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Transformed Follicular Lymphoma: Not all fit in one

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Abstract
Follicular Lymphoma (FL) is the second most frequent non-Hodgkin lymphoma accounting for approximately 10-20% of all lymphomas in Western Countries. Histologic transformation (HT) is a frequent event in the clinical course of patients with indolent lymphoma that is often accompanied by a dramatic change in the clinical features of the disease towards a more aggressive course. Although the transformation of Follicular Lymphoma (tFL) was described several decades ago, there is a strong need for a better understanding of both the dynamics of the tumor clonal evolution and the genetic events leading to ()transformation. In addition, the management of patients with tFL is challenged by the heterogeneity of the previous treatments. The present review describes the state of art of tFL, outlining recent advances in the understanding of genetic basis and the evolutionary process governing the initiation and persistence of tumor evolution. It will be also addressed the key questions pending on this incurable disease, such as a lack of a standard therapeutic strategy for tFL patients as well as its outcome in the Rituximab (R) era.

Keywords: Non Hodgkin Lymphoma, Follicular Lymphoma, Transformed Follicular Lymphoma, immunochemotherapy

Introduction

Follicular Lymphoma is defined by the World Health Organization (WHO) classification (Swerdllow SH, Campo E 2008) as a "neoplasm composed of follicle center (germinal center – GC) B cells, typically both centrocytes and centroblasts which usually has at least a partially follicular pattern". FL arises then by a malignant transformation of the normal germinal center B cells and therefore carries the characteristics of centrocytic/centroblastic morphology.
The disease is usually characterized by an indolent clinical course, excellent response to initial therapy with frequent relapses and shorter duration responses to salvage therapy.
At present, thanks to the advances in the treatment of FL, the disease is moving from an incurable to curable one. Regarding the management chemoimmunotherapy – usually followed by Rituximab maintenance – is the standard of care; whereas patients with nonbulky or asymptomatic disease may be treated with Rituximab monotherapy or simply observed (Jonathan W Friedberg et al. 2009). Although many asymptomatic patients with low-volume disease may not require early therapy and can be observed, the majority of patients will lastly experience disease progression and will need therapy during the course of the disease. In particular, some patients have long-term remission lasting years, others have a rapidly progression of the disease and develop treatment resistance and/or transformation to aggressive lymphoma (Link et al. 2013; S. M. Smith 2013). Priorities in goals of care include avoiding relapses, transformation to aggressive subtypes and death.

In the past, approximately 25% of cases transform to aggressive disease, mostly Diffuse Large B-cell Lymphoma (DLBCL),with a very poor prognosis (Montoto et al. 2007). The histologic changes seen in patients with HT are, in the great majority of cases, accompanied by a change in the clinical features of the disease towards a more aggressive course (Montoto 2015).

More recently, contradictory data are emerging with respect to the impact of initial treatment on the risk of transformation (Montoto 2015), In particular, the adoption of Rituximab in first line therapy seems associated with a lower risk of transformation. Therefore, decisions on the management of tFL patients come from extrapolation data of retrospective studies or from prospective trials in DLBCL, as this is the commonest transformed lymphoma.

The present review will be focused on the state of art of tFL and will try to address pending questions about this condition.

Definition of tFL

Definition of tFL is still a great challenge as it varies among different series. Over the past years, definition of transformation have been largely varying from "*an histological features of DLBCL as opposed to cytologic progression with an increase in the proportion of large cells (from grade 1/2 to grade 3 FL)*" (Montoto et al. 2007) to "*refractory/recurrent disease with either clinical or pathologic diagnosis of transformed lymphoma*" (Link et al. 2013); passing through other definitions. The main issue in considering a unique definition is the fact that transformation is diagnosed in different series based on cytological samples, on histologic samples or in some cases on clinical grounds alone. Indeed diagnosis should be based on biopsy or adopting clinical criteria in the cases in which it is not possible to obtain a biopsy, either because of the poor performance status of the patient or because of progression of the disease in inaccessible areas (Montoto and Fitzgibbon 2011). In 2008, Al-Tourah et al. (Al-Tourah et al. 2008) published clinical criteria to define transformation: a rapid discordant lymphadenopathy growth, unusual sites of extranodal involvements, a sudden rise in the LDH level, hypercalcemia, or presence of new B-symptoms.

