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Original Research

Primary refractory follicular lymphoma: a poor outcome entity with high risk of transformation to aggressive B cell lymphoma

Sara Alonso-Álvarez [a,*], Martina Manni [b], Silvia Montoto [c], Clémentine Sarkozy [d], Franck Morschhauser [e], Marielle J. Wondergem [f], Attilio Guarini [g], Laura Magnano [h], Miguel Alcoceba [i], Martine Chamuleau [f], Sara Galimberti [j], Maria Gomes da Silva [k], Harald Holte [l], Emanuele Zucca [m], Sandra Lockmer [n], Igor Aurer [o], Luigi Marcheselli [p], Yana Stepanishyna [b,q], María Dolores Caballero Barrigón [i], Gilles Salles [r], Massimo Federico [b]

[a] *Department of Haematology, Hospital Universitario Central de Asturias, Spain*
[b] *CHIMOMODepartment, University of Modena and Reggio Emilia, Modena, Italy*
[c] *St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom*
[d] *INSERM 1052, Charles Mérieux Lyon-1 Faculty, Claude Bernard University, Lyon, France*
[e] *Department of Clinical Haematology, CHU Lille, Unite GRITA, Universite de Lille 2, Lille, France*
[f] *Department of Hematology, VU University Medical Center, Amsterdam, the Netherlands*
[g] *Haematology Unit, IRCCS IstitutoTumori "Giovanni Paolo II", Bari, Italy*
[h] *Department of Haematology, Hospital Clinic of Barcelona, Spain*
[i] *Department of Hematology, Hospitalario Universitario de Salamanca (HUSIBSAL) and CIBERONC, Salamanca, Spain*
[j] *Section of Hematology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[k] *Instituto Portugués de Oncologia, Departamento de Hematologia, Lisboa, Portugal*
[l] *Department of Oncology, Radiumhospitalet, Oslo University Hospital, Norway*
[m] *Oncology Institute of Southern Switzerland (IOSI), Ospedale San Giovanni, Bellinzona, Switzerland*
[n] *Dep. of Hematology, Karolinska University Hospital and Dep. of Medicine, Karolinska Institutet, Stockholm, Sweden*
[o] *Division of Hematology, Department of Internal Medicine, University Hospital Center Zagreb and Medical School, University of Zagreb, Croatia*
[p] *Fondazione Italiana Linfomi (FIL) Onlus, Modena, Italy*
[q] *Department of Oncohematology, National Cancer Institute, Kiev, Ukraine*
[r] *Gilles SALLES, Lymphoma Service, Memorial Sloan Kettering Cancer Center, NY, USA*

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* *Corresponding author*: Hospital Universitario Central de Asturias, Department of Haematology, Av. Roma, s/n, 33011 Oviedo, Asturias, Spain. Fax: +34 985 10 87 53.
E-mail addresses: saralonsoalvarez@gmail.com, sara.alonso@sespa.es (S. Alonso-Álvarez).

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Abstract ***Background:*** Primary refractory (PREF) follicular lymphoma (FL) has a completely different clinical course from that of FL that responds to front-line treatments. In addition to having poor responses to salvage therapies, it seems that patients with PREF are at increased risk of histological transformation (HT). The Aristotle consortium presented the opportunity of investigating the risk of HT in a very large series of cases. Thus, we investigated the risk of HT in patients with PREF FL compared with that of responding patients or in stable disease and ultimately their outcome.

Methods: Six thousand three hundred thirty-nine patients from the Aristotle database were included in the analysis. These patients had a histologically confirmed grade 1, 2 or 3a FL diagnosed between 1997 and 2013. The primary end-points were the cumulative incidence (CI) of HT at the first progression or relapse and the survival after transformation.

