Outcome of transformed follicular lymphoma worsens according to the timing of transformation and to the number of previous therapies. A retrospective multicenter study on behalf of Fondazione Italiana Linfomi (FIL)

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Introduction

Histologic transformation (HT) refers to a biologic event leading to the development of a high grade non-Hodgkin lymphoma, mostly diffuse large B-cell lymphoma (DLBCL), in patients with an underlying indolent lymphoma, a follicular lymphoma (FL) in most cases. Despite an increasing amount of data on biology (Bouska *et al,* 2016; Pasqualucci *et al* ,2014; Blaker *et al*, 2016; Brodtkorb *et al*, 2014), incidence (Bastion *et al*, 1997; Al-Tourah *et al*, 2008; Montoto *et al*, 2007; Conconi *et al*; 2012) and predictive factors (Wagner-Johnston *et al*, 2016; Alonso-Alvarez *et al,* 2017) of FL transformation to DLBCL, the disease course, prognosis and optimal treatment for this heterogeneous disease entity are still to be fully defined. The potential role of autologous stem cell transplantation (ASCT) and of rituximab maintenance in the treatment algorithm are the most controversial and debated topics (Montoto, 2015). Moreover, very few reports have focused on the rather frequent cases of FL with signs of transformation at initial histological diagnosis, and consequently scanty information about optimal management in this setting is available. These cases include composite lymphomas, defined as the presence of areas FL and DLBCL in a single tissue sample, discordant lymphomas, defined as the concomitant diagnosis of FL and DLBCL at two or more separate anatomic sites, and also some cases of DLBCL which can be considered as FL diagnosed at the time of transformation. This rare condition is characterized by the absence of an overt clinical history of indolent lymphoma and by the recognition of a concomitant follicular cell component in the same tissue sample which allowed DLBCL diagnosis. Histological examination is considered the gold standard for establishing the diagnosis of FL transformation (Montoto, 2015). Considering that performing a biopsy at every clinical suspicion of FL transformation might be difficult, some published series have included cases of transformed FL (tFL) diagnosed on cytologic examination (Bastion *et al,* 1997), or simply based on clinical suspicion of transformation (Al-Tourah *et al*, 2008; Wagner-Johnston *et al*, 2015). The retrospective nature of most studies and the variability of tFL definition might explain the discrepancies that emerged both in the assessment of the risk of HT for FL, which ranged from 8% to 31% at 10 years, and in the historically reported risk of HT per year, from 2% to 3% per year (Bastion *et al,* 1997; Al-Tourah *et al*, 2008; Montoto *et al*, 2007; Alonso-Alvarez *et al,* 2017). The impact of rituximab use on HT incidence is also controversial: some large series showed a similar risk of HT in the post-rituximab compared to the pre-rituximab era (Wagner-Johnston *et al*, 2015; Conconi *et al*; 2012), while other data suggest a decreased HT incidence in the rituximab-exposed FL population (Alonso-Alvarez *et al,* 2017; Link *et al,* 2013; Federico *et al,* 2018). The prognosis of tFL, previously considered very poor with a median survival of approximately 1 year (Al-Tourah *et al*, 2008; Montoto *et al*, 2007), has improved in the immuno-chemotherapy era, as clearly demonstrated by trials conducted after the introduction of rituximab; however, in the rituximab-era post-transformation outcome strongly varies between studies, with a reported 5-year OS ranging from 41% to 75% (Wagner-Johnston *et al*, 2015; Link *et al,* 2013; Federico *et al,* 2018; Ban-Hoefen *et al*, 2013; Guirguis *et al,* 2014; Madsen *et al,* 2015; Gleeson *et al,* 2016). Despite these improvements, the optimal treatment for patients with tFL, who are generally excluded from clinical trials both for indolent and aggressive lymphomas, is still controversial. Treatment approaches for tFL are often individualized, and more often strategies routinely used for DLBCL are applied (Montoto, 2015). The actual role of ASCT as consolidation in all eligible tFL patients is one of the most debated points, considering the excellent outcome reported in some studies after standard immuno-chemotherapy, especially in anthracycline-naïve patients (Link *et al,* 2013; Ban-Hoefen *et al*, 2013; Gleeson *et al,* 2016). Therapeutic strategies in tFL presenting as composite or discordant lymphoma are even less well defined, mainly due to the rarity of these entities (Kim *et al*, 1977; Mokthar, 2007). The efficacy of additional rituximab maintenance after anthracycline-containing immuno-chemotherapy in composite/discordant lymphomas is a most debated issue, although a recently published retrospective study did not show a survival advantage for patients who received rituximab maintenance (Kansara *et al*, 2016). In addition, a standard treatment modality for those patients presenting with transformed DLBCL at initial diagnosis, hence in the absence of overt clinical history of indolent lymphoma has not been established as well (Ghesquieres *et al,* 2006), and the advantage to distinguish them from *de*

novo DLBCL is unclear. Histological transformation may occur in quite different phases of FL clinical history. Therefore some patients' features at transformation, like age, time from initial diagnosis, number and characteristics of pre-HT therapies, confer heterogeneity to tFL population and may strongly impact treatment strategies and arguably influence post-transformation prognosis (Link *et al,* 2013; Guirguis *et al,* 2014).

