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# The Follicular Lymphoma International Prognostic Index (FLIPI) and the histological subtype are the most important factors to predict histological transformation in follicular lymphoma

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**Background:** Histological transformation (HT) is a well-known event in patients with follicular lymphoma (FL) conferring an unfavorable prognosis. The aim of the study was to analyze incidence and risk factors for HT in a large series of FL patients.
**Patients and methods:** 276 patients (median age: 54 years; M139/F137) diagnosed with FL (42% grade 1, 51% 2, 7% 3) in a single institution were studied. Initial treatment consisted of combined chemotherapy in most cases. Median survival was 11.3 years. Main clinic and biological variables were assessed for HT and survival.
**Results:** 30 of 276 patients (11%) presented HT after a median follow-up of 6.5 years, with a risk of 15% and 22% at 10 and at 15 years, respectively. All HT corresponded to diffuse large B-cell lymphoma (DLBCL). Grade 3 histology, nodal areas >4, increased LDH and $\beta_2$-microglobulin, and high-risk IPI and FLIPI were associated with HT. In multivariate analysis, grade 3 histology and FLIPI retained prognostic significance. Only FLIPI predicted HT in grade 1–2 patients. 28 patients received salvage treatment for HT, with a CR rate of 52%. Median survival from transformation was 1.2 years, with 6/13 CR patients being alive >5 years after HT.
**Conclusion:** FLIPI and histology were the most important variables predicting HT. Upon HT, only patients achieving CR reached prolonged survival, thus emphasizing the need for effective therapies once this event occurs.
**Key words:** follicular lymphoma, transformation, FLIPI



## introduction

Follicular lymphoma (FL) is characterized by an indolent clinical course, with a relatively long survival, but with a continuous pattern of relapses resulting in a currently incurable disease. Moreover, as in other indolent lymphoid disorders, histological transformation (HT) into a high-grade lymphoma can be observed in an important proportion of patients. HT is associated with a progressive clinical course, poor response to treatment and short survival [1–3]. The biological mechanisms underlying disease transformation are not completely understood, but accumulation of secondary genetic alterations due to genetic instability [4], nonrandom chromosomal changes [5–7] and specific genetic alterations involving c-MYC [8], p53 [9–10], p16 $^{INK4A}$, p15 $^{INK4B}$ [11–12] and BCL-6 [13] have been related to this event. HT has been usually considered unrelated to prior therapies in FL because the classical observation of a similar incidence of such a complication either in patients receiving treatment or in patients under a wait and watch policy [14]. However, in some studies it has been suggested that treatment with newer agents such as purine analogs or monoclonal antibodies might facilitate HT [15].

The incidence of HT ranges from 10 to 70% in different series [1, 3, 16–17]. This wide range of incidence is probably due to the heterogeneous definition of HT in different studies, as well as to the difficulties in obtaining a diagnostic biopsy when HT is clinically suspected. Thus, it is of note that in necroptic studies up to 70% of patients with FL showed evidence of HT when all the lymph node territories were assessed [18–19]. Since HT is a very unfavorable event in the history of patients with FL, an accurate prediction of HT development could be of importance. However, prognostic studies on HT are relatively scarce, probably because of the above mentioned difficulties. Classical variables associated with high risk of HT are not achieving CR after initial therapy, as well as low serum albumin, and high serum $\beta_2$-microglobulin at diagnosis [3]. To the best of our knowledge, in spite of several preliminary data [20, 21], no

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studies have been formally published on the value of the FLIPI in predicting HT in patients with FL.

The treatment of HT is not well established. Overall, the prognosis after HT is poor with a median survival inferior to one year in most series using CHOP-like regimens as salvage treatment [3]. Patients with chemosensitive disease could benefit from more intensive therapies, including autologous stem-cell transplantation. With the latter approach, about 30% of disease-free survival at 5 years has been observed in selected series [22–24]. This encouraging data need to be confirmed in series with a longer follow-up [16, 22, 25].

The aim of the present study was to analyze the risk of HT in a large series of patients from a single institution homogeneously diagnosed, treated and followed-up. In addition, treatment results after HT are reported.

