Transformed follicular lymphoma

Thais Fischer¹ · Natalia Pin Chuen Zing¹ · Carlos Sergio Chiattone² · Massimo Federico³ · Stefano Luminari³,4

Abstract Follicular Lymphoma (FL) is the second most common type of non-Hodgkin lymphoma and is considered to be the prototype of indolent lymphomas. Histologic transformation into an aggressive lymphoma, which is expected to occur at a rate of 2 to 3% each year, is associated with rapid progression, treatment resistance, and poor prognosis. Recent modifications to the physiopathologic mechanism of transformed follicular lymphoma (t-FL) have been proposed, including genetic and epigenetic mechanisms as well as a role for the microenvironment. Although t-FL is considered a devastating complication, as it is associated with treatment-refractory disease and a dismal outcome, recent data in the rituximab era have suggested that not only is the prognosis less severe than reported in the previous literature but the risk of transformation is also lower. Thus, this study aimed to review the most recent research on t-FL in an attempt to better understand the clinical meaning of transformation from FL to diffuse large B cell lymphoma (DLBCL) and the impact of current treatment strategies on the curability of this intriguing subentity of lymphoma.

Keywords Lymphoma · Lymphoma, follicular · Lymphoma, non-Hodgkin · Lymphoma, large B cell · Diffuse · Diffuse large cell lymphoma · Epigenetic · Prognosis, cell neoplastic transformation · Cell transformation, neoplastic · Genetic transformation

Introduction Follicular Lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL) in the USA and Europe (10–20% of NHL), with approximately 15,000 newly diagnosed cases per year [1, 2]. It is considered the prototype of indolent lymphomas, has an equal distribution between men and women, and has a median age of 65 years at presentation [3–5]. These patients are frequently diagnosed at an advanced stage, and bone marrow (BM) involvement is present in approximately 50% of the cases. Translocation t(14;18)(q32;q21) places the antiapoptotic BCL-2 oncogene under the control of the immunoglobulin (Ig) heavy-chain enhancer and is a genetic hallmark of FL. The presence of this translocation has been used recently to support diagnosis and to monitor response to therapy [3, 6–12]. The occurrence of relapse characterizes the natural history of FL, which has a shorter duration of remission at every recurrence. Although major improvements have been achieved with therapy, this type of lymphoma is still considered an incurable disease. Recently, however, the natural history of the disease has been measured in decades, and a high proportion of FL patients will die due to reasons other than lymphoma progression [3, 4, 13, 14].

In spite of the improvement in the diagnostic accuracy and the efficacy of chemoimmunotherapy regimens, progression and transformation still occur [15]. The 3-year progression-free survival rate after chemoimmunotherapy is approximately...
and transformation responsible for lymphoma persistence, resistance, recurrence, existence of a common progenitor cell (CPC) that may be this relationship. In addition, other authors have suggested the segments, and common somatic mutations might contribute to the presence of the same immunoglobulin, immunoglobulin unknown [29]. Therefore, the objective of this review is main incompletely understood, and many questions remain logical and clinical events that characterize transformation re-described more than 65 years ago by Gall and Mallory, the biology, diagnosis, prognostic factors, and treatment. This ef-Aims to offer a better understanding of HT in FL, and this t(14;18) translocation sufficiently lengthens the consequence of treatment effectiveness.

Physiopathology of the transformation process

To better understand the biology of the transformation process, it is important to rely on the transformation concept. Therefore, HT refers to the evolution of a clinically indolent NHL (i.e., FL) into a clinically aggressive lymphoma (i.e., DLBCL, Burkitt lymphoma, gray zone lymphoma or lymphoblastic lymphoma, and other high-grade B cell lymphomas). In addition to FL, transformation can also occur in other subtypes of indolent lymphoma, such as marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia, and lymphocyte predominant Hodgkin lymphoma [14, 30].

Another important concept is that transformation is not frequently a “linear” process that involves the subsequent accumulation of oncogenic mutations. In contrast, a “nonlinear” transformation, which begins with an immature precursor, seems to be the rule rather than the exception [11] (Fig. 1). Despite the existence of these two mechanisms, they are not mutually exclusive and may be independently activated in the same patient or even in the same lymph node [31] (Fig. 2). Genetic alterations that are shared between FL and t-FL are evidence of this clonal relationship [18, 31].

