Review Article

Unmet needs in histological transformation of follicular lymphoma: a clinical and biological review

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Abstract: Histological transformation, with its profound diagnostic and therapeutic implications, is considered to be one of the most unfavorable events in the natural history of follicular lymphoma (FL). No optimal treatment of transformed follicular lymphoma (tFL) has been identified because of its rarity and heterogeneous presentation, and the lack of data from randomized clinical trials. Consequently, its treatment has been based on that used in *de novo* diffuse large B-cell lymphomas. However, patients with tFL present a different behavior, with a worse clinical course and poor response to treatment, although their prognosis seems to have improved significantly since the introduction of rituximab into therapeutic schemes. There is no consensus definition of tFL, which prevents the genuine identification of transformation when a biopsy is unavailable. There are no biomarkers at diagnosis that accurately identify patients who will transform. A better knowledge of the pathways leading to transformation would clearly help to identify patients at risk of transformation, and to distinguish them from patients who will relapse with FL and from those who will remain disease-free. This would also facilitate the identification of new drug targets, the design of clinical trials and the treatment of transformation when it arises. In the present review we provide a comprehensive overview of the current open questions in the field of transformation of FL. Large-scale international collaborative studies are required to address these gaps in our knowledge.

Keywords: Transformed follicular lymphoma (tFL); histological transformation

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Introduction

Non-Hodgkin lymphoma (NHL) is the most frequent hematological malignancy, with the seventh highest incidence of all cancers of 12.5 new cases per 100,000 inhabitants per year (1). Follicular lymphoma (FL) is the most common indolent NHL, with an estimated incidence of 20–30% of all lymphomas in western countries (1,2). The emergence of new drugs, especially for immunotherapy in induction and maintenance regimens, has improved median survival to up to 20 years (3-5). However, despite the high response rates and the slow course of the disease, FL is still considered to be an incurable disease characterized by a pattern of multiple relapses, decreasing duration of response, and gradual acquisition of resistance to different drugs (1,2). Up to 20% of patients progress within

24 months of treatment, and half of them die within 5 years (6,7), while those who remain in complete remission at this time have a similar overall survival (OS) as the general population (8). Moreover, an undefined percentage of FL with an estimated risk of 3% per year, either as a first or as a later event after one or several treatment lines, will transform into an aggressive lymphoma, usually diffuse large B-cell lymphoma (DLBCL). Outcomes of patients with transformed follicular lymphoma (tFL) have tended to be poor, but several studies carried out in the rituximab era suggest that survival may be more favorable than previously described (9-11). The prediction of histological transformation at diagnosis remains a challenge (12).

In this review, we focus on the biological mechanisms that underlie the process of histological transformation of FL to DLBCL, and the therapeutic strategies available for its treatment. Our review does not address other atypical forms suggestive of presentation of histological transformation, such as FLs that are already undergoing transformation at diagnosis (at the same or at different sites), or those that undergo a process of reverse transformation, from an aggressive lymphoma to a lower grade. This is not to deny their importance, however, and we urge that they be reviewed, since they might have different clinical behaviors.

Definition of FL transformation

The gold standard definition of FL transformation is based on the histologically confirmed progression of grade 1, 2, or 3A FL to a high-grade lymphoma (10), consisting of a predominance of large cells that eradicate the follicular architecture.

Since the tumor is disseminated, it should be borne in mind that, in addition to the transformation area, several tumor areas might have a concurrent FL component. Therefore, a single biopsy may not represent the entire tumor (10,13). There are several reasons why exclusive use of a histological criterion may make the detection of cases of transformation less likely: inaccessibility of the tumor that prevents a biopsy being performed, lack of available metabolic tests guiding the puncture, patients' own limitations, or refusal to have their lesion surgically excised. Indeed, according to previous reports only half of the potential biopsies were performed (14).

Clinical criteria have been proposed when a biopsy is not feasible. However, there is no consensus about these, since they vary between studies (15-17). These criteria are arbitrary, based on clinical observations in patients with transformed lymphoma (15-17), but are also common clinical symptoms of FL progression (15-18). Overall, these include rapid discordant lymphadenopathy growth, a rapid increase in lactate dehydrogenase levels to 2 or 3 times normal values, the novel involvement of unusual extranodal sites, new B symptoms, and hypercalcemia (15-17). Although patients with a strong clinical suspicion of transformation might be clinically comparable to those with histologically confirmed transformation (16,17), there is not enough evidence to justify considering them on an equal footing. In fact, in some cases in which clinical suspicion would lead to the diagnosis of tFL, pathology reports have confirmed FL relapse (14).