## patients and methods

### patients: features at diagnosis and initial treatment

Two hundred and seventy six patients (median age, 54 years; male/female distribution: 139/137) consecutively diagnosed with FL between January 1977 and January 2004 in a single institution were the basis for this study. The histological distribution according to the *WHO* classification [26] was as follows: grade 1, 104 cases (42%); grade 2, 125 cases (51%); grade 3, 18 cases (7%); 29 patients (11%) could not be subclassified. Histological review had been performed in most cases by EC and AM for previous analyses [27, 28]. For the current study, the initial biopsies and those at the moment of transformation were specifically reviewed by EC and AM.

Twenty-eight patients (10%) presented in stage I, 25 (9%) stage II, 45 (16%) stage III, and 178 (65%) in stage IV Ann Arbor disease. Extranodal involvement could be demonstrated in 179 patients, including bone marrow in 157 cases (60% of assessable patients). The distribution of the patients according to the FLIPI [29], assessable in 253 patients (92% of the series), was the following: low-risk, 97 patients (38%), intermediate-risk, 73 (29%) and poor-risk, 83 (33%). In addition, the International Prognostic Index for Aggressive Lymphoma (IPI) [30] was available in 246 patients (89%), the distribution being: low-risk, 116 patients (47%); low/intermediate risk, 80 patients (33%); high/intermediate risk, 27 (11%) and high-risk, 23 patients (9%). Finally, the Italian Lymphoma Index for Follicular Lymphoma (ILI) [31] was assessable in 199 patients (72%) of which 102 (51%) were at low-risk, 50 (25%) at intermediate-risk and 47 (24%) at high-risk (Table 1).

Initial treatment varied over the years, but basically consisted of: alkylating agents alone or in combination, 67 patients (25%); anthracycline-containing regimens (mainly CHOP), 164 patients (60%); fludarabine-based regimens 14 patients (5%); and other treatments, 10 patients (4%). All patients with histology grade 3 were treated with an anthracycline-containing regimen. Sixteen patients (6%) did not receive any therapy at diagnosis. Among 248 assessable patients, 124 (50%) reached CR, 93 (38%) PR, while 31 (12%) were considered as non-responders. After a median follow-up of 6.5 years (range: 0.2–24.7), 144 of 207 responders (70%) eventually showed progression of the disease. The median overall survival was 11.3 years (Figure 1a and b).

**Table 1.** Initial characteristics of 276 patients with follicular lymphoma

| Parameters | No. of patients (%) |
|---|---|
| Median age (range) | 54 years (23–88) |
| Gender | 139M/137 F |
| Histology ($n$ = 247) | |
| 1 | 104 (42%) |
| 2 | 125 (51%) |
| 3 | 18 (7%) |
| ECOG ≥2 | 40 (14%) |
| B symptoms ($n$ = 272) | 63 (23%) |
| Bulky disease | 48 (18%) |
| Extranodal involvement | |
| None | 86 (33%) |
| 1 site | 125 (47%) |
| ≥2 sites | 54 (21%) |
| Bone marrow involvement ($n$ = 261) | 157 (60%) |
| Ann Arbor stage | |
| I | 28 (10%) |
| II | 25 (9%) |
| III | 45 (16%) |
| IV | 178 (65%) |
| LDH (>450 U/L) ($n$ = 241) | 51 (21%) |
| β2-microglobulin (>2.3 mg/dl) ($n$ = 137) | 47 (34%) |
| FLIPI ($n$ = 253) | |
| Low risk (0–1) | 97 (38%) |
| Intermediate (2) | 73 (29%) |
| Poor risk (3–5) | 83 (33%) |
| IPI ($n$ = 246) | |
| Low risk (0–1) | 116 (47%) |
| Low/intermediate risk (2) | 80 (33%) |
| High/intermediate risk (3) | 27 (11%) |
| High risk (4–5) | 23 (9%) |
| ILI ($n$ = 199) | |
| Low risk (0–1) | 102 (51%) |
| intermediate risk (2) | 50 (25%) |
| High risk (≥3) | 47 (24%) |

### staging, evaluation of response, and follow-up policy

Initial staging procedures included computed tomography of the thorax, abdomen and pelvis, as well as unilateral bone marrow biopsy. In 74 patients diagnosed before 1985, lymphography was performed instead of CT scan. Post-therapy restaging included the repetition of the previously abnormal tests and/or biopsies.