Incidence, Prognosis and Outcome of tFL

Historically, transformation was largely considered a catastrophic event. Although the clinical course of FL patients may span more than ten years, transformation occurrence heralds a change from an indolent to an aggressive disease course, and is associated with major morbidity and mortality (14). In particular, most of the studies have reported a poor prognosis after transformation, with a median duration of survival generally ranging from 2.5 months to 2 years, with most deaths being due to lymphoma (5,7,12,13,15–21).

The incidence of HT have wavered over the past several decades, due to the adoption of different diagnostic methods, definition of transformation and duration of follow-up. Thus, the considerable variability in the incidence of tFL reported in literature may be explained by the heterogeneity in the definition of transformation, population included and diagnostic tools.

The clinical significance of transformation was seen in 325 FL patients from the St Bartholomew's Hospital of London, in which the risk of transformation by 10 years was 28% and the median survival after transformation was 1.2 years. Patients with tFL had a significantly shorter OS and a shorter survival from progression compared to others (Montoto et al. 2007).

Al-Tourah et al. analyzed the incidence of HT in a population based-study of 600 patients. The annual risk of transformation was estimated to be 3% per year, and the median survival after transformation was 1.7 years (7).

In another recent study from the University of Iowa/Mayo Clinic (Link et al. 2013), the cumulative risk of transformation and death without transformation (competing risk) increased steadily over time up through 5 years of follow-up and then appeared to slow, with only four transformations observed beyond 5 years from diagnosis. Transformation rate at 5 years was highest in patients who were initially observed and lowest in patients who initially received Rituximab monotherapy (Link et al. 2013).

However, in a group of 107 patients with advanced FL and low tumor burden registered in

the F2 database and managed with a W&W policy, the 5-year risk of transformation was quite low. After a median follow-up of 64 months, five patients experienced transformation to aggressive non-Hodgkin lymphoma, two during the W&W no treatment period and three after progression, with an estimated rate of less than 1% per year (Solal-Céligny et al. 2012).

Wagner-Johnston et al. have investigated the incidence, prognostic features, and outcomes associated with tFL among 2652 patients with FL prospectively enrolled in the US National LymphoCare Study. At a median follow-up of 6.8 years, 14.3% of patients underwent transformation; patients who were treated at diagnosis had a reduced risk of transformation as well as maintenance Rituximab was associated with reduced transformation risk. The median OS post transformation was 5 years (Wagner-Johnston et al. 2015).

The clinical and laboratory findings with better Overall Survival (OS) at the time of transformation include normal LDH levels, limited disease extent, good performance status, absence of B symptoms, fewer number of previous relapses, transformation after expectant management, having had no prior CR, or having had no response to salvage chemotherapy (5,7,12,13).

Despite the overall poor outcome of tFL patients, Yuen et al., identified a subset of patients having a relatively good outcome (Yuen et al. 1995). Limited extent of disease, attainment of Complete Remission (CR) to treatment given at the time of transformation and no prior therapy had a particularly favorable prognosis. In addition, patients who achieved CR after transformation had a better OS than those with advanced stage disease (108 vs 18 months) (Yuen et al. 1995). The impact of limited disease on tFL patients' prognosis was also seen by Bastion et al., (Bastion et al. 1997) and Al-Tourah et al.,(Al-Tourah et al. 2008). This latter group shown that the 5-year OS was 66% for patients with a limited transformation compared to 19% for those with advanced-stage at transformation in a significant way (Al-Tourah et al. 2008).

Only slight improvement were observed in recent studies, mostly showing the shorter OS of tFL patients in comparison to non-transformed FL patients. This adverse effect of transformation on survival was clearly illustrated by Al-Tourah et al., where the 10-year OS for non-transformed FL patients was 75%, whereas was only 36% for tFL patients were alive 10 years from the time of their initial FL diagnosis (Al-Tourah et al. 2008). Similar behaviors were also seen in other studies (Montoto et al. 2007).

