogenase†							
High	34	32	20	16	15	23	< .001
Normal	66	68	80	84	85	77	
Nodal site†							
≥ 5	67	54	68	63	74	66	.02
< 5	33	46	32	37	26	34	
Bone marrow							
Positive	83	90	92	94	93	91	.049
Negative	17	10	8	6	7	9	
EN sites							
≥ 2	44	36	28	36	15	30	< .001
< 2	56	64	72	64	85	70	
PS							
≥ 2	1	1	1	4	1	2	.18
< 2	99	99	99	96	99	98	
FLIPI†							
≥ 3	77	76	80	72	74	76	.7
< 3	23	24	20	28	26	24	

Abbreviations: CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; FND, fludarabine, mitoxantrone, and dexamethasone; R, rituximab; EN, extranodal; PS, performance status; FLIPI, follicular lymphoma international prognostic index.

**P* values of different parameters among 580 patients in five studies.

†Data lacking on hemoglobin for three patients, lactate dehydrogenase for four, number of nodal sites for seven, and FLIPI score for 14.

(CHOD-Bleo), etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP), and mitoxantrone, vincristine, prednisone, and procarbazine (NOPP) with IFN-α maintenance from 1988 to 1992[14]; ATT versus fludarabine, mitoxantrone, and dexamethasone (FND) with IFN-α maintenance in a randomized study from 1992 to 1997[15]; and concurrent FND and rituximab versus sequential FND followed by rituximab and IFN-α maintenance in a randomized study from 1997 to 2002.[16,17]

In the current report, we analyzed overall survival (OS), failure-free survival (FFS), and survival after first relapse (SAR) in these five

Table 2. Regimens Employed for Five Consecutive Cohorts

Cohort No.	Regimen*	Date Range	No. of Follicular Lymphomas	No. of Other Indolent†
1	CHOP-Bleo	1972-1982	94	2
2	CHOP-Bleo + IFN maint.	1982-1988	112	19
3	ATT + IFN maint.	1988-1992	111	25
4	ATT *v* FND, + IFN maint.	1992-1997	112	30
5	*R*-FND *v* FND → R, + IFN maint.	1997-2002	151	49

Abbreviations: CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; FND, fludarabine, mitoxantrone, and dexamethasone; R, rituximab; maint., maintenance.

*Component agents of regimens described in text.

†Patients with other indolent histologies (small lymphocytic, marginal zone) were entered onto the studies, but are excluded from this report.

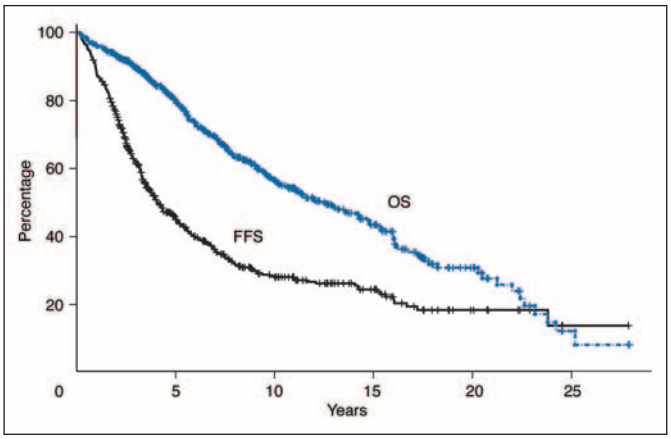

Fig 1. Overall survival (OS) and failure-free survival (FFS) in 580 assessable stage IV follicular lymphoma patients in five consecutive studies spanning 25 years.