In cases with clinical suspicion of tFL, the high standardized uptake value (SUV) of 18[F] fluorodeoxyglucose positron emission tomography and computerized tomography (PET/CT) is correlated with more aggressive histology, and therefore could help predict the transformation area (19-23). Previous studies have indicated that a maximum SUV value (SUVmax) of more than 17 could be enough to predict transformation (21,22). However, the scarcity of FL patients in the two studies may have led to a high SUVmax being overlooked in some FL cases, and in that sense, an SUVmax >17 at FL diagnosis or relapse has been reported (23). Moreover, and considering only the FL patients included in both studies, about one-third of tFL patients have an SUVmax <17, and up to 20% have an SUVmax of <10 (21,22). Thus, PET/CT may be helpful in guiding biopsies for the detection of histological transformation (21), although given the overlap of the SUVmax of FL and DLBCL, better imaging tools could contribute to a more reliable tFL diagnosis.

Incidence of transformation

It is well known that some patients with FL may eventually transform into an aggressive lymphoma, commonly DLBCL or, less frequently, Burkitt lymphoma or undifferentiated B-cell high-grade lymphoma (10,24). The study of the cell of origin (COO) shows that most of the tFLs (~80%) are of the germinal B-cell subtype (GCB-DLBCL) (25,26). Such transformation has also been observed in other indolent B-cell lymphoproliferative disorders (B-LPDs), such as chronic lymphocytic leukemia, marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, and nodular lymphocyte-predominant Hodgkin lymphoma (10,11,27-31).

The incidence of tFL is not well established, mainly due

Table 1 Incidence of transformation (only series with >200 cases are reported)

References	Criteria of tFL	Rituximab era	n	tFL (n)	Proven biopsy (%)	Follow-up (year)	Incidence of transformation
Bastion (15)	HT + clinical	No	220	52	65	9	22% at 5 years
Gine (14)	HT + clinical	No	276	30	83	6.5	15% at 10 years
Montoto (9)	HT	No	325	88	100	15	28% at 10 years
Al-Tourah (16)	HT + clinical	No	600	170	63	9.1	3% annually
Conconi (32)	HT	No	281	37	100	10	15% at 10 years
Bains (33)	HT + clinical	*	237	34	74	7.4	18.5% at 10 years
Link (17)	HT + clinical	Yes	631	60	85	5	10.7% at 5 years
Wagner-Johnston (34)	HT + clinical	Yes	2,652	379	39	6.8	14.3% at 6.8 years
Sarkozy (35)	HT	Yes	1,017	40	100	6.1	4.1% at 6 years
Alonso-Álvarez (11)	HT	Yes	1,734	106	100	6.2	5% at 5 years; 8% at 10 years
Federico (36)	HT	Yes	7,405	439	100	–	5.5% at 5 years; 7.1% at 10 years

*, Limited-stage follicular lymphoma. HT, histological transformation; tFL, transformed follicular lymphoma.

to the use of the previously mentioned different criteria for defining and classifying transformation, cohort size, and duration of follow-up of the studies, among others (9,11,14-17,32-36) (*Table 1*). In addition, in most studies, clonality testing to distinguish between actual transformation to *de novo* DLBCL has not been carried out, thus including ~5–10% of cases that are clonally unrelated (37,38). Taking all these points into consideration, the incidence of tFL has been estimated to be 15–30% at 10 years in the pre-rituximab and rituximab eras, with a consistent risk of ~3% of tFL per year, although a recent work suggests a reduction in the rituximab era (16,17,36,39). The report of a 70% incidence in an autopsy series suggests that tFL is a common terminal event in FL (40).

In the rituximab era, only two large studies have analyzed the incidence of tFL using strictly histological criteria. First, in the PRIMA trial, which enrolled patients achieving partial or complete response after first-line treatment, showed that the incidence of tFL was 4% at 6 years (35). When estimating the incidence of transformation, we must bear in mind that Kaplan-Meier curves consider only one possible event, and the censored cases are an estimated risk in the future. Therefore, patients who die before transformation should not be censored, making a competing risk model a better choice for analyzing cumulative incidence (41). In the recently published study of the Spanish GELTAMO group, we calculated the cumulative incidence of tFL in a large cohort series, considering death as a competing risk, estimated as 5% at 5 years, and 8% at 10 years (11).