Importantly, most of the patients in the reported studies received therapies not incorporating Rituximab. However, differences in patients' series, treatment and outcome is not a good condition to take advantage of; a lot of work is still needed to find out standard clinical criteria. Table 1 summarizes transformation risk in recent series.

Table 1. *Outcome of tFL patients in recent series*

Studies	Transformation risk
Montoto et al., 2007	**17%** at 5 years (100% biopsy proven) **1.9 RR in W&W**
Al-Tourah et al., 2008	**18%** at 5 years (63% biopsy proven) 30% at 10 years **(18% Doxo vs 30% Alk P=0.001)**
Link et al., 2008	**10.7%** at 5 years (85% biopsy proven) **14.4% in W&W** **3.2% in Rituximab**
Wagner et al., 2005	**12.8%** at 5 years (39% biopsy) **13.4% Rituximab chemotherapy** **18.3% NonRituximab chemotherapy**
Sarkozi et al., 2016	**4.1%** at 6 years (100% biopsy proven)

Can we assess any improvement in the outcome of tFL in the Rituximab era?

Whether the addition of Rituximab in intial treatment modifies the outcome of tFL patients, still needs to be addressed. However, over the last 5 years, several studies have been suggesting that the outcome of tFL patients has improve in the Rituximab era (Conconi et al. 2012; Ban-Hoefen et al. 2013; Lerch et al. 2015; Link et al. 2013; Guirguis et al. 2014).

Very recently Sarkozy and all analyzed risk factors, incidence and outcome of HT at first recurrence in the PRIMA patient cohort: after 6 years after a chemoimmunotherapy induction, the cumulative incidence of HT was 4.1% (Sarkozy et al. 2016).

Literature suggests that patients treated with Rituximab-containing chemotherapy achieve a longer OS compared with retrospective cohorts of patients treated with chemotherapy alone (Link et al. 2013; Bastion et al. 1997). In contrast, the most recent trial comparing a W&W

approach vs R did not show any differences in terms of risk of transformation (Ardeshna et al. 2014). As commented by the same authors, in the most of the reported series, the majority of patients have received chemotherapy prior to the diagnosis of HT and have advanced stage at the time of transformation so the better outcome cannot be attributed to an earlier identification of transformation leading to a better risk population (Montoto 2015).

Controversial results were also found in whether prior treatment with Rituximab has a good effect on the outcome after transformation. In a recent study, Lerch et al. (Lerch et al. 2015), showed that the treatment with Rituximab before the diagnosis of tFL was not correlated with a worse outcome in those patients. In contrast, patients with relapsed DLBCL treated with Rituximab have a significantly worse prognosis at progression (Montoto 2015). Other two studies demonstrated that prior R treatment did not result in a worse outcome in tFL patients who received high dose therapy with autologous stem cell rescue (HDT-ASCR) (Ban-Hoefen et al. 2013; Madsen et al. 2015). Patients who have previously received CHOP (Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Vincistrine [Oncovin], Prednisone) chemotherapy, with or without R, are frequently treated with second line regimens for DLBCL (Montoto 2015).

The role of Rituximab maintenance in DLBCL patients is also still unconcluded. In a recent study, R Maintenance was associated with reduced transformation risk. The median OS post transformation was 5 years, suggesting an improved outcomes for transformation in the modern era (Wagner-Johnston et al. 2015). Habermann et al., (Habermann et al. 2006) showed that addition of maintenance with R did not improve the outcome of DLBCL patients treated with R-CHOP. Other two studies showed that R maintenance after HDT-ASCR in DLBCL patients was not associated with a better outcome (Haioun et al. 2009; Gisselbrecht et al. 2012).

Based on heterogeneity of the treatment used before diagnosis of HT, it is a challenge to pull out any co clusions about specific regimen.

Pathology and biology of tFL

Although the FL transformation to DLBCL was described several decades ago, there is a strong need for a better understanding of both the dynamics of tumor clonal evolution and the genetic events that are responsible for transformation.

The pathogenesis of FL is best explained by a unifying hypothesis that takes into account genetic alterations harbored by the neoplastic B cells and an immunological model that suggests prominent crosstalk between the tumor cells and non-neoplastic immune cells in the tumor microenvironment, which include T cells, macrophages, follicular dendritic cells and stromal elements (de Jong and de Boer 2009; de Jong 2005; I S Lossos 2005).