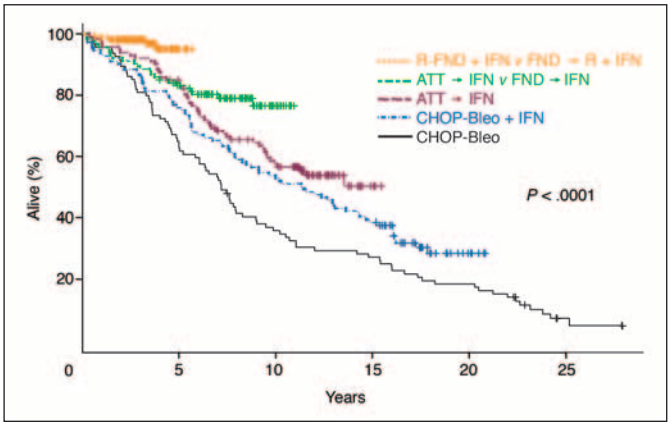

Fig 2. Overall survival according to treatment regimen. The overall *P* value for all curves is $P < .0001$. R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

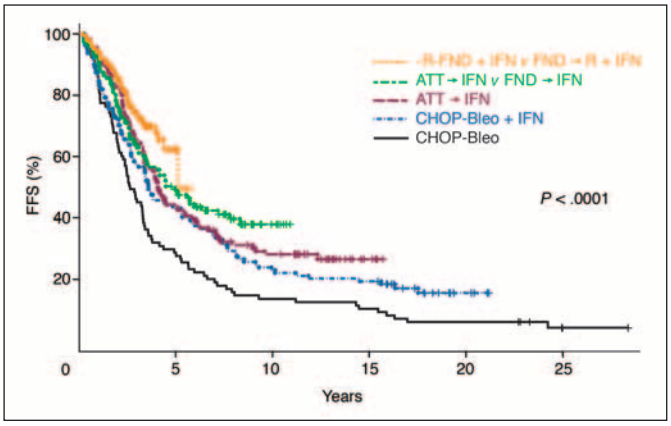

Fig 3. Failure-free survival according to treatment regimen. The overall *P* value for all curves is $P < .0001$. R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