Findings.: The 5-year CI of HT among patients with PREF was 34% (95% confidence interval (CI): 27–43), whilst it was 7.1% (95% CI: 6.0–8.5) in the group of patients with partial response (PR) or stable disease (SD) (PR + SD) and 3.5% (95% CI: 3.0–4.2) in the group of patients achieving complete response (CR). The 5-year survival after relapse (SAR) was 33% (95% CI: 28–39) for the PREF group, 57% (95% CI 54–61) in patients with PR, 51% (95% CI 43–58) in the SD group after first-line therapy and 63% (95% CI: 66–72) in patients with CR after initial treatment (p-value <0.001). The 5-year SAR for those patients with PREF who developed HT was 21% (95% CI: 12–31), clearly diminished when compared with those patients with PREF who did not experience HT (38% [95% CI: 31–44]) (p-value = 0.001).

Interpretation.: Patients with PREF FL have a dismal outcome and an associated very high rate of HT that further worsens their poor prognosis.

1. Introduction

Transformed follicular lymphoma (FL) is the denomination of an aggressive lymphoma that develops in a patient affected by FL and which is presumably biologically related to the latter. The definition of histological transformation (HT) has historically varied considerably among different studies [1] which has made comparisons amongst studies misleading. In addition, the timing of the onset of this event is variable as it can occur as the first event from the time of initial diagnosis of FL or after several relapses of the indolent entity. Some groups describe a plateau in the cumulative incidence (CI) of transformation after 5 years of follow-up; [2] however, this has not been corroborated recently [3]. Although the yearly transformation of FL to an aggressive disease is infrequent, HT modifies the indolent evolution of FL [4], with an overall survival (OS) approaching that of the general population in responding patients [5], to an aggressive behaviour with an OS [6] considerably shortened for a high percentage of patients. In addition, we are yet to answer which is the most effective treatment for this group of patients with lymphoma. For these reasons, efforts are being made to improve knowledge of HT [7,8], by identifying the biological characteristics and clinical events that allow us to predict which patients are most likely to develop FL transformation. Within the biological processes related to histological transformation, we could highlight in particular some newer ones: during the somatic hypermutation process, some patient-specific N-glycosylation sites are introduced and that these sequences could be relevant in sustaining the disease progression, probably together with other genetic events [9]. Best known is how some somatic mutations, such as those affecting TP53 [7], CDKN2A [10] or EZH2 [11,12] seem to be more frequently found in transformed cases.

As part of the Aristotle study [13], we have previously reported that the risk of HT as a first event has been significantly reduced by the use of rituximab. The objective of this subanalysis of the Aristotle study is to understand which groups of patients have a higher transformation rate, constituting the target population for preventing this event. Patients with an early relapse after first-line therapy have a well-known unfavourable prognosis [5,14], so we investigated the risk of HT in patients with primary refractory (PREF) FL, to understand to what degree the decreased survival of this group can be attributed to an increased risk of HT.

2. Methods

2.1. Patients' selection

We performed a retrospective analysis of the Aristotle study cohort of patients with newly diagnosed FL who received active treatment (n = 6970) and had an evaluable response at the end of induction therapy. The

Aristotle study included newly diagnosed FL cases (grade 1, 2 or 3a), diagnosed between 1997 and 2013 in 11 institutions across Europe.— Only biopsy-proven HTs occurring as a first event after first-line systemic therapy were included. The initial diagnosis and type of HT were based on reporting by the local pathologists at the participating institutions; a central pathology review was not performed. The initial therapy included different treatment strategies (e.g. single-agent or combined chemotherapy with or without rituximab or rituximab monotherapy). Moreover, maintenance with rituximab was also prescribed in some patients. Detailed information on patient characteristics and their systemic therapies have been previously described [13].

2.2. Response assessment

A centralised review of the response to front-line therapy was not performed, but this was evaluated retrospectively based on what was reported by the local investigator. Given the time frame considered in the Aristotle study, response assessment at the local site was performed only by computed tomography (CT) scan [15]. Positron-emission tomography (PET) scan was not used for stage definition or response assessment—.

Complete response (CR) was defined as the disappearance of all evidence of disease, whereas partial response as the regression of measurable disease and no new sites. Stable disease (SD) was defined as the failure to attain CR/ partial response (PR) or PD. Relapse or recurrence was defined as the presence of FL disease after the achievement of a CR or PR to first-line therapy lasting at least three months. PREF was defined as progressive disease or relapse within three months from the end of induction therapy. Transformation was defined as the presence, at the time of recurrence, relapse or progression, of a biopsy-proven aggressive lymphoma (from an initial diagnosis of indolent lymphoma).