It is well known that the translocation t(14;18) characteristic of most cases of FL leads to constitutive B-cell Lymphoma 2 (BCL2) protein expression and is a critical early event in the development of FL (Izidore S. Lossos and Gascoyne 2011). These cells then slowly proliferate, but do not die by apoptosis, and they can acquire genetic alterations. This condition can include chromosomal alterations that result from the localization in the GC (Küppers 2005). Others are driver mutations and alterations that provide the malignant cells with a growth advantage including gains, losses of chromosomal material and even balanced translocations involving the activation of dominant oncogenes, such as MYC (Izidore S. Lossos and Gascoyne 2011).

Recent studies have shown divergent pathways of disease progression and transformation in FL.

Recent whole-exome studies have highlighted that low-grade FL at diagnosis frequently shows some "driver" mutations not found in the transformed clone (Okosun et al. 2014; Pasqualucci et al. 2014; Carlotti et al. 2009). Some of these data derived from genetic methods, and suggest that FL may evolve as a "non linear" transformation (Okosun et al. 2014; Pasqualucci et al. 2014; Bouska et al. 2014; Wartenberg et al. 2013; Green et al. 2013; Eide et al. 2010; Carlotti et al. 2009; Ruminy et al. 2008; Halldórsdóttir et al. 2008) , in which the clone detected at transformation is more closely

related to a common progenitor than the clone predominating at the time (or site) of prior sampling (Casulo, Burack, and Friedberg 2015). The clonal evolution models to tFL were defined by investigating genomic alterations that are present in the dominant clone of both pre- and post- specimens ("Shared lesions"), and contrasting them to those that are present exclusively in the FL or tFL biopsy ("phase-specific lesions"). This analysis allowed to discriminate between i. a linear model, in which the tFL dominant clone will maintain all lesions present in the original FL clone, in combination with additional tFL-acquired alterations; ii. a divergent evolution model, where there are lesions that are unique to the dominant clone of the FL or the tFL, in addition to the set of shared alterations (Pasqualucci et al. 2014).

Thus, data mostly supported a divergent evolution model in a significant proportion of patients undergoing transformation, whereby FL and tFL arise from a common mutated ancestor through the independent acquisition of distinct lesions (Pasqualucci et al. 2014). Most FL and tFL derive from a common mutated precursor cell through divergent clonal evolution. There are some shared molecular determinants such as chromatin modification and apoptosis and some tFL specific determinants such as cell cycle, proliferation and DNA damage response.
Interestingly, the most commonly affected genes in both FL and tFL where those encoding for histone/chromatin modification enzymes, including methyltransferases and acetyltransferases (Pasqualucci et al. 2014). These early lesions in FL generally affect epigenetic regulators (genes controlling chromatin structure), including the H3H4 trimethyl-transferase *MLL2* mutation, never lost at transformation, EZH2 and the acetyltransferases *CREBBP* and *EP300* (Okosun et al. 2014; Pasqualucci et al. 2014; Morin et al. 2010; Morin et al. 2011).
Other frequent dysregulation in both FL and tFL was represented by programmed cell death genes, in particular BCL2 translocations, and thus presumably in the common ancestor clone (Pasqualucci et al. 2014).
Among tFL specific determinants there were alterations of cell cycle control, through mutation or deletion of cyclin-dependent kinase 2A/B (CDKN2A/B). These latter are two tumor suppressor genes, whose protein products p14-ARF, p16-INK4A and p15-INK4B, are important for negative regulation of cell cycle G1 progression and stabilization of the tumor suppressor p53 (Pasqualucci et al. 2014; Sherr 2004).
Alterations in *Myc* (Okosun et al. 2014; Pasqualucci et al. 2014), as well as DNA damage response, through losses of genes associated with regulation of the immune response, were also consistent in tFL only. Among the mutations that affect the immune response, recent studies found the entire HLA class I locus, specifically in β-2-microglobulin (B2M) and CD58 (Pasqualucci et al. 2014; Bouska et al. 2014; Morin et al. 2010).