Complete response (CR) was defined as the disappearance of tumor masses and disease-related symptoms, as well as the normalization of the initially abnormal tests and/or biopsies lasting for at least 1 month. Partial response (PR) was considered when measurable disease decreased by at least 50% [32]. Patients not included in these categories and those who died before completing treatment were considered as non-responders.

The follow-up surveillance policy after treatment consisted of physical examination, blood count tests and biochemistry and chest roentgenogram (if initially abnormal) every 3 months during the first year, every 4 months during the second and third year, every 6 months during the next 2 years and every year afterwards. Abdominal CT scans were performed every 6 months during the first year and yearly for the following 5 years when the abdomen was the principal involved site. Molecular follow-up was systematically performed only from 1999 in the setting of a clinical trial.

### criteria of histological transformation

At the time of clinical relapse or progression, a new lymph node biopsy was performed whenever possible. However, as previously described [27], such a procedure was carried out in only one half of the patients due to old age, poor performance status or patient refusal. Transformation into

a high-grade lymphoma was defined as a histological progression into a high-grade lymphoma with a diffuse pattern. Cytological study showing a massive large cell infiltrate was accepted as criteria of transformation in cases with clear clinical suspicion of transformation. On the other hand, in the present series, HT was suspected in eight additional patients in absence of cytological or histological evidence. Six of these eight patients were old people with poor performance status who were candidates for only palliative measures. The remaining two patients, who had a non-biopsied abdominal mass, were treated with adriamycin-containing regimens as for HT. Moreover, in three additional patients, HT was suspected, but the new biopsy was diagnostic of FL grades 1 or 2. According to the above mentioned criteria, none of these cases were considered as having HT.

### parameters evaluated

In each patient the following data were recorded and assessed for the risk of transformation:

- Initial variables: Age, gender, performance status (according to the Eastern Cooperative Oncology Group [ECOG] scale), B-symptoms, histological subtype, hemoglobin, WBC count, lymphocyte count, leukemic expression, platelet count, serum albumin, lactic dehydrogenase (LDH) and β2-microglobulin (β2M) levels, number of nodal and extranodal involved sites, presence of splenomegaly, Ann Arbor stage, bulky disease (defined as a tumor diameter ≥7 cm), bone marrow (BM) infiltration, IPI, ILI, FLIPI.
- Treatment: Monotherapy with alkylating agents or combination chemotherapies without adriamycin versus adriamycin-containing regimens.
- Response to therapy: CR versus PR versus no response. In addition, the following variables at the time of transformation were analyzed for prognosis: (a) clinical data (age, performance status, presence of B-symptoms), (b) tumor extension data (bulky disease, Ann Arbor stage, extranodal involvement, bone marrow involvement, serum LDH, β2M, hemoglobin), (c) FLIPI, IPI and ILI (d) number of previous relapses, (e) salvage treatment, and (f) response to salvage treatment.

### statistical analysis

The main end-points of the study were the transformation risk and survival from transformation (SFT). In addition, time to treatment failure (TTF) and overall survival (OS) were also analyzed. Survival analysis was performed according to the method described by Kaplan and Meier [33], and the curves compared by the log-rank test [34]. The univariate analysis was carried out for each of the parameters indicated above. All significant prognostic factors in the univariate study were included in a multivariate analysis performed by the stepwise proportional hazard regression method of Cox [35].