2.3. Groups and outcomes definition

For the purpose of this analysis, patients were grouped into four categories, based on the response to the front-line treatment. Thus, patients were categorised as those achieving a CR at the end of induction therapy, patients achieving a PR or SD and those who had PREF disease.

The main end-points were the CI of HT and survival after relapse (SAR), measured from diagnosis of refractory disease or relapse till either the date of death from any cause or last clinical contact. Time to HT was calculated from the date of FL diagnosis to the date of HT. We compared the CI of histologically proven transformation among groups. In addition, we analysed SAR in the three groups, and particularly in the group of patients with PREF, as per whether they present HT or not.

2.4. Statistical methods

The CI of HT was calculated using the Nelson-Aalen estimator with a 95% confidence interval (CI) [16], whereas the SAR was estimated using Kaplan–Meier methods.

Continuous variables were summarised as the median value and the 2.5 to 97.5 percentiles. Categorical variables were reported as absolute and percentage frequencies. Continuous prognostic variables were dichotomised as per the usual clinical thresholds reported in the literature. The Fisher's exact test or chi-squared test was used to compare variables as appropriate.

As previously detailed [13], for this study, a specific sample size was not initially calculated. All statistical tests were two-sided, and p-values <0.05 were considered to indicate statistical significance. All analyses were performed using the statistical package Stata 14.2 (StataCorp LLC, College Station, TX).

3. Results

Of 6970 patients included in the Aristotle database and treated upfront with systemic therapy, 631 cases (9%) were excluded for incomplete data. Thus, 6339 patients (91%) were considered for this analysis: 4096 (65%) patients achieved a CR, 1954 (31%) patients achieved a PR or maintained an SD, whereas 289 were patients with PREF (4%) (Fig. 1). Patient characteristics by response to first-line treatment are detailed in Table 1.

3.1. HT regarding response to first-line therapy

The five-year CI of HT was 34% (95% CI 27–43) for patients with PREF, whilst it was 7% (95% CI: 6–9) in the group of patients with PR + SD and 4% (95% CI 3–4) in the group of patients achieving CR. The rate observed in the PREF group had a hazard ratio (HR) of 11 (95% CI 9–15) compared with patients achieving CR and 6 (95% CI 5–8) when compared with patients achieving PR + SD. All comparisons and estimations showed a p-value below 0.001. The risk of HT as per the response to initial therapy is represented in Fig. 2.

To confirm that initial therapy was not a confounder for this analysis, we performed the analysis as per the different first-line therapy used, considering different clusters. The risk of transformation was homogeneous in the different treatment groups (Supplementary Table 1).

3.2. SAR as per response to induction therapy

The five-year SAR for the PREF group was 33% (95% CI 28–39), with a median SAR of 1.1 year (95% CI 0.8–1.8). The SAR at 5 years for patients with PR and SD after initial therapy who subsequently relapsed was

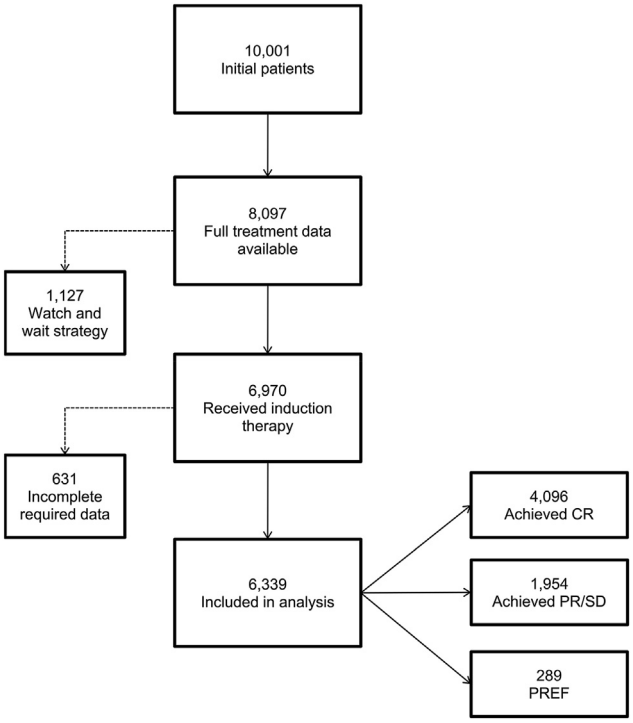

Fig. 1. **Number of patients included in analysis**. Flow chart showing how patients were collected and excluded due to lack of inclusion criteria until reaching the series referred to in the current study.