Although a large number of prognostic markers have been implicated as contributing to survival in FL, only a handful have specifically examined the role of biological factors impacting risk of transformation.
It is becoming evident that phenotype variations related to genetics events (MYC, BCL2, p16, p53) should be routinely identified. FISH analysis could also be required to identify genetic alterations in MYC, BCL2 and BCL6.
The incidence of CD30 expression in tFL has also been reported to be 20% in a recent retrospective series of cases and CD30 expression should be also routinely identified by IHQ.
In summary, there is not a single mechanism driving transformation from FL to DLBCL (Okosun et al. 2014; Pasqualucci et al. 2014; Bouska et al. 2014; Andrew J. Davies et al. 2007). Rather, there are several mechanisms involved in transformation.

Treatment of tFL
Optimal treatment strategies for tFL still represents an unmet need. Unfortunately, most clinical trials exclude patients with tFL and there are no randomized studies in the modern era, with the result that level of evidence is very limited.
In historic series, as described before, the outcome of tFL patients was very poor, with a median OS of approximately 1 or 2 years (Montoto and Fitzgibbon 2011). However, the majority of published studies were conducted in the pre-Rituximab era, making difficult to draw any conclusion on the current scenario.

In the study conducted by Lynk and colleagues in 60 out of 631 patients with biopsy-proven tFL, the median OS was 50 months with an OS rate of 73% at 5 years after treatment with R-CHOP chemotherapy (Link et al. 2013). Survival was similarly in the National Comprehensive Cancer Network (NCCN) database study, with a median OS around 5 years in 118 biopsy confirmed tFL patients, was (Ban-Hoefen et al. 2013). Similar results were seen in early-stage FL experiencing tFL, with a 3-year OS of 44% (Bains et al. 2013). The estimated median OS for the patients with a histological diagnosis of HT from the PRIMA trial was 3.8 years after a median 6 yea follow up (Sarkozy et al. 2016).

As response after conventional chemotherapy, high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) has been studied by several research groups (Witzig et al. 2002; Schouten et al. 1989; Freedman et al. 1991; Foran et al. 1998; Berglund et al. 2000; Chen et al. 2001; Williams et al. 2001; J W Friedberg et al. 1999; Andreadis et al. 2005; Sabloff et al. 2007; Ramadan KM, Connors JM 2008).

Of historical relevance, the efficacy of ASCT was shown in tFL patients in old phase 2 and transplant registry series prior to the incorporation of immunotherapy (Wang and Hou 2010; Montoto and Fitzgibbon 2011). In particular, 40% of patients experienced long-term benefit, with survival rates similar to patients with relapsed aggressive lymphoma receiving the same treatment (Williams et al. 2001). However, most of the transplant studies are based on only small retrospective series of 20 to 50 patients (Hamadani et al. 2008; Williams et al. 2001; Chen et al. 2001; J W Friedberg et al. 1999; Sabloff et al. 2007). The role of ASCT has been further investigated in the Rituximab era, and so more relevant to current practice with the result that the addition of the antibody has improved the outcomes of tFL patients practice.

The Canadian Bone Marrow Transplant group (CBMTG) analyzed 172 patients with tFL , 53 treated with rituximab containing chemotherapy alone and 97 underwent instead ASCT. This latter approach improved OS and Progression Free Survival (PFS) of patients over Rituximab-containing chemotherapy regimens, although the difference was modest (Villa et al. 2013). Other groups observed that patients who were Rituximab naïve prior to ASCT, seemed to achieve better results than those with prior Rituximab exposure (Wirk et al. 2014; Kuruvilla et al. 2015; Ban-Hoefen et al. 2012; Gisselbrecht et al. 2010; Villa et al. 2013; Madsen et al. 2015) paralleling the observation in de novo DLBCL patients undergoing ASCT (Gisselbrecht et al. 2010). In addition, patients with early tFL performed significantly better in terms of OS, compared to those with late tFL(Link et al. 2013). ASCT had similarly outcomes in the large NCCN database, with an OS of 83% being superior compared to chemotherapy alone or ASCT without the incorporation of monoclonal antibodies (S. D. Smith et al. 2009; Villa et al. 2013).