Considering all the aforementioned uncertainties in defining the disease course and the optimal treatment strategy for transformed and composite/discordant FL, we retrospectively collected histologically confirmed tFL and composite/discordant FL consecutive patients from 9 centers of the Fondazione Italiana Linfomi (F.I.L.) whose detailed clinical histories throughout the disease course were available. We assessed the clinical characteristics of patients at transformation, including type of transformation, pre-HT number of therapies, time to transformation, in order to determine their effect on post-HT survival; additionally, we analyzed post-transformation therapies, focusing on the role of anthracycline, rituximab maintenance and ASCT, with the aim to identify treatment strategies which can impact post-transformation outcome.

Patient and Methods

Study population

Consecutive patients aged ≥ 18 years with histologically proven transformation of FL (grade 1-3A) to DLBCL or composite/discordant lymphoma with FL (grade 1-3A) as low-grade and DLBCL as high-grade component were retrospectively identified from participating centers' institutional datasets. Patients with FL grade 3B or HIV infection were excluded. Patients were included in the present analysis if first diagnosis in the composite/discordant population or transformation in the tFL population occurred in the timeframe from 2002 to 2014. The study was approved by the Institutional Review Board at each site and registered on ClinicalTrials.gov (identifier: NCT02927756). Data management and analysis were performed in accordance with the tenets of the Declaration of Helsinki, as revised in 2000. Pathology reports were reviewed by local investigators in order to confirm transformation. Clinical, treatment and outcome data were gathered from clinical records. Outcome measures were considered overall response rate, complete remission rate, progression-free survival, and overall survival. Response to treatment was evaluated according to the revised international criteria for malignant lymphomas (Cheson *et al,* 2007).

Definition of Histological Transformation

Patients were required to meet at least one of the following definitions of HT to be included in the study: (I) co-existence of FL and DLBCL in a single tissue sample with a variable proportion between indolent and aggressive component (hereafter referred to as composite lymphoma); (II) simultaneous presence of FL and DLBCL in two different tissue samples (hereafter referred to as discordant lymphoma); (III) biopsy-proven diagnosis of DLBCL after a previous biopsy-proven diagnosis of FL, with no limits in terms of time interval between the two biopsies. For each specimen, the morphologic aspects of large B-cell and small B-cell components were described in accordance with the 2008 WHO classification (Swerdlow *et al*, 2008). Patients with solely clinical suspicion of transformation were not included in this study.

Based on the type of HT, patients were divided into two groups: Group 1 comprised patients affected by composite and discordant lymphoma in which transformation occurred at initial diagnosis, and Group 2 included patients who experienced transformation after a previous FL diagnosis. Group 2 patients were further split into 3 subgroups, depending on pre-HT number of therapies they received: treatment-naïve patients at time of transformation, in which HT occurred after a watch and wait strategy for FL (Group 2A); patients who received a single therapeutic line pre-HT, since transformation occurred at first relapse/progression (Group 2B); patients who received at least 2 therapeutic lines for FL pre-HT, and for which transformation is defined as "late" event, irrespectively of time interval from FL diagnosis to HT (Group 2C).

Statistical Analysis

The continuous variable age was summarized as median and range, while categorical variables were summarized as absolute and percentage frequencies. The comparison of age distribution between two groups was performed using the non-parametric test of Mann-Whitney, while the Kruskal-Wallis test was used for the comparison between more than two groups. Categorical variables between groups were compared by means of the Fisher's exact test or χ^2 test, when appropriate.

Overall survival (OS) was calculated from the date of histological transformation to date of death due to any cause or date of last clinical follow-up. Progression-free survival (PFS) was defined as time from the date of histological transformation to the date of progression or death due to any cause or date of last clinical follow-up. Survival curves were reported using the Kaplan-Meier estimates and statistical comparisons between curves were made using the log-rank test. The covariate effect was estimated by means of the Cox proportional hazard (PH) regression, and the effect was reported as hazard ratio (HR) with 95% confidence interval (95CI). All statistical tests were two-sided, and we considered significant p-value lower than the conventional value of 0.05.

Results

Patient characteristics

One hundred and seventy-six histologically proven t-FL were included and analyzed; HT occurred at initial diagnosis (Group 1) in 91 cases (52%) and after a previous FL diagnosis (Group 2) in 85 cases (48%).