57% (95% CI 54–61) and 51% (95% CI 43–58), with a median SAR of 6.3 years (95% CI 5.8–9.0) and 5.2 years (95% CI 2.8–10.4), respectively. Finally, in the group of patients with initial CR who eventually relapsed, the 5-year SAR was 63% (95% CI 66–72), with a median of 10.4 years (95% CI 10.0–12.2). The difference among groups was statistically significant (p-value <0.001, Fig. 3). The HR for the PREF group was 3.4 (95% CI 2.9–4.0) compared with the CR group and 2.2 (95% CI 1.9–2.6) and 1.4 (95%CI 1.1–1.9) compared with the PR and SD group, respectively.

The cross-term response by treatments did not show a modifying effect on the SAR (Supplementary Table 2).

3.3. SAR for the PREF group as per HT events

SAR was analysed in the PREF group as per whether patients developed HT or not. The 5-year SAR for patients with PREF who developed HT (n = 73) was 21% (95% CI 12–21), and the corresponding median SAR was 0.6 years (95% CI 0.5–1.0). In contrast, patients with PREF who did not experience HT (n = 216) had a 5-year SAR of 38% (95% CI 31–44), with a median SAR of 1.8 years (95% CI 1.0–2.9) (Fig. 4). The HR between patients who did not experience HT and patients who underwent HT was 1.7 (95% CI 1.2–2.3; p = 0.001).

4. Discussion

Patients with PREF have a well-known adverse prognosis [5]. On the other extreme, patients with a long response duration after initial immunochemotherapy seem to have a survival approaching those of the general population for the same age and sex. To predict who will become a long-term survivor, different groups have tried to find surrogates to predict which patients will achieve a sustained response over time [5,14]. In addition to refractoriness to treatment, HT is another event associated with an unfavourable prognosis [3,6].

Previous studies have shown that the degree of response to treatment was associated with the risk of transformation [17]. We analysed the incidence of transformation among patients with PREF after initial treatment and compared it with that observed in patients partially responding to treatment or with SD and in patients achieving a CR (accordingly to what was described in the paragraph 'Groups definition' of the Methods section). We found that patients with PREF have the highest rates of HT.

Subsequently, we investigated the relationship between PREF and HT. We questioned to what degree the evolution of patients with PREF is owing to their already poor prognosis and in what part it was influenced by their increased risk of transformation. Thus, we analysed SAR based on the development or not of HT in the group of patients with PREF after the first line. We observed that the unfavourable effect of the PREF is even worse when HT happens, and while 5-year SAR was 38% when HT did not occur, it dropped to 21% in the group of PREF patients with HT. In a recent retrospective study [18] of real practice patients with FL receiving rituximab + bendamustine as front-line therapy, 76% of patients with early progression (Progression of disease within 24 months [POD24]) had HT. This group of patients had very adverse outcomes, which can

Table 1
Patients' characteristics by response to treatment.

Factor		CR	PR/SD	PREF
		n (%)	n (%)	n (%)
Age >60	>60	1580 (39)	883 (45)	136 (47)
Gender F	F	2165 (53)	949 (49)	138 (48)
Histology	gr 1-2	2683 (66)	1285 (66)	169 (58)
	gr 3	660 (16)	231 (12)	33 (11)
	NA	753 (18)	438 (22)	87 (30)
FLIPI	0–1	1260 (34)	370 (22)	40 (15)
	2	1212 (33)	564 (33)	56 (22)
	3–5	1185 (32)	786 (46)	163 (63)
Rituximab-containing regimens at front-line	Yes	3233 (79)	1455 (74)	162 (56)

F, female; PR/SD, partial response/stable disease; CR, complete response; PREF, primary refractory.