Previous studies have already demonstrated that t-FL most commonly arises from immature CPCs and that these cells may remain in BM niches during treatment, where they acquire new genomic lesions [32–34]. Even though the existence of CPCs has not been physically demonstrated, it can be postulated, and the genetic lesions that are shared between FL and t-FL may help in the understanding of the sequence of events [18]. This theory of cancer-initiating cells has been previously described in epithelial cell cancers and is associated with the cell’s ability to self-renew, proliferate, and gain resistance to chemical or physical insults [31, 32].

Recent genetic studies have contributed to the expansion of the knowledge associated with transformation; however, the sequence of successive genetic hits or simultaneous alterations that produce an aggressive phenotype remains unclear [33]. The most common genetic lesions in FL and t-FL may be classified into the following cell processes (Fig. 3):

- Programmed cell death–apoptosis: t(14;18) translocation places the antiapoptotic BCL-2 oncogene under control of the immunoglobulin (Ig) heavy-chain enhancer (IGH/BCL-2) [10, 34]. This is a typical genetic lesion in FL; however, this lesion alone seems to be insufficient for the induction of clinical disease, which is reinforced by its occurrence in healthy individuals [9, 35–37]. Moreover, this t(14;18) translocation sufficiently lengthens the lifespan of cells to permit the acquisition of secondary alterations as well as other genetic mutations [38]. Mutated BCL-2 is seen at a higher frequency in t-FL, which thus reaffirms the importance of the accumulation of secondary alterations in the genesis of lymphoma [8]. It is important to emphasize that BCL-2 translocation has been always described in FL and t-FL, and its occurrence ensures its participation in clonal precursor expansion [18].

Similar to BCL-2 translocation, CREBBP expression, mutation, or the occurrence of some other alteration has been described to occur at a high frequency. Each has a uniform representation and functions as a “driver” in t-FL pathology. On the contrary, MLL2 has a variable representation, given its plausible function as an “accelerator” [38]. Therefore, the presence of alterations in MLL2 gives a selective advantage to a given clone compared with other competing clones [38].

The CREBBP and MLL2 genes were described as the most commonly affected genes in clinical FL. Alterations in these genes are present at diagnosis and are never lost during progression or transformation, which also suggests that they are early acquisitions by CPCs [18, 39].
- Cell cycle and DNA damage response: one of the most important events in the transformation process is CDKN2A/B loss, which is associated with inactivation
of the p53 tumor suppression gene (DNA damage response) and with expression of p16 protein (part of cycle cell regulation). These cause changes in G1 phase of the cell cycle and result in genomic instability [18, 40].

Those alterations are not typically seen in FL but are the most common aberrations in t-FL, which suggests that they are specifically acquired during transformation [18, 19].

- MYC aberration: MYC activation through copy number gain, amplification, deletions, or loss of heterozygosity is another important cell disruption in t-FL. It provides multiple advantages to lymphoma cells and supports cell growth, metabolism, and genetic instability [18, 41]. MYC aberrations are rare at diagnosis, but are frequently found at the time of progression as well as during transformation. The acquisition of MYC activation in FL in which BCL-2 translocation has already occurred, characterizes “double-hit” lymphoma. According to some authors, this is the second most common genetic alteration in t-FL [18, 41–43].

In addition to that, BCL-6 translocation, which may also occur during transformation, characterizes “triple-hit” lymphoma (MYC/BCL-2/BCL-6) and confers an even worse prognosis [41, 44].

It is important to emphasize that MYC alterations associated with FL might have a different origin than BL, considering that in FL, this alteration results from the cooperation between BCL-2 and the deregulation of activation-induced cytidine deaminase (AID), while in BL, it is a consequence of t(8;14) translocation [45].

- Other lesions (non-phase-specific lesions):

  The following alterations have heterogeneous contributions to lymphoma transformation but are still the focus of some studies [18]: (a) TNFRSF14 [14, 18], member of TNF receptor superfamily, which functions in T cell signaling and is disrupted in 56.4% of t-FL cases; (b) STAT6 [18], DNA-binding transcription factor implicated in IL4- and IL3-mediated responses and is mutated in 23.1% of t-FL cases; (c) CARD 11 and
CD79B [18], alters signaling pathway responses involved in the engagement of BCR and CXCR4 and is present in 10.3% of the t-FL cases; TNFAIP3 [18], regulator of NFkB, lost in 15% of t-FL cases; and (d) deregulation of immune responses HLA class 1 locus and complement (CD58) [46].