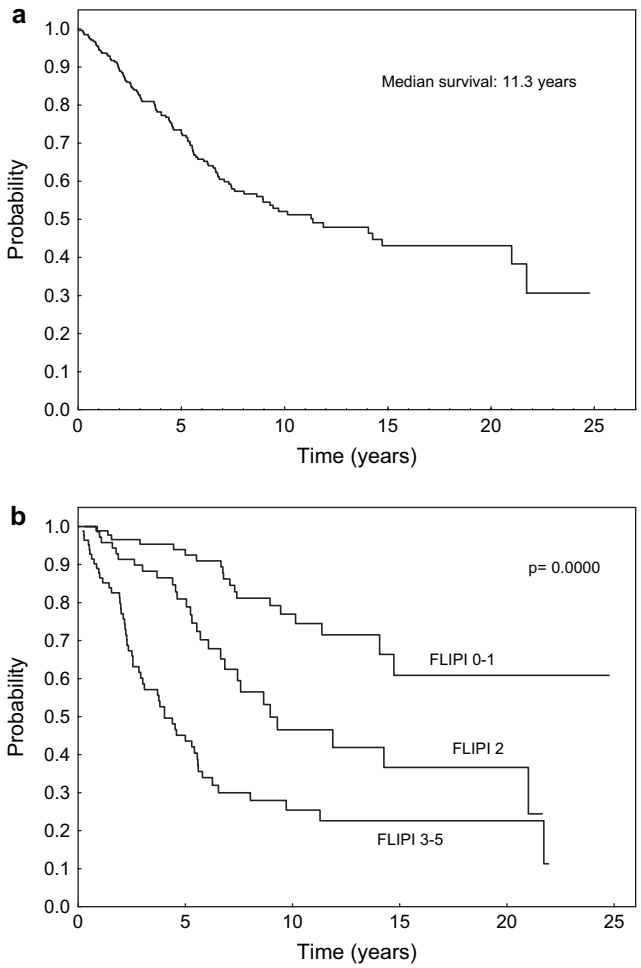


**Figure 1.** (**a**) Overall survival (OS) of 276 patients with follicular lymphoma. (**b**) Overall survival (OS) according to FLIPI score at diagnosis.

## results

### incidence, diagnosis and clinical features of histological transformation

Thirty of 276 patients (11%) presented HT during the follow-up, with an estimated risk of HT of 15% (95% CI 9–21%) and 22% (95% CI 12–32%) at 10 and at 15 years from diagnosis, respectively (Figure 2). The median time from diagnosis to HT was of 3.5 years (range 0.6 to 20 years). The diagnosis was established by means of a tissue biopsy in 25 patients and by a cytological assessment in five cases. In all cases in whom a biopsy was available, HT corresponded to a

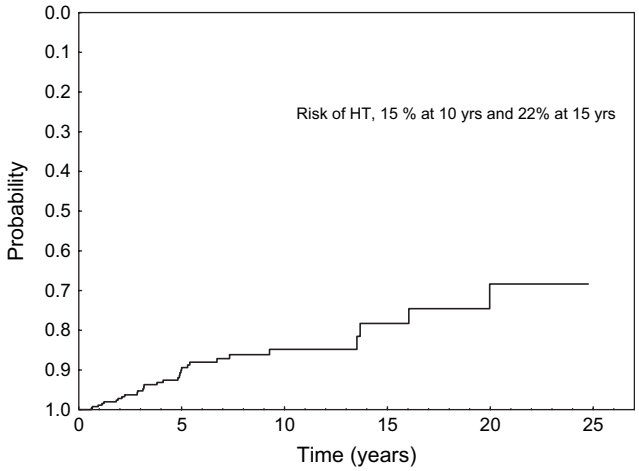


**Figure 2.** Risk of histological transformation (HT), 15% and 22% at 10 years and 15 years from diagnosis, respectively.

diffuse large B-cell lymphoma (DLBCL). Likewise in those patients in whom transformation into a large cell lymphoma type was detected on cytological grounds, clinical criteria consistent with disease transformation as fast growing of lymph nodes, pleural effusions, superior cave vein syndrome or increasing LDH serum levels were also present. In two cases, HT was detected after 22 and 34 months of follow-up, prior to any treatment for FL. In fourteen cases HT was detected at first disease progression and in 14 patients at second or more progressions. Up to 73% of HT patients had received CHOP among previous therapies for FL.

The main features of the 30 patients at the time of HT are listed in Table 2. Of note, 44% of patients presented with ECOG ≥2, 33% with B symptoms, 22% with bulky disease, 68% with stage III and IV and 81% with high levels of serum LDH at HT. Up to 48% of the patients who experienced histological transformation presented a high/intermediate or a high-risk IPI score whereas 76% presented an intermediate or high-risk FLIPI score.

## predictors of histological transformation

In the univariate analysis, the initial factors associated with HT were the following: grade 3 histology, number of nodal involved areas >4, high serum LDH (Figure 3) and high serum $\beta_2$-microglobulin levels. In addition, the FLIPI also showed a significant statistical correlation with HT ($P = 0.014$) (Figure 4), with those patients with higher FLIPI having a higher risk of transformation. Moreover, the IPI was also associated in the univariate analysis with HT, whereas the ILI score did not correlate with HT. Finally, the modality of treatment (chlorambucil or COP versus CHOP) or the degree of response obtained (CR versus no CR) had no influence in HT. Of interest, no case of HT has been detected among the 14 patients that received fludarabine-based regimens to the last follow-up. However, the low number of cases and the short follow-up prevented any definitive conclusions.