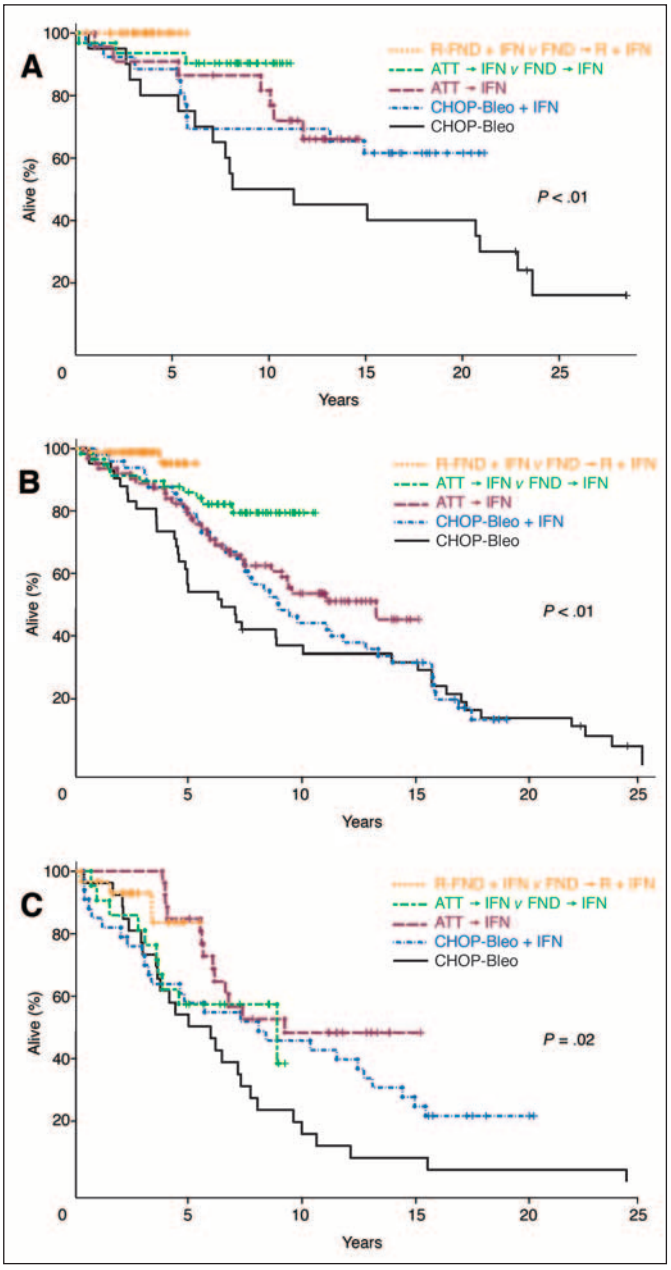

Fig 4. Overall survival according to treatment regimen, by follicular lymphoma international prognostic index (FLIPI) score. (A) FLIPI 1 to 2. The overall *P* value for all curves is $P = .009$. (B) FLIPI 3. The overall *P* value for all curves is $P < .0001$. (C) FLIPI 4 to 5. The overall *P* value for all curves is $P = .02$. R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

consecutive studies, with follow-up periods of up to 25 years. To control for differences in prognostic factors in the sequential cohorts, we performed a Cox (proportional hazards) analysis. We also used the follicular lymphoma international prognostic index (FLIPI) to critically assess for heterogeneity of clinical features among cohorts.[18] Our study demonstrates stepwise improvements in OS from 64% to 95%,

FFS from 29% to 60%, and a trend toward a plateau in FFS after approximately 8 to 10 years.

METHODS

Patients and Treatments

Five hundred eighty assessable patients with stage IV follicular lymphoma were treated on five consecutive studies, two of which were randomized trials. To focus this study on a uniform population, 125 patients with small lymphocytic lymphoma or other nonfollicular lymphomas entered on the protocols were excluded from the current analysis.

Clinical features of the patients, including the five parameters of the FLIPI score, are outlined in Table 1. All had stage IV disease. FLIPI scores (1 to 2 adverse factors for good prognosis; 3 for intermediate prognosis; and 4 to 5 for poor prognosis) were used for the subset analyses.

The regimens, and time spans of their use are presented in Table 2. All protocol patients gave informed consent in accord with institutional review board policy. Institutional review board approval was granted for the current update of cohort 1.[12]

Staging Studies

In all five studies, the staging evaluation for most patients included a complete physical examination, CBCs, chemical survey including renal and liver function tests, bilateral iliac crest bone marrow aspirates and biopsy, chest radiography, and computed tomography (CT) of the abdomen and pelvis. In the earlier studies, lymphangiography was often performed instead of CT.

Histologic findings are herein reported according to The Working Formulation classification.[19] A repeat histology review was not done for the current report, but had been done in prior reports of these trials.[12-17] For most of the years of this review, the Mann-Berard criteria were used for the subclassification of follicular lymphoma.[20] Hence, the assigned Working Formulation classifications in the report are approximately equivalent to the current WHO grades of follicular lymphoma.[21] Throughout the years of this review, there was a steady increase in the designation of cases as follicular mixed histology, from 17% of cases in cohort 1, to 45% in cohort 5. We doubt the clinical significance of this trend. There is a paucity of follicular large cell lymphomas in these cohorts (just 4% of cases in cohort 4 and 1% in cohort 5; none in earlier cohorts) because most patients with this diagnosis during this period were enrolled onto trials designed to treat aggressive lymphoma.[22]

Patient Monitoring During Therapy

Restaging evaluations, including bone marrow biopsy and CT of the abdomen and pelvis, or follow-up lymphangiography, were performed at least every 3 to 4 months during the first year, every 3 to 6 months during the next 3 to 4 years, and thereafter every 6 to 12 months when possible. During the years of these trials, molecular monitoring for cells with *bcl-2* gene rearrangement was introduced as a measure of treatment efficacy.[23-25]

Disease Evaluation and Statistical Methods

All patients registered and treated in the five studies were considered assessable for outcome and were analyzed on an intent-to-treat basis. OS was measured from the start of therapy until last follow-up or death from any cause. FFS was measured from the start of therapy to the date of disease progression, relapse, or disease- or treatment-related death.[26] SAR was measured from the time of relapse until last follow-up or death from any cause. The χ^2 test was used to investigate the independence between two categorical variables. Survival curves were estimated by using the Kaplan-Meier method.[27] The two-sided log-rank test was used to analyze the association between variables and OS, FFS, or SAR. The Cox proportional hazards model was used to evaluate the effect of multiple variables on OS and FFS.[28]