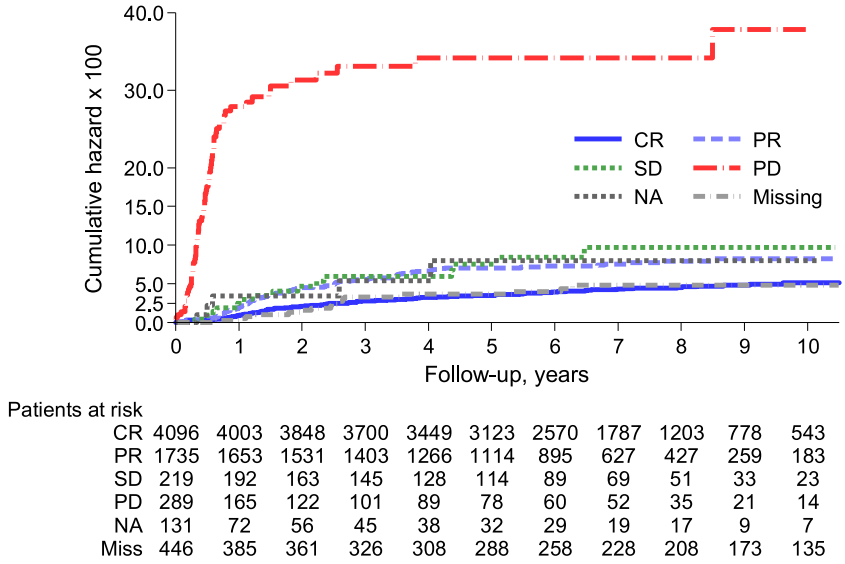

Fig. 2. **Cumulative Incidence of Histological Transformation according to response to initial therapy**. We represent the incidence curves for each group of patients, with the dotted curve representing PREF patients, the discontinuous curve for patients with PR or SD, and the solid line for patients with CR. Likewise, patients at risk are defined for each follow-up time. *p*-value <0.001.

be also explained by a particular high incidence of HT in the progressive disease group of patients, as we had also observed. The striking high incidence observed in this group might be influenced by the type of induction therapy used. Both groups (PREF and POD24) share a high number of HT patients. As per existing data [5], patients with POD24 have 5-year OS of 50%, whereas patients with PREF had a 5-year SAR of 38%. The analysis of the specific weight of the transformation in both categories would be of great interest in prospective studies.

The limitations of this study are derived from its retrospective nature and the study of subgroups. Unfortunately, some data could not be obtained from the retrospective collection of the different centres. Although the histological grade is not given for all patients, the presence of composite lymphoma, or grade 3B, was an exclusion criterion, and therefore for data where the grade is not detailed, it should be 1, 2 or 3a.

The study included a very high number of patients and has used strict criteria for the selection and diagnosis of patients and the event of HT [13]. Although it is still a small number of patients with PREF who experience HT (n = 71), as per our knowledge, this is the largest series of patients with these characteristics published to date. This study demonstrates that patients with refractory disease have a very unfavourable survival with a high risk of HT with an even worse prognosis.

At present, patients unresponsive to initial therapy represent an unmet need, and new tools able to recognise these patients upfront are urgently needed, with the aim of offering alternative treatment strategies. Furthermore, as this study shows, some of those non-responders eventually experienced HT, more frequently than what was observed in the rest of the groups. Therefore, we should investigate whether this group (PREF + HT) had already features of transformed disease at diagnosis. This might explain their refractoriness and their high-grade progression. Guided by this hypothesis, we should look for the presence of occult HT [18] at the beginning of treatment, to carry out a targeted treatment for this scenario. As we know, the histological analysis of all tumour locations is not possible. However, liquid biopsy is a growing technique [19,20] which offers a non-invasive disease analysis and can provide us with data on the disease as a whole. In spite of the interest of this group of patients, we are aware of the rarity of refractoriness to treatment in FL. And it is important to contextualise this from a clinical point of view. We believe that the strategies aimed at characterising this subgroup of patients should be considered in the experimental, and it is here that economic efforts should be concentrated. The final objective is to identify accessible and suitable markers to be transferred to the usual clinical setting with an acceptable economic impact.