Another mechanism that has been extensively studied is the role of somatic hypermutation (SHM) and class-switch recombination of the immunoglobulin gene in the B cell lymphomagenesis [47, 48]. These are specifically important in lymphomas in which the germinal center is the source of the cell of origin [47, 48]. Accumulating evidence has suggested that lymphoma-associated translocations and the activation of other oncogenes are initiated by AID [49].

The mistargeted activity of AID is associated with genetic instability, cell-cycle arrest, and apoptosis [45]. It is postulated that histone/chromatin modification enzymes (active in FL) may permit non-physiologic genomic regions to be accessed by AID, which leads to the generation of secondary genetic mutations. The high expression of AID has been described to be associated with t-FL [8, 18].

Regarding the genetic signature, t-FL appears to be closely related to germinal center B cell (GCB)-like DLBCL, as they share common features such as BCL-2 rearrangements, REL amplifications, and mutations in EZH2, GNA13, and TNFRSF14. On the contrary, t-FL shows CDKN2A/B deletions, STAT6 mutations, ARID1A mutations, and FAS mutations/deletions that are rarely seen in de novo DLBCL, which demonstrates its specificity [18, 50].

It is important to emphasize that the majority of genetic aberrations that are typical of t-FL can also be observed at a lower frequency in indolent FL [18, 33]. This finding suggests that a single alteration may not be sufficient to drive transformation and that possibly, a major disruption in the molecular machinery is needed.

Additionally, the selective pressure for FL to undergo transformation remains incompletely understood. Carlotti et al. [31] identified clonal evolution in patients who were exposed to different types of treatment, including radiotherapy, chemotherapy, and the “watch and wait” regimen. Pasqualucci et al. [18] also described that mutations do not occur only as a consequence of treatment, considering that untreated patients had been diagnosed with transformation. Therefore, the mutation load should also be considered a complex entity that does not simply reflect a consequence of the treatment or chemotherapy [18, 31].

The complex clonal panorama of FL is consistent with its variable and unpredictable clinical behavior [38]. FL tumor cell populations and subpopulations may undergo multiple “transformations” during their lifespan, and it is also probable that they acquire different mutations and presumably distinct sensitivities to therapies [11, 18, 31].

**Diagnosis**

A key problem in t-FL lies with its definition, which relies on the histologic evidence of DLBCL in patients with a previous or concomitant history of FL. Biopsy is still considered the gold standard that is used to document the event [14, 21, 51, 52]; however, in some cases, clinical aspects can be considered convincing enough to conclude that transformation has occurred [11, 19, 51, 53]. Notably, many of the initial reports on t-FL were based on the clinical definition of transformation, while the most recent data rely on a stricter pathological definition. The comparison between the cohorts is shown in Table 1.

The diagnosis of t-FL may be separated into the following aspects:

**Clinical**

Higher-grade transformation should be suspected in every FL patient who presents with progression and the fast growth of
lymph nodes, new extra-nodal sites (i.e., those in the central nervous system, liver, and bone), the development of B symptoms, new hypercalcemia, or the sudden rise in lactate dehydrogenase (LDH). In addition, most patients present with advanced disease (stage III/IV or bulky stage I/II disease) although limited disease may also be associated with transformation [8, 11, 24, 51, 54]. Additionally, time until progression is important, considering that it might be associated with early progression (< 2 years after the start of rituximab-based regimens) and transformation. Mozessohn et al. described that transformation was documented in 36.3% (8/22) of cases of early progression [55].

Regarding time to transformation, it has been shown that patients who are diagnosed with transformation early (i.e., at the time of diagnosis or after the first 2 years of follow-up) have better outcomes. Thus, transformation that occurs within 18 months seems to be the worst scenario, as patients exhibit a shorter survival [19, 21].