RESULTS

Analysis of Clinical Features of Patients on Different Regimens

It was recognized that prognostic features can vary among study cohorts throughout a 25-year period due to changes in referral patterns or other factors. For instance, the entry criteria for protocols after 1988 included an age limit (75 years or younger). To control for these variations, we analyzed the characteristics of the 580 patients (Table 1). In the more recent studies, there were fewer male patients and fewer patients older than 60 years. Median ages of patients in the five cohorts were 54.5, 54, 52, 49, and 50 years, respectively. Fractions of patients with hemoglobin less than 12 g were comparable, except in the earliest study using CHOP-Bleo. A decline in the fraction of patients with elevated lactate dehydrogenase (LDH) levels was seen in the more recent studies. Conversely, there had been a gradual increase in the fraction of patients with bone marrow involvement in the more recent studies.

Parameters with significant differences in distribution among the five cohorts of patients were nodal sites ($P = .02$), LDH level ($P < .001$), bone marrow involvement ($P = .049$), and extranodal sites ($P < .001$). Using the FLIPI score, the fraction of patients with FLIPI scores of 3 or greater was not significantly different across all five cohorts ($P = .7$).

Table 3. Outcome Comparisons, Stratified by FLIPI Score

	Cohort/Regimen					
	1: 1972-1982 (CHOP-Bleo)	2: 1982-1988 (CHOP-Bleo → IFN)	3: 1988-1992 (ATT → IFN)	4: 1992-1997 (ATT → IFN *v* FND → IFN)	5: 1997-2002 (FND + R → IFN *v* FND → R + IFN)	*P*
Median OS, years (by FLIPI score)						
1-2	8.0	NR	NR	NR	NR	.009
3	6.5	9.1	13.5	NR	NR	< .001
4-5	4.9	8.0	9.1	8.8	NR	.02
Median FFS, years (by FLIPI score)						
1-2	2.9	4.4	6.4	NR	NR	.019
3	2.5	3.5	4.0	3.5	5.0	.0002
4-5	1.9	3.3	3.4	2.1	3.0	.026

Abbreviations: FLIPI, follicular lymphoma international prognostic index; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; FND, fludarabine, mitoxantrone, and dexamethasone; R, rituximab; OS, overall survival; FFS, failure-free survival; NR, not reached.

OS According to Treatment Protocol

The median survival of the 580 patients was 12.7 years (Fig 1). Median follow-up times of survivors for the five cohorts were 23.7 years, 17.5 years, 12 years, 8.2 years, and 3.3 years, respectively.

OS according to treatment protocol is summarized in Figure 2. Median survival times for patients in cohorts 1 to 3 were 7.2, 11.3, and 13.6 years, respectively. To date, the median survival times for patients treated on the two most recent studies (cohorts 4 and 5) have not been reached.

The CHOP-Bleo experience has up to 25 years of follow-up. The survival rate of that group at 25 years was 12.5%. At each landmark time point for which comparisons between treatments can be made, the more recent studies had superior survival data. For example, 15-year survival is 50% for cohort 3, 38% for cohort 2, and 27% for cohort 1. Five-year follow-up is available for all of the studies. Notable survival increments occurred with the incorporation in 1982 of IFN-α, and in 1997 of rituximab.

FFS According to Treatment Protocol

FFS according to treatment protocol is summarized in Figure 3. The follow-up periods were similar to those for survival data. The FFS data, like the survival data, showed stepwise improvement with the more recent studies. For example, at 15 years, 13% of patients in cohort 1 remained disease-free, compared with 24% in cohort 2 and 32% in cohort 3. The overall FFS curve revealed a change in its slope and a trend toward a plateau after 8 to 10 years, suggesting potential cure for a fraction of patients.

The median FFS among all 580 patients was 4.3 years (Fig 1). Median FFS times for patients in cohorts 1 to 4 were 2.8, 3.7, 4.1, and 4.8 years, respectively. The median FFS for patients treated with FND with rituximab and IFN-α has not yet been reached.

