SUBDIVISIÓN DE ESPECIALIZACIÓN
DIVISIÓN DE ESTUDIOS DE POSGRADO
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Follicular Lymphoma in Early Stages: High Relapse Rate and Importance of the *Follicular Lymphoma International Prognostic Index* (FLIPI) in the Outcome of the Patients

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ASUNTO: Autorización del trabajo de investigación del Dr. Francisco Plancarte Zapata.

DR. ISIDRO AVILA MARTÍNEZ
SECRETARIO DE SERVICIOS ESCOLARES
DE LA FACULTAD DE MEDICINA
Presente.

Estimado Dr. Avila Martínez:

Me permito informar a usted que el **Dr. Francisco Plancarte Zapata**, alumno del curso de especialización en **Medicina Interna** en el **Instituto Nacional de Ciencias Médicas y de Nutrición "Dr. Salvador Zubirán"**, presenta el trabajo de investigación intitulado ***"Follicular Lymphoma in Early Stages: High Relapse Rate and Importance of the Follicular Lymphoma International Prognostic Index (FLIPI) in the Outcome of the Patients".***

De conformidad con el artículo 23 capítulo 5º. de las Normas Operativas del Plan Unico de Especializaciones Médicas (PUEM) se considera que cumple con los requisitos para validarlo como el trabajo formal de Investigación que le otorga el derecho de la diplomación como especialista.

Sin otro particular de momento, reciba un cordial saludo.

Atentamente
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Autorizo a la Dirección General de Bibliotecas de la UNAM a difundir en formato electrónico e impreso el contenido de mi trabajo recepcional.
NOMBRE: FRANCISCO PLANCARTE
FECHA: 28/04/05.

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Summary

Background and Objectives: Patients with follicular lymphoma (FL) in advanced stages are currently deemed incurable with standard treatments. However, FL is considered to be eradicable in the small group of patients presenting with localized disease. The objective of this study was to analyze the clinical features and the outcome of a series of patients with FL in early stages with a long follow-up.

Patients and methods: 48 patients (25M/23F; median age: 50 years) diagnosed consecutively with FL in Ann Arbor stage I (25 cases) or II (23) at a single institution with a median follow-up of 9.5 years. Main biological and clinical characteristics at diagnosis, including *FL International Prognostic Index* (FLIPI), treatment and response were assessed and analyzed for prognosis.

Results: The histological subtypes were: FL type I, 20 cases (42%), type II, 24 (50%), type III, 3 (6%), unclassifiable, 1 (2%). Distribution according to FLIPI was: low risk, 36 cases; intermediate risk, 5. Treatment mainly consisted of combination chemotherapy (CHOP in 34 cases) plus involved-field radiotherapy in 26 cases. Forty patients (89%) achieved a complete response (CR), 3 (7%) a partial response (PR), and 2 (4%) were non-responders; the remaining 3 patients did not receive therapy. No initial variable predicted CR achievement. 57% of the patients in CR eventually relapsed, with a relapse risk of 46% at 10 years. Serum β2 microglobulin >1.6 mg/L and intermediate-risk FLIPI predicted failure-free survival. Histological transformation was observed in 6 patients, with a 10-year risk of transformation of 13%. Twelve patients have died during follow-up, in two cases

due to unrelated causes. Overall survival (OS) at 10 years was 79%. The FLIPI was the sole variable predicting OS.

Conclusions: Although the majority of patients with localized FL achieve CR, the risk of relapse is high. The FLIPI is of prognostic value in these patients.

Key words: follicular lymphoma, early stage, FLIPI, prognosis.

Introduction

Follicular lymphoma (FL) is one of the most prevalent types of non-Hodgkin's lymphomas in Western countries, representing about one quarter of them (1-2). The majority of patients with FL have disseminated disease at presentation. After an accurate staging, less than 20% of the cases are in stages I or II (1,3-5). Overall, patients with FL show a relatively indolent course with a median survival of about 10 years (5-7). Nevertheless, the natural history of FL is characterized by a pattern of continuous relapses with a shorter response duration and a shorter survival after each relapse (4-8). However, the natural history of patients with localized FL might be different (9-18). There has been some claim that a proportion of patients in stage I and II might be cured with standard therapies, including radiotherapy or combined chemo-radiotherapy. This, however, should be taken cautiously due to the possibility of late relapses.