**Histopathology**

FL is composed of cells that resemble normal germinal centers, while aggressive lymphomas are characterized by the diffuse proliferation of large cells that efface the follicular architecture [14, 56]. Biopsy with immunohistochemical examination remains the standard that is used to confirm t-FL. The majority of the transformations show the presence of DLBCL (93%) or BL (7%) [51]. Rare histotypes including B lymphoblastic leukemia, plasmablastic lymphoma, and high-grade B cell lymphoma—NOS/with MYC and BCL-2 and/or BCL-6 translocations have also been reported [57–59].

At the time of transformation, 30% of DLBCL cases are BCL-6-positive, and more than 10% demonstrate translocation of MYC and BCL-2 in the germinal center [60]. Furthermore, while FL has a low proliferative index, t-FL usually has high Ki-67 expression (staining and transferrin receptor-related protein), which indicates a high proliferative index [56].

The WHO classification [57] also subdivides FL into four grades based on histology (number of centroblasts). Grades 1, 2, and 3A are considered consistent with the morphological spectrum of FL, while grade 3B is considered to be closely related to de novo aggressive lymphoma [57]. Koch et al. analyzed these groups separately and showed that a large proportion of grade 3A FL harbored areas that resembled FL grades 1/2. In contrast, grade 3B FL rarely coexists with grade 1/2 or 3A FL and was found to be mostly associated with diffuse growth (DLBCL), which indicates a divergent pathogenesis [61]. This last sub classification, however, seems to be important since grade 3A has been linked to an increased risk of transformation [41, 62, 63].

### Table 1

<table>
<thead>
<tr>
<th>First author, year (database)</th>
<th>N patients (database)</th>
<th>N patients (database)</th>
<th>Median time to transformation (months)</th>
<th>Median OS after transformation (years)</th>
<th>Overall transformation rate (median time in years, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastion, 1997</td>
<td>220</td>
<td>211</td>
<td>100 (47)</td>
<td>52 (24)</td>
<td>52 (24)</td>
</tr>
<tr>
<td>Giné, 2006</td>
<td>276</td>
<td>30</td>
<td>1 Not used</td>
<td>1 Not used</td>
<td>1 Not used</td>
</tr>
<tr>
<td>Montoto, 2007</td>
<td>325</td>
<td>600</td>
<td>Not used</td>
<td>Not used</td>
<td>Not used</td>
</tr>
<tr>
<td>Al-Tourah, 2008 (Lymphoid Cancer)</td>
<td>600</td>
<td>600</td>
<td>Not used</td>
<td>Not used</td>
<td>Not used</td>
</tr>
<tr>
<td>Link, 2013</td>
<td>38 (15)</td>
<td>631</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Bains, 2012</td>
<td>34 (25)</td>
<td>342</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Wagner, 2013 (National Lymphoma Care)</td>
<td>579</td>
<td>579</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Ban-Hoefen, 2013 (NCCN)</td>
<td>118</td>
<td>118</td>
<td>83 (45)</td>
<td>60 (45)</td>
<td>83 (45)</td>
</tr>
<tr>
<td>Sarkozy, 2016 (PRIMA)</td>
<td>1018</td>
<td>1018</td>
<td>Not described</td>
<td>Not described</td>
<td>Not described</td>
</tr>
</tbody>
</table>
Moreover, it is already established that t-FL cannot be morphologically distinguished from de novo DLBCL, and similarly, can be divided into molecular subtypes [41]. As expected, Kridel et al. and Bousaka et al. reported that the majority of t-FL is of the GCB phenotype and that the minority can be identified as the activated B cell (ABC) type [41, 64]. They also reported that the exceptional t-FL ABC subtype is BCL-2-negative, CD10-negative, and IRF-4-positive. These rare molecular alterations tend to co-occur to delineate a distinct molecular pathway and possibly a different entity [41, 65].

Another histological feature of t-FL is that FL and DLBCL can co-occur in the same lymph node and be characterized by a composite histology. This finding implies but does not confirm early transformation. Some authors suggest at least a 6-month interval between the initial FL and the DLBCL diagnosis to unequivocally define it as a transformation [14, 53].

**Imaging**

On the one hand, computed tomography (CT) can help to determine the size of lymph nodes, but this type of scan does not show the metabolic activity of the disease [66]. On the other hand, [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET-CT) has emerged as a powerful functional imaging tool for staging and response assessment in Hodgkin lymphoma and DLBCL [13, 67, 68].