A multivariate analysis was performed with the significant variables above described: histological subgroups (1 *and* 2 versus 3), FLIPI score (low versus intermediate versus poor) and IPI score (low versus intermediate/low versus intermediate/high versus high). LDH was not added because it is included in the FLIPI score and β2-microglobulin was excluded because it was only available in one half of the patients. Grade 3 histology ($P = 0.003$; relative risk 2.83) and FLIPI ($P = 0.001$; relative risk: 2.35) retained its prognostic significance for HT (Table 3).

**Table 2.** Main features of 30 patients at the time of histological transformation

| Features | Number of patients (%) |
|---|---|
| Median age (range) | 60 years (29–71) |
| Gender | 18M/12 F |
| ECOG ≥2 | 12 (44%) |
| B symptoms | 9 (33%) |
| Bulky disease | 6 (22%) |
| Extranodal involvement | |
| none | 15 (56%) |
| 1 site | 8 (29%) |
| ≥2 sites | 4 (15%) |
| Bone marrow involvement ($n = 15$) | 5 (33%) |
| Ann Arbor stage | |
| I | 5 (20%) |
| II | 3 (12%) |
| III | 7 (28%) |
| IV | 10 (40%) |
| LDH (>450 U/L) ($n = 21$) | 17 (81%) |
| β2-microglobulin (>2.3 mg/dl) ($n = 15$) | 7 (46%) |
| IPI | |
| Low risk (0–1) | 8 (32%) |
| Low/intermediate risk (2) | 5 (20%) |
| High/intermediate risk (3) | 6 (24%) |
| High risk (4–5) | 6 (24%) |
| FLIPI | |
| Low risk (0–1) | 7 (24%) |
| Intermediate risk (2) | 10 (35%) |
| Poor risk (3–5) | 12 (41%) |

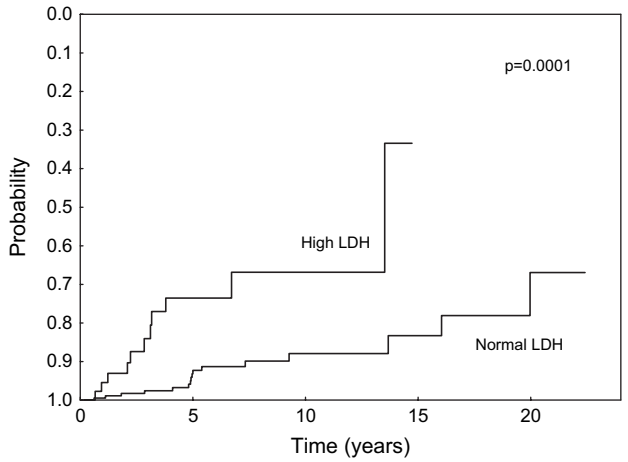


**Figure 3.** Time To transformation (TTT) according to LDH serum levels at diagnosis of FL.

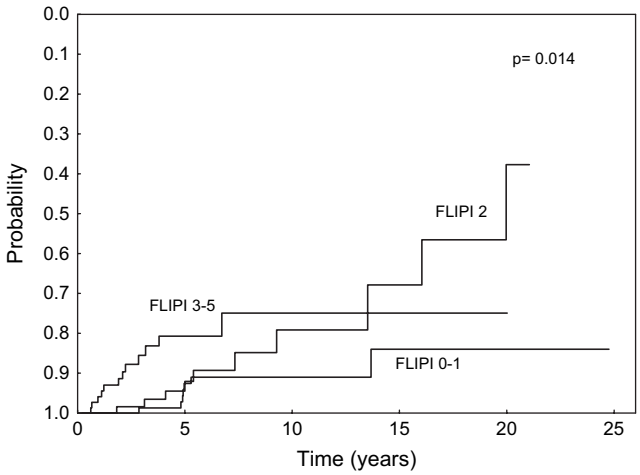


**Figure 4.** Time To transformation (TTT) according to FLIPI score at diagnosis of FL.

**Table 3.** Prognostic features for histological transformation in patients with FL

| Risk of HT | | *P* value |
|---|---|---|
| Univariate analysis | All patients ($n$ = 276) | Grade 1–2 patients ($n$ = 258) |
| Grade 3 WHO | 0.0066 | – |
| Number of nodal involvement >4 | 0.0076 | ns |
| Elevated serum LDH | 0.0001 | 0.002 |
| Elevated serum β2-microglobulin | 0.0001 | 0.0009 |
| IPI | 0.0002 | 0.05 |
| FLIPI | 0.014 | 0.0359 |
| ILI | ns | ns |
| Multivariate analysis | | |
| Grade 3 WHO | 0.003; RR 2.83 | – |
| FLIPI | 0.001; RR 2.35 | 0.013; RR 1.97 |