Group 1 included 82 (47%) patients with composite lymphoma and 9 (5%) patients with discordant lymphoma. Group 2 included 15 pts (8%) who were treatment-naïve at HT (Group 2A), 39 pts (22%) who transformed at first relapse or progression (Group 2B) and 31 (18%) patients who experienced late HT (Group 2C). Median age at HT was 60 years (range: 20-83 years).

Baseline demographic and clinical characteristics of patients in different subgroups according to type of transformation are summarized in Table I. No statistically significant differences in baseline characteristics between Group 1 and Group 2 were found.

First line treatment modalities for Follicular Lymphoma in Group 2 patients are listed in Table II.

Treatment Modalities for Histological Transformation

In Group 1, 85 patients (93%) received rituximab combined with first-line chemotherapy and 19 patients (21%) also as maintenance. Seventy-five patients (82%) in Group 1 received CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like regimens. Anthracycline-based induction was followed by a platinum-based treatment phase in 10 patients (11%) and by cyclophosphamide and intermediate dose cytarabine in 3 patients (3.5%), this latter treatment strategy being referred to as sequential therapy; the remaining 2 patients (3.5%) did not receive antrachycline. Consolidation was delivered to 28 patients (31%) in Group 1 and consisted of ASCT in 13 patients (14%) and radiotherapy in 15 patients (16%). In Group 2, post-HT treatment consisted of CHOP or CHOP-like regimens in 38 patients (45%), platinum-containing regimens, such as DHAP (dexamethasone, cytarabine, cisplatinum), ICE (ifosfamide, carboplatinum, etoposide) or ESHAP (etoposide, dexamethasone, cytarabine, cisplatinum), in 15 patients (18%) and high dose sequential therapy in 11 patients (13%). Rituximab was added to induction chemotherapy in 61 cases (72%) while 10 patients (12%) also received rituximab as maintenance. Twenty-nine patients (35%) received consolidation, consisting of ASCT in 17 patients (23%), radiotherapy in 5 patients (6%) and radioimmunotherapy in 5 patients (6%). Treatment modalities for HT in both groups are summarized in Table III.

Outcome

Response

Treatment modalities for HT allowed to achieve a complete remission (CR) in 123 patients (70%) and a partial remission (PR) in 15 patients (8%), with an overall response rate (ORR) of 78% in the entire study population.

ORR for patients with HT at initial diagnosis (Group 1) was 94%, with 77 patients (84%) obtaining CR and 9 (10%) PR.

ORR for patients with HT after a previous FL diagnosis (Group 2) was 61%, with 46 pts (54%) achieving CR and 6 (7%) PR.

The difference in CR rate between Group 1 (84%) and Group 2 (54%) was statistically significant (p<0.001).

In Group 2, the number of therapy lines received pre-HT had a negative correlation with probability to achieve a CR, since CR rates in subgroups 2A (treatment-naïve patients), 2B (HT at first relapse/progression) and 2C

(late HT) were 80%, 56%, and 39%, respectively (p= 0.027).

Survival

With a median follow-up of 44 months (range: 1-179), the post-HT 5-year PFS and 5-year OS of the entire study population were 47% and 67%, respectively (Fig.1).

Five-year PFS was 59% for patients with HT at initial diagnosis (Group 1) and 33% for patients with HT after a previous FL diagnosis (Group 2), while 5-year OS was 84% and 51%, respectively; both differences in survival between the two groups were statistically significant (p<0.001). (Fig.2)

In the entire Group 2, an inverse trend was found between the number of pre-HT lines of therapy and both PFS and OS. Five-year PFS was 52% in Group 2A with no statistically significant difference with Group 1 (59%) (p=0.248), 25% (HR: 2.89, p<0.001) in Group 2B, and 36% (HR: 3.15, p<0.001) in Group 2C. Likewise, 5-year OS was 72% in treatment-naïve patients at time of transformation (Group 2A), with no statistically significant difference with Group 1 (84%) (p=0.310), 50% (HR: 3.46, p=0.001) in patients who received a single therapeutic line pre-HT (Group 2B), and 42% (HR: 4.94, p<0.001) in patients who received at least 2 therapeutic lines for FL pre-HT (Group 2C) (Fig.3). Similarly, within Group 2C, 5-year OS was 52% for patients who received 2 pre-HT lines of therapy and 20% for patients who received more than 2 pre-HT lines of therapy (p=0.004) (Fig.4).

Additionally, in Group 2 patients' time to transformation, meant as time interval since first FL diagnosis to HT, inversely correlated both with OS and PFS: 5-year OS for time to transformation > 12 months vs ≤ 12 months was 56% vs 29% (p=0.023); 5-year PFS for time to transformation > 12 months vs ≤ 12 months was 37% vs 17% (p=0.005) (Fig 5).