Against this background, we analyzed the main clinico-pathological features at diagnosis, the treatment and the outcome of a series of patients diagnosed with early stage FL in a single institution and with a long follow-up.

Material and methods

Patients and treatment

Forty-eight patients consecutively diagnosed with FL in localized stage (Ann Arbor stage I or II) in a single institution between September 1977 and December 2002 were the subject of the present study. The diagnosis of FL was based on the criteria established in the World Health Organization classification of lymphoid malignancies (2). The histological subclassification, according to the above-mentioned classification, was as follows: type 1 (small cleaved cells), 20 cases (41.6%); type 2 (mixed), 24 cases (50%); type 3 (large cells), 3 cases (6.2%); and non-further-classifiable, 1 case (2%). The main characteristics of the patients at diagnosis are detailed in table 1.

Staging maneuvers included CT scan of thorax, abdomen and pelvis, as well as unilateral bone marrow biopsy. Treatment slightly varied over the years, but in most cases consisted of combination chemotherapy (COP [cyclophosphamide, vincristine and prednisone], 5 cases; CHOP [COP plus adriamycin], 34 cases). Treatments given are detailed in the Results section. In 26 patients, involved-field radiotherapy was used in addition to chemotherapy due to either bulky disease or stage I lymphoma. Post-therapy restaging included repetition of all the previously abnormal tests and/or biopsies.

Complete response (CR) was defined as the total disappearance of tumor masses and disease-related symptoms, as well as normalization of initial abnormal tests for at least 1 month. Partial response (PR) was considered when tumor masses or organ infiltration decreased by at least 50%, along with the disappearance of

disease-related symptoms. Patients not included in these categories and early deaths were considered as nonresponders (19).

The median follow-up of the surviving patients was 9.5 years (range, 2.4 to 24.8).

Parameters evaluated and statistical methods

In each patient the following initial data were recorded and evaluated for prognosis: 1) clinical data: age, gender, performance status (PS, according to the Eastern Cooperative Oncology Group [ECOG] scale) and presence of B-symptoms; 2) histolologic subtype; 3) hematological and biochemical parameters: hemoglobin, WBC count, lymphocyte count, platelet count, erythrocyte sedimentation rate, total serum proteins, serum albumin, serum gamma-globulins, serum M component, serum LDH levels and serum β2-microglobulin; 4) tumor extension data: number of nodal and extranodal involved sites, Ann Arbor stage, presence of bulky disease (tumor with a diameter >7cm); 5) the International Index for aggressive lymphomas (IPI)(20); and 6) the Follicular Lymphoma International Prognostic Index (FLIPI) (5). The actuarial survival analysis was performed according to the method described by Kaplan & Meier (21), and the curves were compared by the log-rank test (22). The univariate analysis was carried out for each of the parameters mentioned above. All significant prognostic variables in the univariate study, as well as age, were considered for multivariate analysis performed by the stepwise proportional hazard regression method of Cox (23), using the SPSS statistical software package.

Risk of relapse was measured from the time of CR achievement until relapse or last follow-up. Failure-free survival (FFS) was considered from the start of any treatment to the time of relapse / progression or to the last follow-up. Finally, overall survival (OS) was considered as the time between the date of diagnosis and death or last follow-up.

Results

Patient characteristics

The main initial characteristics of the 48 patients with stage I-II FL are detailed in table 1. Median age was 50 years (range: 24-88) and the male / female ratio was 25 / 23. Twenty-five patients (52%) were in stage I. Only 3 patients (6%) had a poor performance status (ECOG>2). Waldeyer's ring as primary site was observed in 4 cases, whereas extranodal involvement was recognized in 6 cases, including thyroid, parotid gland, pancreas, ampoule of Vater, skin, and central nervous system (1 case each). Increased serum LDH (≥450 IU/L) and β-2microglobulin (≥2.6 mg/L) levels were present in 3 of 44 (6%), and 3 of 26 (11%) patients with this information available, respectively. All the patients showed a low-risk score according to the IPI. The distribution according to the FLIPI, detailed in table 1, showed no patients of high-risk, 5 patients (12%) of intermediate-risk, and 38 patients (88%) of low-risk FLIPI.