In diffuse large B-cell lymphoma, several studies correlated prognosis with the detection of circulating tumour DNA amount [21,22]. The detection of circulating genetic material that corresponds specifically to the tumor and its correlation with the prognosis has been performed by detecting specifically B-cell clonality in peripheral blood or plasma [23] and later on, this strategy has been done but tracking for specific somatic mutations [24,25].

Regarding FL, a recent article has used the detection and allelic frequencies of *EZH2* mutations in plasma of patients with FL to detect early disease progression/transformation [26].

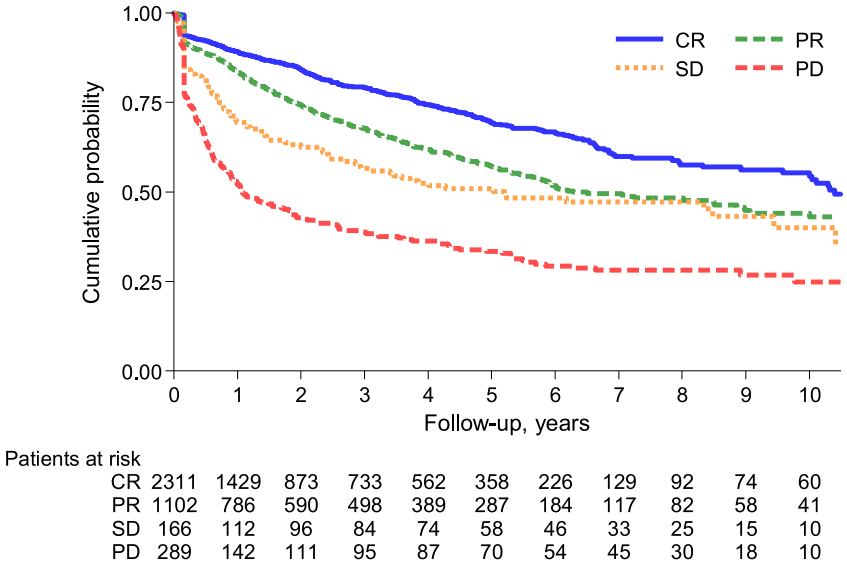

Fig. 3. **Survival after relapse according to response to induction therapy**. We represent the survival curves for each group of patients, with the dotted curve representing PREF patients, the discontinuous curve for patients with PR or SD, and the solid line for patients with CR. Likewise, patients at risk are defined for each follow-up time. See Methods section. HR for PREF group was 3 (95% CI 3–4) compared to CR group, and 2 (95% CI 2–3) compared to PR/SD group, p-value<0.001.

Hence, it is likely that we will soon have more data that will allow us to refine liquid biopsy and use it for detecting hidden FL transformation.

However, another group of patients with PREF may relapse exclusively with FL histology. In these cases, it would not only be a question of identifying hidden transformation but of investigating what type of treatment would be ideal to prevent relapse of these patients. In this regard, different variables should be taken into consideration, some referring to the tumour cell and others regarding patients' characteristics.

The limitations of this study are derived from its retrospective nature and the study of subgroups. This was of particular interest regarding evaluation of response. As explained in the Methods section, response evaluation was reviewed retrospectively based on what was reported