Whether the risk of tFL is constant over time is open to question. Two series in the pre-rituximab era found a plateau at ~17 years (9,32), while most of the other studies find no such plateau (11,14-17,33-35). However, the former studies had a median follow-up of 10–15 years, while those of the latter studies were relatively shorter (<10 years). A longer follow-up in a large series is required to answer this question as it applies in the rituximab era.

The recent ARISTOTLE project launched by the European Lymphoma Institute (ELI), integrates the retrospective data of ten collaborative national groups studying lymphoma, including those of the PRIMA trial, and the GELTAMO studies, and is likely to go some way to providing answers to these outstanding questions (36). Preliminary results, considering histological criteria and only first events, suggest an incidence of tFL of 7% at 10 years (36). A reduction in the incidence of transformation at 10 years was observed in patients receiving rituximab in the induction and maintenance regimen, compared with those receiving it only at induction. A longer follow-up of the series is required to determine the role of maintenance in delaying or decreasing the risk of transformation (36).

Clinical and biological factors related to transformation risk

One of the major challenges in the treatment of FL is

to identify predictors of histological transformation at diagnosis (12). Previous studies have shown that patients with high-risk clinical factors (high FL international prognostic index—FLIPI) have a greater risk of transformation (9,11,14,17,35). However, a considerable proportion of patients with low-risk clinical factors will transform, while, conversely, some patients with multiple high-risk factors will not transform (9,11,17,35,42).

The suboptimal response to first-line treatment has also been associated with a higher risk of transformation in the pre-rituximab and rituximab eras (11,15,43). However, it is well documented that transformation can occur in responding and non-responding cases, and even in untreated patients (11,15,35). The fact that shorter survival was observed in patients who transformed within 18 months of diagnosis (17), suggests that the acquisition of certain alterations drives a faster progression of the disease in some tFL cases. Recurrent gene alterations in the transformation include *TP53*, *CDKN2A/B*, and *MYC*, which are common in relapsed/refractory patients of different hematological disorders, including FL, and probably cause the aggressiveness of the disease (42,44). Although our knowledge of the molecular mechanisms involved in FL transformation has increased in recent years, the etiology and pathogenesis of the transformation are still unclear.

It remains to be clarified whether early treatment is associated with lower transformation risk compared with a "watch and wait" strategy as has been suggested in several papers (9,17,34). The phase 3 clinical trial conducted by Ardeshna *et al.* (45) which randomized patients to early rituximab therapy or observation, is best suited to answering this question. With a median follow-up of almost 4 years, no difference in the time to transformation, or incidence of histological transformation, was detected, although a longer follow-up will be required to achieve definitive conclusions.

Pathogenesis of tFL

The advent of next-generation sequencing (NGS) has enabled the mutational landscape of different hematological malignancies to be determined. Most studies of NHL have focused on FL and/or DLBCL (46-48), and do not include tFL or reflect it as a subgroup; therefore, few studies have specifically addressed tFL (49,50). Most of these studies are largely descriptive and compare the condition with other disorders, meaning that few studies have investigated the clinical significance of the majority of these gene mutations (51-56).

Two studies have used NGS and copy-number alteration (CNA) to show that the tFL genomic landscape shares alterations with FL and GCB-DLBCL (e.g., *CREBB*, *EZH2*, and *MLL2* mutations); alterations exclusive to tFL have also been described (e.g., *CDKN2A/B* deletions, *EBF1* and *TNFAIP3* mutations) that might have diagnostic and potentially therapeutic implications (49,50). The major limitation of both studies was the absence of an association between genetic alteration and clinical behavior or the risk of transformation. Although these studies imply that there is clonal evolution in tFL, which is consistent with a model of divergent transformation from a common progenitor cell rather than a lineal model, the small number of cases (12 and 10, respectively) prevents conclusive results being drawn (49,50). Indeed, various studies suggest that the presence of *TP53* alterations is a risk factor for transformation in FL (42,49,50).

In a very recent study comparing FLs that progress or relapse with those that transform (either as an initial or subsequent event), transformation was the result of drastic changes of subclones present at very low frequencies (<1%) at diagnosis compared with progression, where the clone responsible was observed at diagnosis (42). These authors analyzed a custom 94-gene panel in 118 FL-tFL pairs and FL patients without transformation ≥5 years after diagnosis, identifying frequent genes in each group. Since most of the FL patients without transformation (>75%) had a low-risk FLIPI, a thorough comparison with patients with matched high-risk factors (high-FLIPI) at diagnosis has not been carried out. Another recent study combining CNA and NGS from 35 tFLs, identified, several deregulated pathways, including JAK-STAT, NF-kB, and immune surveillance (57).