The Lugano classification recently included PET in the response assessment for indolent lymphoma subtypes, such as FL [69, 70]. Metabolic response, as defined by PET-CT, was demonstrated to be a strong predictor of OS and PFS after R-induction therapy, and this risk was found to be independent of the FLIPI and FLIPI-2 scores [71].

18F-FDG avidity was also described to be correlated with proliferation levels (Ki-67 expression). A high-standardized uptake value (SUV) on PET-CT in FL may suggest aggressive disease and possible transformation into DLBCL [72]. Studies of indolent lymphomas have reported that an SUV > 10 could predict aggressive lymphoma histology with 80% certainty, an SUV > 13 with 90% certainty and an SUV > 17 with 100% certainty [73, 74]. Moreover, patients with DLBCL and t-FL showed similar SUV rates [11, 66]. Noy et al. described that the SUVs in biopsy-proven sites of transformation had a median value of 12 but ranged widely from 3 to 38. Although the majority of the transformations were associated with a high SUV in this study, many were not. Therefore, transformation might be suspected but not proven with PET-CT. These authors also reaffirmed the recommendation of biopsies of sites with the highest FDG uptake [75].

More importantly, according to this new concept of PET-directed biopsy, it is likely that in the near future, an increasing number of t-FL will emerge; however, the clinical meaning of the discovery of hidden t-FL is not clear and warrants future investigation.

**Risk of transformation**

Histological transformation, which remains a rare event in the natural history of FL, ranges from 4 to 27% (Table 1), and the identification of reliable predictors of transformation at the time of FL diagnosis remains a challenge. The identification of patients who are at high risk for transformation would allow appropriate monitoring, effective treatment, and the development of potential novel therapeutic approaches. Evidence from the literature regarding risk factors of t-FL can be divided into clinical, therapeutic, pathological, and genetic features.

**Clinical and treatment-related risk factors**

Until now, clinical factors have been the most important features that are used to predict the risk of transformation [15] (Table 2). The items already described are: elevated beta-2-microglobulin levels, high IPI, high FLIPI, and advanced stage (III and IV) [24, 51, 53, 76]. The most recent studies, which were conducted during the rituximab era, described LDH, anemia, an Eastern Cooperation Oncology Group (ECOG) performance status > 1, and high FLIPI as independent risk factors for transformation [15, 19, 21, 77]. Furthermore, Conconi et al. affirmed the importance of bulky mass and extra-nodal disease, while Sarkozy et al. also suggested B symptoms and histological grade 3A as predictors of transformation [15, 77].

With regard to time as a risk factor, some authors have described that transformation seems to be an early event in the natural history of FL, while progression shows a linear risk over time [15, 53]. Sarkozy described that more than half of HTs in FL were documented during the first year after induction; Link et al. reported a reduction in the risk of HT after 5 years of follow-up [15, 19, 53]. In contrast, other groups have suggested that the risk of transformation over time appears uniform, at least during the first 15 years of follow-up [51, 53]. Until now, it has not been possible to conclude whether the risk of HT is time-dependent since studies have used different patterns for follow-up, inclusion criteria, and treatments [15].

Different treatment approaches have also been evaluated as risk factors for HT such as expectant management, number of therapies, anthracycline use, and rituximab use. Considering that “watch and wait” is a first-line therapy for FL, Montoto et al., Link et al., and Wagner-Johnston et al. have described that the transformation rates were higher among patients who were primarily observed than those who were initially treated. On the contrary, Conconi et al. found that the “watch and wait” approach was associated with a lower risk of transformation, [19, 21, 24, 77] while Ardeshna et al. in a randomized trial, observed that the risk of transformation was similarly low between the two study arms (observation vs. rituximab) [78].
With respect to treatment outcomes, patients were described to be at a higher risk if they did not achieve complete response at the end of induction therapy [53, 76]. However, Sarkozy et al. described that the quality of the response did not impact the risk of transformation [15]. In addition, no consensus exists in the literature regarding the use of anthracycline. Some authors have suggested no correlation [15, 19, 21], while others have reported lower risk with the use of this drug [51].