OS of Patients Stratified by FLIPI Score, According to Treatment Regimens

To control for differences in the clinical features of the 580 patients on the five consecutive studies, we performed a Cox regression analysis, and we analyzed the patients using three FLIPI subgroups (1 to 2 *v* 3 *v* 4 to 5 adverse features). There were no significant differences in the breakdown of patients by FLIPI score in the five cohorts (Table 1): 72% to 80% of patients in the five cohorts had FLIPI scores of 3 or more, and 20% to 28% had scores of less than 3. The analysis of OS according to treatment regimens, controlling for FLIPI score, is presented in Figure 4 and Table 3. In all FLIPI groups (1 to 2; 3; 4 to 5), there was a significant stepwise improvement in survival over time. The improvement was most striking in the FLIPI 3 category, probably in large part because of the larger number of patients in the FLIPI 3 category.

FFS of Patients Stratified by FLIPI Score, According to Treatment Regimens

The FFS data were also analyzed by FLIPI score (1 to 2 *v* 3 *v* 4 to 5) according to treatment regimens (Fig 5 and Table 3). As with the survival analysis, the more recent treatment regimens resulted in significant improvements in FFS in all FLIPI risk groups. Improvement was most striking in the FLIPI 3 category. Through the 25-year interval, the 5-year FFS increased from 40% to 71% for patients with FLIPI 1 to 2, from 29% to more than 40% for those with FLIPI 3, and from 12% to more than 30% for FLIPI 4 to 5. Notable improvements ($P \leq .05$) occurred with the incorporation of IFN-α in 1982 and rituximab in 1997. Although the gains appear modest in the FLIPI 4 to 5 subset, the apparent impact of the intensive ATT regimen in this high-risk subset is noteworthy. As can be seen in Table 4, the FLIPI 4 to 5 subset is notable for being the only comparison in which we saw a slight rise in the hazard ratio for both survival and FFS between the ATT and FND versus ATT trials.