In recent years, genome-wide analyses have identified the 6p21.3 region as a susceptibility region for a range of NHLs, including FL (58-60). The human leukocyte antigen (HLA) system, which is located in this region, has a central role in the anti-tumor immune response and in the apoptosis of lymphoma cells (61), and could therefore have a role in disease control. Earlier studies have shown a relationship between different HLA polymorphisms and a higher susceptibility to developing FL or DLBCL, including a group of HLA polymorphisms that confer a worse prognosis in DLBCL (62-65). However, no studies have investigated the role of HLA polymorphisms in the risk of transformation, while single-nucleotide polymorphisms (SNPs) within the 6p21 region, such as rs6457327, have been associated with both a higher risk of transformation and lower survival from transformation (66,67).

Composition of the microenvironment

The cellular microenvironment is important for the control, development, and proliferation of tumors. Molecular studies have demonstrated its involvement in various hematological malignancies and the current possibility of using molecules that inhibit the inhibitory signals (e.g., anti PD-1, or CTLA-4) of the immune response which act on tumor-infiltrating cells, suggest that the microenvironment is able to terminate the tumor cells (68,69).

CD4+ and regulatory T-cells (Tregs) have not been uniformly associated with the increased or decreased risk of transformation, either in the pre-rituximab era, or in the current scenario with new drugs. Published studies yielded apparently inconsistent findings, probably due to the different combinations of chemotherapy used. Taking this into consideration, in a cohort of differently treated patients, a follicular pattern of FOXP3+ Tregs was associated with an increased risk of transformation (70). Furthermore, CD4-positive T-helper cells, and specifically T-helper 1 cells, have more frequently been found within the neoplastic follicles of FL patients who underwent early transformation to an aggressive histology than in those who did not (71).

Similarly, a high level of tumor- or lymphoma-associated macrophages (TAMs) has been associated with an adverse outcome in the pre-rituximab era (chemotherapy-treated FL patients), with respect to PFS and OS (72,73). However, this association might be conditioned by the type of chemotherapy received (fludarabine- or cyclophosphamide-based) (74). Moreover, the most recent studies have detected that associations between macrophages and outcome might have changed after rituximab, so that more TAMs would be correlated with longer survival rates (75,76). Moreover, macrophages cannot be considered individually, since an abundance of tumor-associated mast cells has been linked to an adverse prognosis, even in cases with a favorable level of TAMs (77). The role of macrophages in predicting FL transformation in the current scenario in which immunochemotherapy coexists with a wide spectrum of new drugs is still unknown.

Finally, it is noted that increased angiogenesis in FL tumor samples is associated with worse survival and a higher risk of transformation (78).

Therefore, there is very limited information about the role of the composition of the microenvironment in the risk of transformation under the current scenario. Newer technologies have made it possible to determine not only the number and spatial distribution of tumor-associated cells, but also their gene expression profiles, and their different functional status. This leads us to conclude that it is time to comprehensively analyze these characteristics in large series in conjunction with other biological and clinical factors.

Therapeutic strategies in tFL

No prospective studies have investigated patients with tFL in the rituximab era, so treatment is generally based on that used in *de novo* DLBCL. Even though the same therapeutic schemes are used, tFL patients have been considered to behave differently from *de novo* DLBCL, with a worse clinical course, poorer response to treatment, and shorter survival, usually less than two years in the pre-rituximab era (10). The introduction of the monoclonal antibody rituximab improved *de novo* DLBCL prognosis (79-81), and also seems to have improved the prognosis of tFL patients, as shown in *Table 2* (82-102), extending the median survival to 4–5 years (10,17,84). In fact, recent studies have not found any significantly different outcome between tFL and *de novo* DLBCL (97,103).

It seems clear that the treatment should not be the same for patients who have or have not previously been treated for FL. Thus, a therapeutic model has been proposed that recommends treating treatment-naïve patients with rituximab plus chemotherapy (R-CHOP), as if they were *de novo* DLBCL cases (104). Consolidation with autologous stem cell transplantation (auto-SCT) has been a standard therapy for tFL patients, as it has been for relapsed chemosensitive NHL (105). However, given the good results obtained with R-CHOP in chemotherapy-naïve patients, the need for auto-SCT has been called into question, and it could be obviated in patients who achieve complete remission after R-CHOP (83,103).