Rituximab, as part of induction therapy and based on either retrospective [19, 21, 51, 79] or clinical trials data [15], has been suggested or reported to reduce the risk of transformation, especially when used as a maintenance therapy. These latest studies clarified previous questions with respect to the benefits of rituximab [78].

Pathological and genetic risk factors

Pathological and genetic factors are emerging as novel predictors of risk, but the literature remains contradictory in some aspects, and these new biomarkers need to be validated in large prospective cohorts [33].

Considering the pathological findings, the grading of FL has been associated with survival and transformation. Despite this, high-grade FL has historically been associated with poor survival [57], but the most recent studies have shown a better outcome for grade 3A/B FL [80]. Grade 3A has also been linked to an increased incidence of transformation in some studies, and both 3A/B have been associated with certain molecular findings that have been described as risk factors for transformation, such as BCL-6 translocation, absence of prototypical BCL-2 translocation, and/or positive expression of IRF4 [41, 62, 63].

The immunohistochemical assessment of IRF4 warrants special attention since it is associated with a worse prognosis, poor progression-free survival (PFS), high proliferation rates, and transformation [41, 63, 81]. This protein deserves further validation but has a plausible potential to predict transformation [33].

Genetic features represent another means to predict transformation risks. The alterations that have been described in the literature thus far are chromosomal changes (i.e., segmental deletions within 1p and 6p or gains involving 2, 3q, and 5) [82–85], somatic gene mutations such as those in the BCL-6 gene [86] and BCL-2 gene [8, 87] and MYC rearrangements [43]. Other alterations include the loss of heterozygosity or mutations in Tp53 [88, 89], deregulation of MDM2 (key p53 regulator) [88], and inactivation of CDKN2A/B by deletion mutations and hypermethylation [90].

### Table 2  Risk factors for transformation

<table>
<thead>
<tr>
<th>First author, year (database)</th>
<th>Risk factors at diagnosis</th>
<th>Other risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before rituximab era</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bastion, 1997</td>
<td>High B2microglobulin;</td>
<td>Less than CR at the end of treatment induction</td>
</tr>
<tr>
<td></td>
<td>low albumin levels</td>
<td></td>
</tr>
<tr>
<td>Giné, 2006</td>
<td>Grade 3 histology;</td>
<td>Less than CR at the end of treatment induction</td>
</tr>
<tr>
<td></td>
<td>nodal areas &gt; 4;</td>
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<tr>
<td></td>
<td>high LDH;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>high B2microglobulin;</td>
<td></td>
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<tr>
<td></td>
<td>high IPI;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>high FLIPI</td>
<td></td>
</tr>
<tr>
<td>Montoto, 2007</td>
<td>Advanced stages;</td>
<td>Expectant management as initial therapy</td>
</tr>
<tr>
<td></td>
<td>high FLIPI;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>high IPI</td>
<td></td>
</tr>
<tr>
<td>Al-Tourah, 2008 (Lymphoid Cancer-British Columbia)</td>
<td>Advanced stage</td>
<td>Multiples lines of therapy alkylator with purine analogue</td>
</tr>
<tr>
<td>After rituximab era</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conconi, 2012</td>
<td>Bulky;</td>
<td>R-chemo increased the risk</td>
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<tr>
<td></td>
<td>extranodal disease</td>
<td></td>
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<tr>
<td>Link, 2013</td>
<td>LDH;</td>
<td>Expectant management as initial therapy</td>
</tr>
<tr>
<td></td>
<td>anemia (Hb &lt; 12);</td>
<td></td>
</tr>
<tr>
<td>Wagner-Johnston, 2015 (National Lymphoma Care)</td>
<td>ECOG &gt; 1; extranodal sites &gt; 1</td>
<td>Expectant management as initial therapy</td>
</tr>
<tr>
<td>Sarkozy, 2016 (PRIMA)</td>
<td>ECOG;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anemia;</td>
<td></td>
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<tr>
<td></td>
<td>high LDH;</td>
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<td></td>
<td>B symptoms</td>
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<tr>
<td></td>
<td>high FLIPI score;</td>
<td></td>
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<tr>
<td></td>
<td>grade 3A</td>
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CR complete response, LDH lactate dehydrogenase, IPI International Prognostic Index, FLIPI Follicular Lymphoma International Prognostic Index

1 Independent factors in multivariate analysis
As has been described previously, other individual genes have also been studied. Consequently, Pastore et al. proposed a risk model (m7-FLIPI) that combines the mutational status of seven genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11) into a predictive score that also includes the FLIPI and ECOG performance status. This model introduces a new concept for risk stratification in FL and is a promising approach that may be used to identify the subset of FL patients at highest risk for treatment failure. Although no data have been generated regarding transformation in this risk model, m7-FLIPI may be a promising marker that can be used in risk stratification for transformation [33, 91].