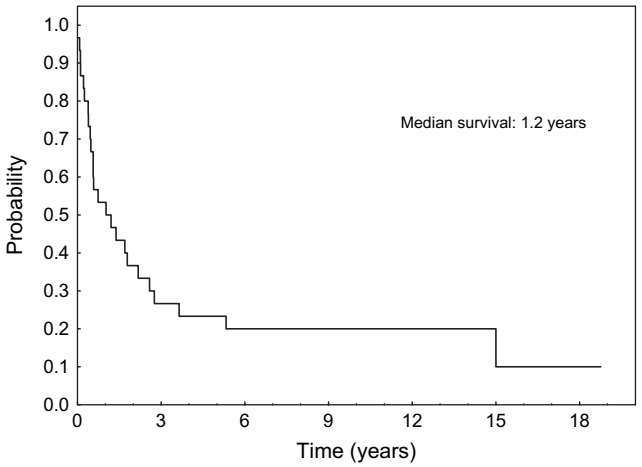


**Figure 5.** Survival From Transformation (SFT), median of 1.2 years ($n$ = 30 patients).

The same analysis of factors predicting HT was performed in the subset of patients with FL histological grade 1 or 2. In these cases, high LDH and serum β2-microglobulin levels, FLIPI and IPI score predicted HT (Table 3). In the multivariate study the only parameter retaining prognostic significance for HT was the FLIPI score.

### evolution after histological transformation

Twenty-five of 30 patients (83%) received intensive treatment, whereas the remaining five patients only received palliative measures, including chlorambucil in three of them. Seven patients received CHOP (25%), 17 patients a combination of iphosphamide and VP-16 (VIA) or MINE/ESHAP regimens (54%) and one patient, who refused chemotherapy, radiotherapy alone. CR was reached in 13 cases (52%) and PR in three cases (12%). Seven patients treated either with CHOP or VIA eventually underwent autologous stem-cell transplantation. Five of those seven patients were in CR, one in PR and one has failed to chemotherapy when autologous transplant was performed. Thirteen out of 16 patients in response after salvage treatment eventually relapsed or progressed. In eight cases a new biopsy could be taken, the diagnosis being of DLCL in six cases and FL in two cases.

Twenty-five patients of 30 HT patients having experienced HT died during the follow-up, in 23 cases due to disease progression and in two cases due to apparently unrelated causes (melanoma and fatal cardiac arrhythmia, respectively). The median survival from transformation was 1.2 years (Figure 5). Six patients presented prolonged survival over five years after HT (5.6+, 7+, 9.2+, 11.2+, 15+ and 18.8+ years). Early stage (I–II) ($P$ = 0.02), ambulatory performance status (≤1) ($P$ = 0.028), and intermediate/low or low IPI score (<3) ($P$ = 0.0046), all at the time of transformation, correlated with longer survival after HT. In addition, the response to salvage therapy was very important to predict survival after HT (5 years survival of 43% versus 0% for patients reaching CR versus no CR, respectively; $P$ = 0.0001). No differences in terms of survival from transformation were seen between the seven patients who underwent intensification with autologous stem-cell transplantation and those that for a variety of reasons were not autografted.