A different scenario arises in relation to patients with tFL who have already received R-CHOP during their FL stage. In these cases, initial therapy should be different from R-CHOP, using platinum-based regimens, and autotransplant intensification may be appropriate (84-97).

The role of allogeneic stem-cell transplantation (allo-SCT) in tFL has been tested in very small series of patients, in which there has often been high transplant-related mortality (*Table 2*) (84,85,95,96,98-102). Whether a better outcome may be achieved by using reduced-intensity conditioning in contrast to the predominantly used myeloablative conditioning is unknown (96).

Patients with transformed lymphoma are often excluded

Table 2 Studies on outcomes of chemotherapy, auto-SCT, and allo-SCT in tFL

References	Rituximab era	tFL (n)	PFS		OS		TRM		Comments
			Time (year)	%	Time (year)	%	Time	%	
Chemotherapy									
Kaminski (82)	No	14	Median	13.9 months	4	20	–	–	Prospective clinical trial—RT + Tositumomab
Gleeson* (83)	Yes	70	5	40	5	64.5	–	–	Excluded 17 cases treated without rituximab (n=8) and with auto-SCT as consolidation (n=9). R-CHOP (n=55), 37% 5-year PFS and 64.3% 5-year OS
Ban-Hoefen*† (84)	Yes	50	N.D.	–	2	53	–	–	Prospective study
Villa* (85)	Yes	53	5	40	5	61	–	–	Only <65 years patients; 32% treatment-naïve at HT
Madsen (86)	Yes	18	5	6	5	36	–	–	Only <67 year patients
Auto-SCT									
Foran (87)	No	19	5	52	5	50	100 days	5	
Williams (88)	No	50	5	30	5	51	100 days	8	
Andreadis (89)	No	22	‡Median	1.4 years	Median	4.6 years	100 days	2	
Sabloff (90)	No	23	5	25	5	56	1 year	0	
Hamadani (91)	Yes	24	5	33	5	52	100 days	8	
Smith† (92)	Yes	25	§3	64	3	63	100 days	0	
Eide (93)	No	30	5	32	5	47	100 days	0	Prospective clinical trial
Ban-Hoefen (94)	Yes	16	2	59	2	82	100 days	0	Rituximab naïve better PFS
Reddy (95)	Yes	44	‡5	45	5	62	2 years	4.6	≥1 line from HT to auto-SCT
Ban-Hoefen*† (84)	Yes	50	N.D.	–	2	83	Overall	2	Prospective
Villa* (85)	Yes	97	5	55	5	65	100 days	2	
Wirk (96)	Yes	108	5	35	5	50	1 year	8	
Kuruvilla† (97)	Yes	46	‡4	45	4	65	N.D.		Prospective clinical trial; 58% of tFL received R as maintenance
Madsen (86)	Yes	33	5	53	5	62	N.D.		3 low-grade NHL; auto-SCT better when R-naïve at HT

Table 2 *(continued)*

Table 2 *(continued)*

References	Rituximab era	tFL (n)	PFS		OS		TRM		Comments
			Time (year)	%	Time (year)	%	Time	%	
Allo-SCT									
Rezvani (98)	Yes	16	3	21	3	18	3 years	42	Non-MAC, auto-SCT previous in 44%
Hamadani (99)	Yes	8	4	56	4	66	100 days	12.5	75% MAC
Ramadan[†] (100)	Yes	25	3	32	3	48	1 year	33[¶]	MAC
Thomson (101)	Yes	18	4	61	4	60	1 year	29[¶]	RIC, auto-SCT previous in 56%
Clavert (102)	Yes	9	5	89	5	67	1 year	25	RIC; auto-SCT + allo-SCT; numbers estimated for the 9 tFL; 68% PFS and OS at 4 years for the whole series (n=19)
Reddy (95)	Yes	7	[‡]5	45	5	69	2 years	31.4	43% MAC
Ban Hoefen[*†] (84)	Yes	18	N.D.		2	65	Overall	22	Prospective
Villa[*] (85)	Yes	22	5	46	5	46	100 days	5	>95% MAC
Wirk (96)	Yes	22; 11	3; 3	11; 48	3; 3	11; 67	1; 1	57; 0	22 MAC; 11 RIC