Treatment and response

The majority of the patients were treated with chemotherapy (CHOP in 34 cases, COP in 5, and chlorambucil in 2). Radiotherapy and surgery were the sole treatment in 3 and in 1 patient, respectively. In addition, a watchful waiting policy was applied to 2 patients and 1 patient with indolent FL died of ischemic cardiopathy before starting any treatment for the lymphoma. In 26 patients, involved-field radiotherapy was used in addition to chemotherapy due to either bulky disease or stage I lymphoma.

After treatment, 40 patients (88%) achieved a complete response (CR), 3 (7%) a partial response (PR), whereas 2 patients (4%) failed to therapy. The CR rate according to the histological subgroup was 90% (type I), 71% (type II), and 100% (type III), respectively ($p>0.1$). No initial variable was able to predict the CR achievement.

Relapse, risk of relapse and failure-free survival (FFS)

Sixteen of the 40 patients in CR eventually experienced relapse during the follow-up. At that time, the disease was localized (stage I) in 3 cases, whereas 6 patients were in stage II, 3 patients in stage III, and 5 in stage IV. In two cases a new tissue biopsy demonstrated histological transformation into a diffuse large B-cell lymphoma.

The risk of relapse at 10 years was 49% (95% confidence interval [CI]: 29-69%), as plotted in figure 1. No initial parameter predicted the relapse from the time of CR achievement. Particularly, no differences in the risk of relapse were found according to the stage (10-year risk of relapse: 52% *vs.* 47% for stage I and II, respectively). Moreover, patients receiving complementary radiotherapy showed a risk of relapse similar to those who did not receive such a treatment (10-year risk of relapse: 47% *vs.* 50%, respectively).

FFS of the 45 patients who received treatment is plotted in figure 2. Median FFS was 9.0 years, with a 10-year FFS of 49% (95% CI: 32-66%). No initial single variable predicted FFS. Serum β2-m levels did not predict FFS when normal *vs.* elevated levels were compared. However, when 1.6 mg/L was selected as a cut-off

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(this value was the median of β2-m levels in the present series), patients with serum β2-m levels ≤1.6 mg/L showed a higher FFS than those with β2-m below this level (median FFS: not reached *vs.* 4.0 years, respectively; p=0.02). In addition, patients with FLIPI of low risk had a higher FFS as compared to those with intermediate-risk FLIPI (median FFS: 11.1 years *vs.* 2.4 years, respectively; p=0.02) (figure 3). No other initial variable significantly predicted FFS.

As salvage therapy, 8 patients received adriamycin-containing regimens (CHOP, 4 cases; CNOP, 1 case; MINE/ESHAP, 3 cases), 4 patients fludarabine combinations, 3 patients alkylators therapy and 1 patient was not treated. Upon treatment, 10 of 13 assessable patients reached a CR.

Risk of transformation

Six out of the 48 patients eventually showed histological transformation to a diffuse large B-cell lymphoma during the follow-up. This occurred at the first relapse in 2 cases. The risk of histological transformation at 10 years was of 13% (95% CI: 3-23%). No variable predicted such an event.

Survival

Twelve patients have died during the follow-up. The causes of death were related to the FL in 10 patients (progression, 7 cases; transplant related toxicity, 2 cases; and pneumonia, 1 case), and non-related to the FL in 2 patients (ischemic cardiopathy and sudden death in CR, 1 case each). The overall survival (OS) of the series is plotted in figure 2. Ten-year OS was 79% (95% CI: 65-93%).

The FLIPI was the only factor that predicted OS: median OS was not reached and 7.4 years for patients with low-risk and intermediate-risk FLIPI, respectively (p=0.01; relative risk: 8.5) (figure 4).

Seven of the 16 patients who eventually relapsed after a CR have died during the follow-up. In all these cases the cause of death was related to the lymphoma. The median survival from the time of relapse was 4.2 years.

Discussion

While patients with advanced stage FL are currently considered to be incurable, those with localized disease may enjoy prolonged disease-free survival, this indicating that some of these patients might be cured (15). Patients with FL, however, have a prolonged natural history, which is marked by a continuous pattern of relapses. Therefore, the analysis of patients with localized FL and a long follow-up may contribute to determine whether or not some of these patients are indeed cured.

In the present series, no evidence of plateau in neither disease-free nor OS was observed after a long follow-up (figure 2). In fact, as shown in figure 1, late relapses could be seen after 10 years of CR, with the risk of relapse being superior to 60% at 15 years. Relapses in these patients are most likely due to the fact that minimal residual disease persists below the threshold of standard procedures. Although neither in other nor in the present series minimal residual disease studies are available, it is worth noting that the bcl2/JH rearrangement can be detected by PCR in bone marrow or in peripheral blood of almost all the patients with FL in stage I, this indicating that there are not in fact patients with "localized" FL (24-26).