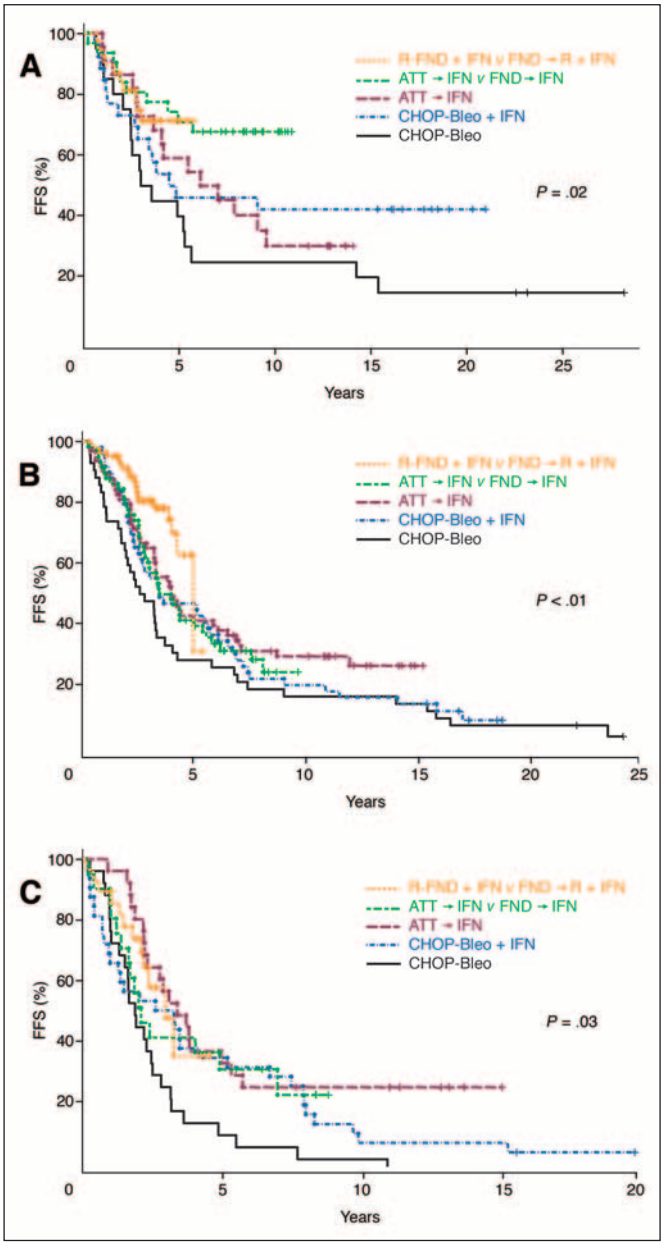

Fig 5. Failure-free survival according to treatment regimen, by follicular lymphoma international prognostic index (FLIPI) score. (A) FLIPI 1 to 2. The overall *P* value for all curves is $P = .019$. (B) FLIPI 3. The overall *P* value for all curves is $P = .002$. (C) FLIPI 4 to 5. The overall *P* value for all curves is $P = .026$. R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

Impact of Clinical Features on OS and FFS

Age older than 60 years, an elevated LDH level, and involvement of more than four nodal sites all had a significant ($P \leq .01$) negative

Table 4. Cox Regression Analysis of Treatment Effect Adjusted for FLIPI Score

Cohort Comparison	Overall Survival			Failure-Free Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Cohort 1 *v* 2	0.705	0.510 to 0.974	.03	0.673	0.498 to 0.811	.01
Cohort 2 *v* 3	0.760	0.575 to 1.100	.15	0.812	0.598 to 1.101	.18
Cohort 3 *v* 4						
FLIPI 1-2	0.478	0.115 to 1.982	.31	0.451	0.202 to 1.007	.05
FLIPI 3	0.482	0.239 to 0.974	.04	1.109	0.723 to 1.703	.63
FLIPI 4-5	1.511	0.654 to 3.493	.33	1.258	0.638 to 2.481	.51
Cohort 4 *v* 5	0.270	0.099 to 0.736	.01	0.668	0.443 to 1.008	.05

NOTE. Cohort 1: CHOP-Bleo (1972-1982), cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; Cohort 2: CHOP-Bleo → IFN (1982-1988), CHOP-Bleo followed by interferon alfa; Cohort 3: ATT → IFN (1988-1992), ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; Cohort 4: ATT *v* FND → IFN (1992-1997), ATT *v* fludarabine, mitoxantrone, and dexamethasone followed by IFN; Cohort 5: R-FND → versus FND → R + IFN (1997-2002), rituximab and FND followed by R + IFN. The Cohort 3 *v* 4 comparison is broken down by FLIPI score because of interactions between FLIPI and treatment in that comparison (see text).

Abbreviations: FLIPI, follicular lymphoma international prognostic index; HR, hazard ratio.

impact on both OS and FFS, consistent with the FLIPI model. A hemoglobin level less than 12 g correlated with a significantly inferior FFS ($P = .05$), but not OS in our patients. A FLIPI score ≥ 3 had a highly significant adverse effect on both OS and FFS compared with FLIPI 1 to 2 ($P < .0001$).

We also performed a univariate analysis of the impact on both OS and FFS of some parameters not included in the FLIPI score, including sex, bone marrow involvement, and number of extranodal sites. Being male and having two or more extranodal sites had a significant adverse impact on both OS and FFS.

Among the subset who had monitoring of *bcl-2* status, molecular response rates were 65% and 62% in the ATT and ATT versus FND trials, and increased to 78% in the FND/rituximab trial. FFS of molecular responders was 64% at 5 years compared with 36% for molecular nonresponders ($P = .0026$).

Proportional Hazards Analysis

The Cox regression analysis data showed improvements over time for both OS and FFS when controlling for component features of the FLIPI model. In virtually all stepwise comparisons (particularly significant in cohorts 1 *v* 2 and 4 *v* 5), there is a declining hazard ratio, correcting for FLIPI score, indicative that the improving results are related to improvements in therapy. Because there was a significant interaction between FLIPI and treatment regimen in cohorts 3 *v* 4 ($P = .0297$ for survival, and $P = .008$ for FFS), that analysis was done by FLIPI score subset. The notable improvement in FFS during that era was in the FLIPI 1 to 2 subset, while in OS, the notable benefit was in the FLIPI 3 subset.