* includes tFL without prior treatment (21% in chemotherapy in Gleeson; 32% in chemotherapy, 10% in auto-SCT, and 11% in allo-SCT in Ban Hofen; 32%, 16%, and 14% respectively in Villa); † includes all indolent transformed NHLs (percentage of tFL as follows: 86% in Ban Hofen; 72% + 20% tFL at diagnosis in Smith; 90% in Kuruvilla; 84% in Ramadan); ‡, event-free survival; §, relapse-free survival; ¶, referred to the total series, not restricted to tFL (n=40 including 15 tFL at diagnosis in Ramadan; n=48 including 30 relapsed DLBCL in Thomson). N.D., not described; MAC, myeloablative conditioning; OS, overall survival; PFS, progression-free survival; RIC, reduced intensity conditioning; RT, radiotherapy; tFL, transformed follicular lymphoma; TRM, transplant-related mortality.

from prospective clinical trials, so information about the efficacy of new drugs for treating tFL is scarce. Czuczman *et al.* reported a phase 2 study using the immunomodulatory agent lenalidomide that produced an overall response rate of 57%, and a median response duration of over 1 year in patients with tFL (106). Likewise, promising results were obtained from patients with histological transformation treated with radio-immunotherapy (82). More recently, a plethora of new drugs targeting crucial pathways in B-cell lymphomas has been developed, including PI3K pathway inhibitors (idelalisib), B-cell receptor inhibitors (ibrutinib), new anti-CD20 monoclonal antibodies (ofatumumab, obinutuzumab), BCL-2 inhibitors (venetoclax), immune-checkpoint inhibitors (e.g., PD1-PDL1/PDL2 pathway inhibitors nivolumab, pidilizumab, or pembrolizumab), and EZH2 inhibitors, among others (107-116). Some of these new molecules (e.g., ibrutinib, lenalidomide) have been shown to be more effective in a specific DLBCL subtype (113,117). Clinical trials of new drugs in tFL should include an analysis of the COO. Unfortunately, patients with transformed lymphoma have been excluded from most of these clinical trials. Some of the drugs (e.g., ibrutinib, idelalisib, venetoclax) revert the bad prognosis of *TP53* alterations in different B-LPDs, providing a therapeutic option for these patients and, thereby, the possibility of reducing the risk of transformation (118).

In summary, increasing knowledge of the biology and treatment of FL and DLBCL patients, which translates into new therapeutic strategies, contrasts with the limited advances in or understanding of tFL. It is expected that a better knowledge of the biology of tFL will lead to well-designed clinical trials including or focusing on tFL.

Conclusions and remarks

The implementation of new tools has broadly improved our knowledge of the biology of NHL in general, and of tFL in particular. However, genetic studies on tFL are generally targeted to certain genes or regions. There is a lack of studies that evaluate the predictive role of multiple genes such as the m7-FLIPI for development of transformation. Moreover, most studies do not consider the variety of genetic alterations (CNAs, translocations, mutations) in the same cohort, or consider these along with the composition of the microenvironment, or other potential biological markers (SNPs, HLAs). Furthermore, the studied tFL cohorts have not distinguished whether transformation has presented as a first or subsequent event, which could misinterpret the role of certain gene alterations.

A comprehensive study integrating the results of the previous studies in large-scale series of clonally related FL-tFL sample pairs would help improve our knowledge of the developmental pathways leading to transformation. Consequently, it would be feasible to develop an index based on the most important biological and clinical factors that accurately stratify patients who will transform, distinguishing them from those who will relapse, since they require different therapeutic strategies. Furthermore, identifying patients who will never transform or progress will help individualize treatments in order to reduce toxicity and improve their quality-of-life.

Due to the limited availability of biopsy material for determining histological criteria, there is an unmet need to establish alternative but precise criteria to clearly discriminate transformation from FL progression. Effort needs to be directed towards this objective: a prospective study including clinical, biological, and imaging criteria would enable a specific and sensitive index to be developed. It would also allow the more accurate estimation of the real incidence of FL transformation, and provide an optimized definition of tFL.

The role of treatment strategies for tFL, including new agents, auto-SCT, and allo-SCT, must be determined from large-scale studies. To this end, common efforts of cooperative international groups (e.g., the ARISTOTLE project) could clearly help fulfill these unmet needs.

The hope is that, in the future, biological knowledge will enable personalized approaches to be developed to treat tFL, and/or patients with FL, in such a way as to avoid transformation or refractoriness.

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