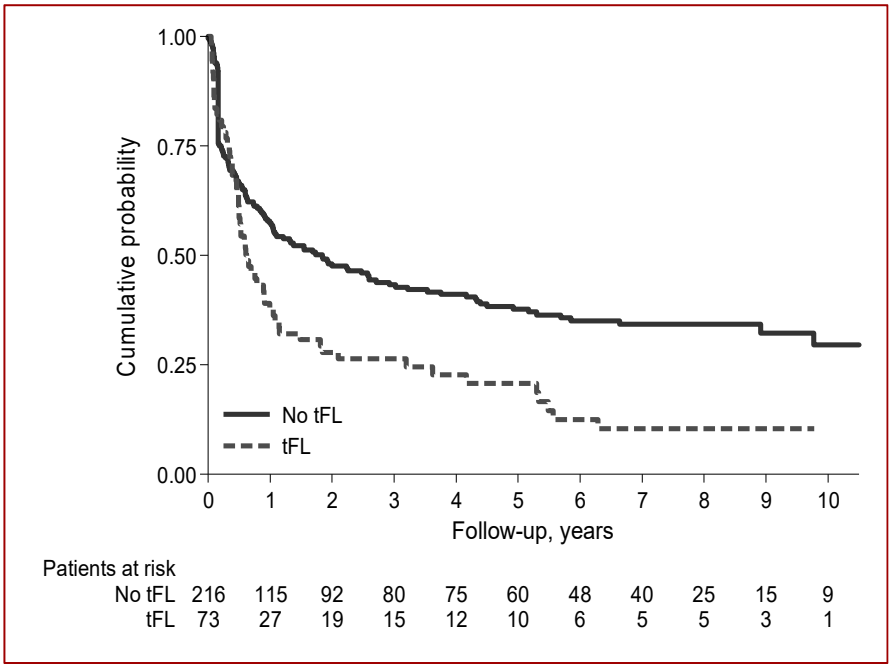

Fig. 4. **Survival after relapse for PREF group according to HT event.** We represent the survival curves for patients with PREF and HT, with the discontinuous curve, and the solid line for patients with PREF and non-HT. Likewise, patients at risk are defined for each follow-up time. See Methods section. Hazard ratio: 2 (95% CI 1–2; $p = 0.001$).

by the local investigator. However, the disadvantages of retrospective statistical analyses, while partially offset by the large cohort, should not be overlooked. Similarly, some data could not be obtained from the retrospective collection of the different centres. Although the histological grade is not given for all patients, the presence of composite lymphoma, or grade 3B, was an exclusion criterion, and therefore for data where the grade is not detailed, it should be 1, 2 or 3a. As previously mentioned, initial PET evaluation was not available for the cohort patients, most of them diagnosed before PET scan performance at diagnosis was indicated in FL disease. The introduction of PET/CT in the initial study of FL has made it possible to optimise the staging of the disease [27]. One could assume that, ideally, patients should have been biopsied in those locations where glycidic metabolism was higher and, likely, some aggressive histologies could be found. However, this has not been widely demonstrated yet [28].

Putting aside these pertinent considerations, we consider that the strengths of the work are the analysis of a very high number of patients and the use of strict criteria for the selection and diagnosis of patients and the event of HT [13]. Although it is still a small number of patients with PREF who experience HT (n = 71), as per our knowledge, this is the largest series of patients with these characteristics published to date. This study demonstrates that patients with refractory disease have a very unfavourable survival with a high risk of HT with an even worse prognosis.

Thus, although we are refining the diagnostic techniques and delving into the biology of FL, the clinical response to first-line treatment continues to be an essential key for the identification of patients with a poor outcome. In this work, we also propose that within the group of patients with refractoriness, there are different subgroups. We should look further for clinical and biological parameters that guide us to transformation phenomena from the onset of the disease (such as liquid biopsy combined with clinical aspects, laboratory routine tests, biopsy details and metabolic techniques) as well as investigate clinical, immunological or tumour cell characteristics that define patients with refractory FL. Research and knowledge in FL should arise in close collaboration between clinical observations and laboratory findings.

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Author contribution

Conceptualisation – SA, MM, MF, MDCB.

Data curation – MF and MDCB.

Formal analysis – LM.

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Investigation – All authors contributed to investigation.

Methodology – MF.

Project administration – MF, SA, MDCB.

Resources – Each of the authors provided all necessary data for the performance of the study.

Software – All analyses were performed using the statistical package Stata 14.2 (StataCorp LLC, College Station, TX).

Supervision – MF, MDCB.

Validation – MF.

Visualisation – Preparation, creation and/or presentation of the published work, specifically visualisation/data presentation.

Writing – original draft – SA, MM and MF.

Writing – review and editing – All authors participated in the edition and review of the original draft till the final version was created.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

A complete list of sites and physicians participating in this study is provided as appendix 1.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.005.

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