Median SAR According to Treatment Regimen

The median SAR for 343 patients in whom therapy failed was 4 years. The median SAR times for patients treated in cohorts 1 to 3 were 3.2, 4.4, and 5.3 years, respectively. To date, the median SAR has not yet been reached in patients on the remaining two studies (Fig 6). The overall SAR results have shown significant improvement over time ($P = .001$), most notably from the 1972 to 1982 study to the 1982 to 1988 study.

The median SAR times for patients with FLIPI score less than 3 treated in cohorts 1 to 3 were 4.1, 4.5, and 10.6 years, respectively. The median SAR has not yet been reached in patients on the remaining studies. The median SAR times for patients with FLIPI ≥ 3 treated in cohorts 1 to 3 were 2.5, 3.8, and 4.3 years, respectively. The median SAR has not yet been reached in patients on the remaining studies.

DISCUSSION

Improvements have occurred in the management of patients with advanced-stage follicular lymphoma. The data reported here summarize and update previously reported management strategies at our institution between 1972 and 2002. To compensate for variations in prognostic features among cohorts, our analysis also incorporates a Cox regression analysis and a widely accepted prognostic model to permit more stringent comparison among prognostically homogeneous populations.

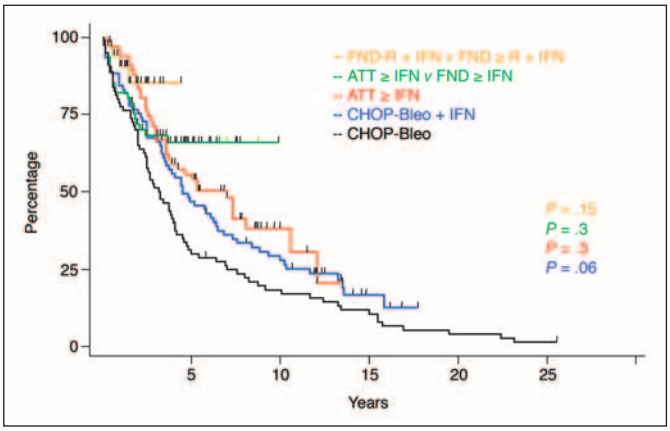

Fig 6. Survival after relapse according to front-line treatment regimen. The overall *P* value for all curves is $P = .001$. Individual comparisons between cohorts: 1 *v* 2, $P = .06$; 2 *v* 3, $P = .3$; 3 *v* 4, $P = .3$; 4 *v* 5, $P = .15$. R, rituximab; FND, fludarabine, mitoxantrone, and dexamethasone; IFN, interferon alfa; ATT, alternating triple therapy with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin, with etoposide, methylprednisolone, cytarabine, and cisplatin, with mitoxantrone, vincristine, prednisone, and procarbazine with IFN maintenance; CHOP-Bleo, cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin.

The follow-up of these 580 patients is mature, ranging from 30 years maximum follow-up for the first study to 7 years for the most recent. This provides the opportunity to analyze trends that might not be as obvious with less mature studies. There has been a stepwise improvement in OS with the introduction of newer chemotherapy regimens during the last 25 years, from 36% at 10 years in the period from 1972 to 1982, to 77% in the period from 1992 to 1997. The median OS improved from 7.2 years in the period from 1977 to 1982, to 13.6 years in the period from 1988 to 1992. To date, the median survival has not yet been reached for the periods from 1992 to 1997, and 1997 to 2002. Results from our studies agree with an analysis of 12,088 patients with follicular lymphoma using data provided by the National Cancer Institute's Surveillance, Epidemiology and End-Results (SEER) program that reported that OS for follicular lymphoma has improved in the last 20 years, likely as a result of changes in management.[29] Recently, the Southwest Oncology Group have also reported an improvement in OS in recent follicular lymphoma studies that included anti-CD20 monoclonal antibodies.[30] A contrasting 25-year experience of managing follicular lymphoma at Stanford University demonstrated no survival improvement,[11] but that review ended in 1992 when newer management options, such as anti-CD20 monoclonal antibodies or stem cell transplantation, were not widely available.