Allogeneic transplantation in tFL has been less well studied, with small numbers of patients in mostly retrospective series. Some of these studies showed significantly inferior results than ASCT (Ramadan KM, Connors JM 2008), most probably due to the higher treatment related mortality (TRM) associated with the allogenic approach (35% versus 10% at 5 years). In contrast, the risk of disease relapse at 5 years was tendentially lower.

For relapses after ASCT, further salvage therapy with allogeneic transplantation seemed to improve the outcome of tFL regardless of the significant transplant related mortality (Ratanatharathorn et al. 1994; Doocey et al. 2005).

Radioimmunotherapy (RIT) has been proposed as primary treatment for tFL. In particular, radioactive nucleotide antibodies yttrium Y^{90} ibritumomab (Zevalin) and iodine I^{131} tositumomab (Bexxar), have shown some anti-lymphoma activity in tFL patients (A. J. Davies et al. 2004; Kaminski et al. 2001; Vose et al. 2000; Witzig et al. 2002). The overall response rates of RIT was 51%, ranging from 39% and 79%, with half of the responsers achieving complete remissions (CR) (Wang and Hou 2010). (Izidore S. Lossos and Gascoyne 2011). In the largest of these studies, Zelenetz et al., (Zelenetz AD, Saleh M, Vose J 2002) evaluated 71 patients from several I^{131} tositumomab studies, and showed a median duration of response of 36 months in responding patients. Although this approach seemed less effective in patients with bulky tumor burden and patients who

have previously received radiotherapy, it might be considered especially in patients not qualifying for more aggressive approaches giving that CR patients have shown prolonged response, often longer than 1 year (Izidore S. Lossos and Gascoyne 2011).
Moreover, an additional area of interest involves the integration of RIT with HDT and transplant in tFL patients, that has the potential to improve disease control, with similar toxicities compare to HDT alone (Krishnan et al. 2008; Wondergem et al. 2012; Reddy and Savani 2011; Mei et al. 2014).

Recently, novel agents have been investigated in tFL. In a phase 2 study, Lenalidomide showed an overall response rate of 57%, with median response duration of over 1 year in tFL patients (Czuczman et al. 2011). Specific inhibitors, targeting Aurora A kinase (alisertib) (Jonathan W. Friedberg et al. 2014), Bruton tyrosine kinase (ibrutinib) (Aalipour and Advani 2013), the δ isoform of phosphatidylinositol 3-kinase (idelalisib) (Gopal et al. 2014; Burger and Okkenhaug 2014) and the BCL2 protein (GDC-0199/ABT199) (Seymour JF et al. 2013), are currently being investigated in both indolent and aggressive lymphomas. These novel agents seem to have a significant impact on the outcome of tFL patients.
Recent efforts are focusing on the immune tolerance towards lymphoma cells as an alternative therapeutic approach. Pidilizumab is currently used as a monoclonal antibody to Programmed death-1 (PD-1), a member of the B7 receptor family that represents an important immune checkpoint regulator. Its efficacy has been recently shown in ASCT patients with DLBCL, including a subset with tFL (Armand et al. 2013).

Conclusions

HT is expected as a relatively frequent event in the clinical course of patients with indolent lymphoma. However, The incidence of HT varies enormously amongst different series, pending on the definition of HT, which is different in different studies., and different treatment approaches of the FL. Based on the available published studies, mostly derived from small retrospective studies, there is still not any standard therapeutic strategy for tFL patients: treatments used are different in different reports and relationship between treatment and outcome does not emerge very well from the literature. The fact that the risk of transformation is rarely an end-point in prospective studies underlined a great obstacle in this field, so there is no clear evidence that the initial management has an impact on the subsequent risk of transformation.
In conclusion, There is need for further studies aiming to provide an answer to pending question, including i. Definition of tFL; ii. Assessement of risk of transformation in non-treated patients; iii. Potential role of a FL stem cell or repopulating cell as a potential cell of origin contributing to histologic transformation; iv. History of clonal evolution; v. Molecular determinants; vi. Response to salvage therapy of tFL; vii. Outcome of tFL in the Rituximab era.
In addition, other several questions should be addressed, such as whether De novo tFL is the same or a different disease; whether FL3b is different from tFL and if there are differences between tFL at first or subsequent relapse.

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