Treatment

Treatment and outcome in historical series

In initial studies, the outcome of t-FL patients was very poor, with a median OS of approximately 1 or 2 years [24]. However, the majority of published studies were conducted in the pre-rituximab era. Most recent studies have confirmed the improvement of OS in patients with t-FL in the rituximab era (as part of induction and post-transformation therapy) [19, 53, 79].

The study conducted by Link and colleagues found that in 60 out of 631 patients with biopsy-proven t-FL, the OS rate was 73% at 5 years after treatment with rituximab-based chemotherapy [18]. The results seen in patients with early-stage FL (treated with radiotherapy only) who experienced transformation were equivalent. The 3-year OS post-transformation was 87 vs. 38.5% for R-chemotherapy and chemotherapy alone, respectively [92].

The R-CHOP regimen is still currently considered a good option with which to treat t-FL, especially anthracycline-naïve patients. It is known that some t-FL cohorts have responded extremely well with only R-chemotherapy [19, 21, 93]. Additionally, Link et al. showed that after transformation, the outcomes were indistinguishable when compared with those of patients with de novo DLBCL and anthracycline-naïve transformed FL [19].

Therefore, the role of autologous stem cell transplantation (ASCT) in the rituximab era does not seem to be mandatory [19]. Wagner-Johnston et al. reported that only a few t-FL patients have undergone ASCT, which reaffirms this idea [21, 94].

Despite the controversy surrounding ASCT, this therapy can be considered part of the treatment for eligible patients with t-FL, especially those who have already been exposed to anthracyclines. In studies from the pre-rituximab era, in patients with chemosensitive transformed lymphoma, the 5-year OS and PFS rates after ASCT were 51 and 30%, respectively, which suggests a long-term benefit of this management strategy [95].

With regard to ASCT in the rituximab era, this approach has been shown to improve the outcomes of t-FL in some studies; Table 3 summarizes the major studies that have been conducted in the rituximab era. The Canadian Bone Marrow Transplant Group (CBMTG) showed better outcomes (OS and PFS) for those treated with additional ASCT, even though this difference was modest at 5 years (OS 65% with ASCT; 61% with chemotherapy; \( p < 0.001 \)) [96].

Ban-Hoefen et al. (NCCN database) also suggested a benefit of ASCT in the rituximab era. The 2-year OS was 74% for patients who underwent ASCT, while for those who did not, the 2-year OS was 59%. This group also emphasized that patients who were chemotherapy-naïve prior to ASCT seemed to achieve better results [22].

For post-ASCT relapses, a few options exist including novel regimens (in the context of clinical trials) and possibly salvage therapy with allogeneic transplantation (AlloSCT) for highly selected patients [97, 98]. However, AlloSCT in t-FL has not been well-studied, and studies to date have been........