The current report also indicates that FFS has improved over the past 25 years. A striking finding is the trend toward an apparent plateau in the FFS curve at approximately 8 to 10 years. The projected 10-year FFS has improved from 16% in the period from 1972 to 1982, to 40% in the period from 1992 to 1997. The median FFS has improved from 2.8 years in the period from 1972 to 1982, to 4.8 years in the period from 1992 to 1997. The ATT regimen's favorable impact on FFS may be most obvious in the FLIPI 4 to 5 subset (Fig 5C), suggesting that our prior observations about its efficacy[14,15] may pertain particularly to higher-risk patients.

The improvement in survival and FFS in our consecutive studies needs to be studied critically, since this report spans 25 years and five regimens. Such an analysis can be confounded if the study groups were made up of patients with important differences in prognostic factors. To assess whether improvements in survival and FFS were the direct results of evolving therapies, as opposed to variations in the patient populations, we analyzed the pretreatment clinical features among the five cohorts using a Cox regression analysis, and we stratified our data using the FLIPI index. While there were significant differences in some clinical features (Table 1), when we analyzed FLIPI scores we found no significant differences across all five studies. Moreover, the Cox regression analysis corroborated that the improvement in outcome was correlated with treatment, and not confounded by minor variations of clinical features among the cohorts. Therefore, the improved survival and FFS data are likely the direct results of evolving therapies. The observed trend for improvement in rates of molecular remission provides another measure that suggests therapy is improving over time.

Our data indicate a more pronounced improvement in OS than in FFS. We analyzed the SAR, and observed that there has also been a steady improvement in SAR over the years. Therefore, the progress in survival is probably due, at least in part, to improvements in salvage therapies. While the impact of salvage therapy can confound the assessment of the front-line therapy's impact on survival, the improvement in FFS is more precisely and solely attributable to successful primary therapy. A trend toward an apparent plateau in the FFS curve, starting approximately 8 to 10 years from the beginning of treatment, was an unexpected finding in this study. This observation raises an important issue related to the curability of these neoplasms, which have been characterized in the past as being incurable in view of their persistent tendency to relapse with time.

In summary, our data show that results of therapy have improved during the last 25 years for patients with advanced-stage follicular lymphoma. While some of the survival improvement is due in part to more effective salvage therapies, our FFS data clearly demonstrate the favorable impact of improved front-line treatments as well, notably including the incorporation of biologic therapies. Our data also show that the FLIPI can facilitate objective comparisons among separate cohorts of stage IV follicular lymphoma patients.

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Authors' Disclosures of Potential Conflicts of Interest

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Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Fernando Cabanillas				Biogen IDEC (A)	Biogen IDEC (B)			
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Author Contributions

Conception and design: Qi Liu, Peter McLaughlin
Provision of study materials or patients: Qi Liu, Luis Fayad, Fernando Cabanillas, Fredrick B. Hagemeister, Jorge Romaguera, M. Alma Rodriguez, Apostolia M. Tsimberidou, Srdan Verstovsek, Anas Younes, Barbara Pro, Peter McLaughlin
Collection and assembly of data: Qi Liu, Ming-Sheng Lee, Mark Hess, Ana Ayala, Peter McLaughlin
Data analysis and interpretation: Qi Liu, Gregory D. Ayers, Mark Hess, Ana Ayala, Peter McLaughlin
Manuscript writing: Qi Liu, Peter McLaughlin
Final approval of manuscript: Qi Liu, Luis Fayad, Fernando Cabanillas, Fredrick B. Hagemeister, Mark Hess, Jorge Romaguera, M. Alma Rodriguez, Apostolia M. Tsimberidou, Srdan Verstovsek, Anas Younes, Barbara Pro, Ana Ayala, Peter McLaughlin