As far as therapy is concerned, there is no gold-standard treatment for localized FL, local radiotherapy being probably one of the most widely employed treatments. Therefore, it could be argued that the lack of systemic therapy might be the cause of relapse in these patients. However, this is not the case in the majority of patients included in the present series, since they were treated with either chemotherapy or combined chemo-radiotherapy regimens. On the other hand, no differences in

outcome were found according to the use or not of radiotherapy after chemotherapy. In terms of OS the lack of differences among the modalities of treatment is not surprising because all patients had a very favorable outcome with a median OS superior to 15 years irrespective of the treatment given. In this regard, it is noteworthy that no patient received rituximab as front-line therapy. The role of this new drug in the setting of patients with early stage FL is still unknown.

Another interesting finding of the present study was that the risk of histological transformation in patients in early stages was similar to that of the patients with FL in stages III or IV. This figure is around 15% at 10 years (data of the whole series not shown).

Recently, the FLIPI was devised to assess prognosis in patients with FL. As expected, most of our patients were included in the low-risk category, whereas only 12% were of intermediate-risk. Nevertheless, this score proved to be important to predict FFS and OS. In fact, FLIPI was the only parameter able to predict OS. In addition to FLIPI, β2-m had some prognostic interest in early stages FL. Since the vast majority of cases had a normal serum β2-m, we selected the median of the β2-m values as the cut-off instead of the standard one (normal vs. elevated). By doing so, β2-m was able to predict FFS.

In conclusion, patients with FL in early stage have a favorable prognosis in terms of OS, with a median survival of over 15 years. However, most of them eventually relapse. In addition, the FLIPI is useful in determining prognosis in these patients. Whether or not new treatment approaches, including monoclonal antibodies (i.e., rituximab), may improve the outcome of these patients warrants investigation.

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Legends for figures

Figure 1. Risk of relapse in 40 patients who achieved complete response after 1st line treatment.

Figure 2. Overall survival (OS) and failure-free survival (FFS) in 48 patients with follicular lymphoma.

Figure 3. Failure-free survival according to the FLIPI (Follicular Lymhoma International Prognostic Index).

Figure 4. Overall survival according to the FLIPI (Follicular Lymhoma International Prognostic Index).

Table 1. Main initial features of 48 patients with early stage follicular lymphoma.

Age (median [range])		50 years	[24 - 88]
Gender (M/F)		25 / 23	
Poor performance status (ECOG≥2)		3	(6 %)
Histology			
Type 1 (small cleaved cells)		20	(42 %)
Type 2 (mixed)		24	(50 %)
Type 3 (large cells)		3	(6 %)
Non-classifiable		1	(2 %)
Ann Arbor stage			
I		25	(52%)
II		23	(48 %)
Bulky disease		8	(17 %)
Extranodal involvement		11	(23 %)
Increased serum LDH*		3	(6 %)
Increased serum β2-microglobulin*		3	(11 %)
Follicular Lymphoma International Prognostic Index (FLIPI)			
Favorable risk	0 unfavorable factors	24	(56%)
	1 unfavorable factor	14	(32%)
Intermediate risk		5	(12%)

*Among 44 and 26 patients with available levels of LDH and β2-microglobulin, respectively