<table>
<thead>
<tr>
<th>First author, year (database)</th>
<th>ASCT or allo</th>
<th>Number of patients</th>
<th>Median age at transplantation (years)</th>
<th>OS, (%)</th>
<th>PFS or EFS, (%)</th>
<th>Median follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, 2009 (ASCT)</td>
<td>ASCT</td>
<td>25</td>
<td>57</td>
<td>3 years, 63</td>
<td>OS, (%)</td>
<td>3 years, 64</td>
</tr>
<tr>
<td>Reddy, 2012 (ASCT)</td>
<td>ASCT</td>
<td>12</td>
<td>61</td>
<td>5 years, 91.7</td>
<td>OS, (%)</td>
<td>5 years, 73.3</td>
</tr>
<tr>
<td></td>
<td>Allo</td>
<td>23</td>
<td>52</td>
<td>5 years, 53.9</td>
<td>OS, (%)</td>
<td>5 years, 43</td>
</tr>
<tr>
<td>Ban-Hoefen, 2012 (ASCT)</td>
<td>ASCT</td>
<td>18(^1)</td>
<td>58</td>
<td>2 years, 82</td>
<td>OS, (%)</td>
<td>2 years, 59</td>
</tr>
<tr>
<td>(National Comprehensive Cancer Network-Database)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS or EFS, (%)</td>
<td></td>
</tr>
<tr>
<td>Villa, 2013 (ASCT)</td>
<td>ASCT</td>
<td>97</td>
<td>56</td>
<td>5 years, 65</td>
<td>OS, (%)</td>
<td>5 years, 55</td>
</tr>
<tr>
<td>(Canadian Bone Marrow Transplant Group)</td>
<td></td>
<td>22</td>
<td>48</td>
<td>5 years, 46</td>
<td>OS, (%)</td>
<td>5 years, 46</td>
</tr>
</tbody>
</table>

*OS overall survival, PFS progression-free survival, EFS event-free survival
1 Included two patients with marginal zone lymphoma and six patients did not received rituximab as an induction therapy*
performed in small cohorts and have involved short follow-ups and significant transplant-related mortality. Reddy et al. compared AlloSCT to ASCT and observed an important difference between these groups. The 5-year post-transplant OS was 53 vs. 91.7%, while the PFS was 43 vs. 73.3%, for the AlloSCT and ASCT groups, respectively. However, Villa et al. (Canadian Bone Marrow Transplant Group) described an OS of 46 vs. 65% and a PFS of 46 vs. 55% for the AlloSCT and the ASCT groups, respectively, at 5-year post-transplant [96, 99]. Therefore, the AlloSCT series demonstrated an inferior result compared with that of ASCT, which was due in part to high treatment-related mortality (35 vs. 10% at 5 years, respectively) and also to heavily pre-treatment conditions [100]. On the contrary, the risk for disease relapse at 5 years was lower in the AlloSCT group, but it is important to consider that those patients comprised a highly selected group [22].

Current management

Our approach to the management of t-FL begins with the correct diagnosis, which reinforces the importance of biopsy at the time transformation is suspected. A PET-CT-guided biopsy may be useful in this scenario. After the diagnosis is confirmed, subsequent decisions would be made based on the age, comorbidities, and performance status of the patient. In both young and old patients who are physically fit, it is important to clarify whether they have been exposed to previous treatments with anthracycline-based regimens. If patients were previously exposed, they should undergo salvage chemotherapy (platinum-containing chemotherapy) and ASCT; however, if the patients are anthracycline-naive, they should receive R-CHOP. ASCT can be discussed, but it is not mandatory. For older unfit patients who have received anthracycline or are too frail to tolerate full-dose chemotherapy, the regimens suggested are mini-CHOP [101] or non-anthracycline-containing regimens such R-GCVP [102]. Clinical trials are strongly encouraged in this situation, especially with the new available single-agent lenalidomide [103], venetoclax [104], ibrutinib [105], and idelalisib [106, 107].

Novel regimens

Novel agents have also been investigated in t-FL. In a phase 2 study, lenalidomide showed an overall response rate of 57%, with a median response duration of over 1 year in t-FL patients [103]. Specific inhibitors that target Aurora A kinase (alisertib) [108], Bruton tyrosine kinase (ibrutinib) [105], the δ isoform of phosphatidylinositol 3-kinase (idelalisib) [106, 107], and BCL-2 protein (GDC-0199/ABT199—venetoclax) [104] are currently being investigated in both indolent and aggressive lymphomas. These novel agents seem to have a significant impact on the outcome of t-FL patients.

Conclusion

HT of indolent lymphoma has been randomly studied over the years, and even now, many are concerned considering the morbidity and mortality rates of t-FL. The incidence varies among different series and according to different definitions of HT and treatment approaches. Most available data are derived from retrospective studies, whereas risk factors and therapeutic strategies are not completely standardized. Furthermore, the most recent data suggest that rituximab (induction or maintenance) is associated with better outcomes and lower risks of transformation. Further studies are still necessary to clarify the biology of transformation as well as the identification of biomarkers, which might be future potential targets for individualized treatment of t-FL.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

References