## discussion

This retrospective study on 276 patients consecutively diagnosed of FL in a single institution over a long period of time, confirms that HT is a common event in the natural history of FL. In the present series, the estimated risk of transformation was of 15% and 22% at 10 and 15 years from diagnosis. Although this is in keeping with other series, the risk of transformation reported in the literature range from 10–70%. The main reasons for these discrepancies are probably the difficulties in assessing histological transformation. Thus, despite the basic criterion that HT is the demonstration of histological progression in a lymph node (or other tissue) biopsy, different criteria are applied in the literature. This is understandable, because sometimes it is difficult to obtain diagnostic tissue, for instance in older patients or those with poor performance status. In this sense, the present study is strict, since only those patients with a histological assessment both at diagnosis and at HT, demonstrating the loss of the follicular architecture and the appearance of a diffuse infiltration pattern by a large cell type, were included. Patients under clinical suspicion of HT but without a histological or cytological examination were not considered as transformed in the present series. As a consequence, the real incidence of HT is probably underestimated. In fact, autopsy studies carried out in the past showed higher rates of HT compared to clinical series. Nevertheless, histological assessment of transformation remains a difficult issue to address. Even when follow-up surveillance procedures after FL diagnosis are rightly performed as well as rebiopsy when clinical progression is observed, older age, poor performance status or patient refusal became important limitations.

Predictive factors for HT in patients with FL have been described in previous series [3, 21, 36]. Low serum albumin, high β2-microglobulin level, and the absence of CR to initial treatment have been noted to be important in large series. In the study of Bastion et al. LDH and histological subtype did not show prognostic importance in predicting HT. This is in opposition to the data herein reported, in which these two variables are among the most important factors to predict HT development, as well as in preliminary data from other institutions where LDH had a significant predictive value for HT. A possible reason for these discrepancies is the low number of patients with grade 3 FL (5% cases) as well as the low availability for LDH levels in the series of Bastion et al. (67%). Moreover, another aspect to take into account is that in this particular study about 25% of HTs were diagnosed on cytological bases and 10% only on clinical criteria.

As expected, FLIPI was an excellent predictor of OS in the present series (Figure 1b). In addition, FLIPI showed to have predictive value for HT (Figure 4). In fact, when a Cox analysis was performed, FLIPI and histological subtype were the only variables retaining prognostic significance. Moreover, FLIPI was the only prognostic factor in patients with histological grade 1–2 FL. On the other hand, IPI also showed a relative value in predicting HT, while ILI did not. The possible role of β2-microglobulin as a predictor for HT could not be analyzed, because this information was not available in half of the patients.

At the time of HT, a higher proportion of patients presented with a poor performance status, high-risk FLIPI and IPI, increase of LDH and β2-microglobulin serum levels, compared with the time of diagnosis. In agreement with previous series, HT was also an early event in our FL patients with a median time to transformation of 3.5 years. Despite this fact, no plateau was achieved and HT over 10 years and up to 20 years from diagnosis was seen in several cases.

After HT, a high proportion of patients (80%) in the present series were treated according to intensive chemotherapies (CHOP, VIA and MINE/ESHAP regimens), including autologous transplantation in 25% of cases. Overall response rate was of 64% and the CR rate 52% of cases. However, despite the relatively high rate of CR, median survival from transformation was only 1.2 years. At HT, parameters significantly associated with a longer survival were the degree of response to salvage treatment (CR versus PR versus failure), disease extension (stage I–II versus III–IV), performance status and IPI score. It is of note that FLIPI assessed at the moment of HT was not able to separate patients with different outcome. Thus, a poor clinical outcome is observed in the present series despite salvage treatments. This fact is consistent with OS reported in the literature. Indeed, only those patients with favorable features such as limited-stage disease and low LDH levels are shown to achieve longer OS after autologous transplantation in some reported series [22–24]. In the present study, up to 68% of patients presented with advanced stage and 79% of cases with increased LDH serum levels. This could explain the scarce benefit of autologous transplantation, if any, in the present series, although it has to be pointed out that only seven patients were transplanted, five of them in CR. Of note, up to six patients have presented prolonged survival over five years after HT. All of them had achieved CR after salvage therapy, which included an autologous transplantation in only one case. These data suggest that although outcome after HT is generally poor, a subset of patients can present prolonged OS. Moreover, it also stresses that obtaining CR with salvage therapy is a crucial event, in agreement with previously published series [14].

In conclusion, HT is a frequent event in the natural history of FL patients, probably underestimated because of the difficulties in reaching a histological diagnosis. The presence of grade 3 FL and high-risk FLIPI at diagnosis of FL are associated with the development of HT. Finally, this event conveys poor prognosis unless a CR is achieved, which unfortunately is not frequent. Improving salvage therapies is therefore crucial to prolonging survival in these patients.

## acknowledgements

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