Fig 1

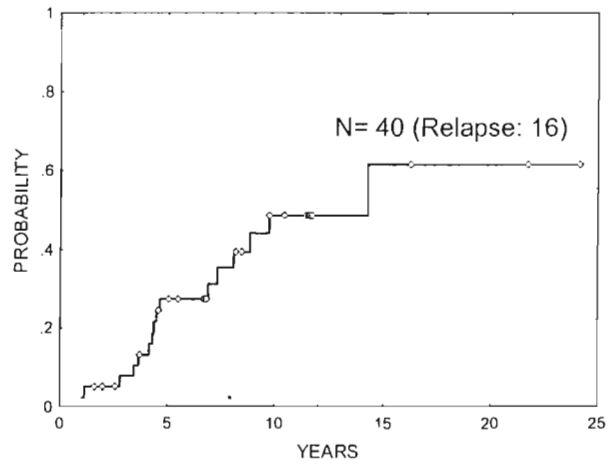


Fig 2

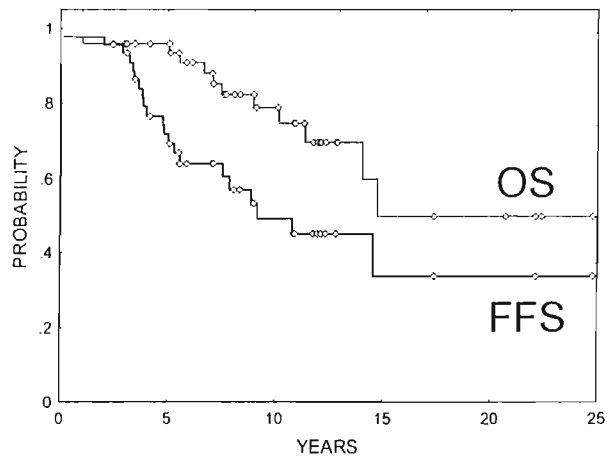
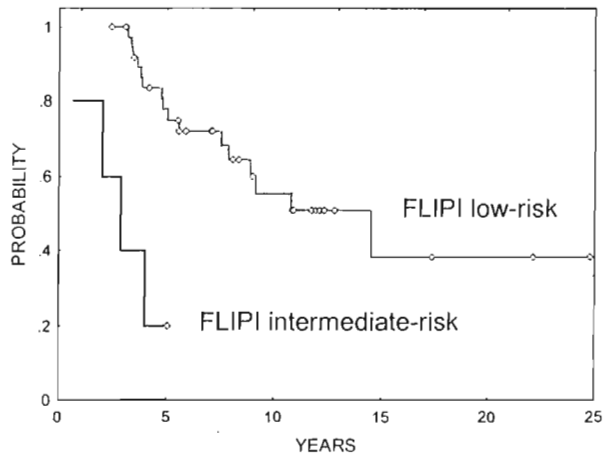


Fig 3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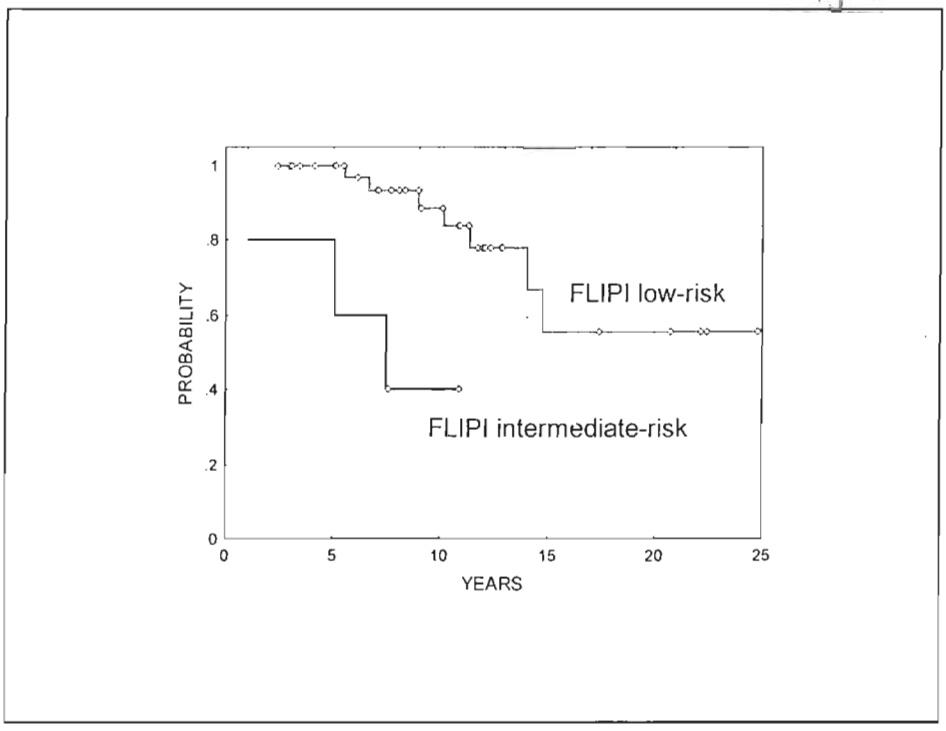
FLIPI intermediate-risk

Fig 4


PROBABILITY
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