Post-transformation treatment strategy and outcome

First-line treatment in Group 1 included anthracycline and rituximab in 96.5% and 93% of patients, respectively. Five-year PFS in Group 1 was 94% for patients receiving rituximab maintenance versus 83% for observation (p=0.024), while no statistically significant difference was observed in 5-year OS (p=0.130). ASCT as first-line consolidation was not associated with any survival advantage, neither in 5-year PFS (p=0.227) nor in 5-year OS (p=0.130). Similarly, no survival advantage was observed for any other post-induction consolidation versus observation, both in PFS and OS (p=0.991 and p=0.719, respectively).

In Group 2A and 2B patients, an anthracycline-containing post-HT treatment strategy was associated with better 5-year OS (75% vs 38%, p=0.017). In Group 2A, 15 of 16 patients were treated with the addition of rituximab and showed a 5-year OS of 77%. Addition of rituximab to post-HT treatment was associated with superior 5-year OS in Group 2B (59% vs 25%, p=0.039) and resulted in superior post-transformation PFS in Group 2C (50% vs 11%, p=0.004). In Group 2 patients, ASCT as consolidation strategy led to superior survival only in the subgroup of patients who did not receive an anthracycline-containing post-transformation treatment (5-year OS for ASCT vs no consolidation, 59% vs 29%, p=0.014; 5-year PFS for ASCT vs no consolidation, 54% vs 21%, p=0.012).

Discussion

Outcome of tFL in the rituximab-era is controversial, and clinicians have scanty tools to rely on for discriminating sub-groups of patients with different prognosis in this heterogeneous population. In this broad retrospective series of patients with histologically proven tFL we explored clinical characteristics affecting post-transformation outcome; two simple and always available variables such as time to transformation during FL natural history and number of therapy lines received before transformation strongly correlated with post-HT survival. We identified two distinct groups of patients: transformed FL at initial diagnosis, including composite and discordant lymphoma, and transformed FL after an overt indolent phase and with a miscellaneous treatment history, including both patients managed with a watch and wait strategy and patients who required a high number of therapy lines. Sample size of both groups favorably compares to previously reported series (Al-Tourah *et al*, 2008; Wagner-Johnston *et al,* 2016; Montoto *et al,* 2007; Conconi *et al,* 2012; Link *et al*, 2013; Ban-Hoefen *et al*, 2013; Guirguis *et al*, 2014; Madsen *et al*, 2015; Gleeson *et al*, 2016; Kansara *et al,* 2016; Ghesquieres *et al,* 2014; Sarkozy *et al*, 2016). Notably, in the present study all patients included had a biopsy proven transformation, thus fulfilling the gold standard test for transformed lymphomas diagnosis (Montoto*,* 2015; Casulo *et al,* 2015). In our analysis, outcome of patients with transformed FL at initial diagnosis (Group 1) was excellent, with a 5-year PFS and OS of 59% and of 83%. These results for tFL at initial diagnosis favorably compare to previously reported outcome for *de novo* DLBCL treated with R-CHOP (Cunningham *et al,* 2013; Vitolo *et al,* 2017) and for non-transformed FL (Wagner-Johnston *et al,* 2016; Federico *et al,* 2013). No plateau was observed in Group 1 survival curves, which showed a pattern of continuous relapses; this finding is similar to what is expected in non transformed FL and to what was reported in previous series with composite histology, thus suggesting a possible different lymphoma biology from *de novo* DLBC (Magnano *et al,* 2017). Group 1 patients who received an anthracycline-based regimen as induction therapy showed an excellent outcome, hence confirming the key role of doxorubicin, that should be considered as a valid therapeutic option and offered to this population whenever possible (Casulo *et al,* 2015; Godfrey *et al,* 2018). Our data did not show a survival advantage for ASCT performed as post-induction consolidation; on the contrary, the small proportion of patients who received rituximab maintenance versus observation had a superior PFS. Published data in this specific setting are particularly scanty, and clinical and therapeutic implications of the co-existence of a DLBCL component in a composite or discordant lymphoma are still uncertain at present. In the pre-rituximab era, a French study reported the outcome of a series of DLBCL with associated indolent B-cell component, consisting of FL in only 37% of cases; an anthracycline containing regimen was administered to all patients, while 38% of patients underwent ASCT as part of initial treatment. This strategy allowed to obtain a 5-year OS of 57%, with similar outcome across various low-grade components. Not surprisingly, survival data of this cohort are inferior to those reported in the immune-chemotherapy era, and to those reported in the present survey as well (Ghesquieres *et al,* 2006). In the National LymphoCare Study (Wagner-Johnston *et al,* 2016), 47 patients with transformation at initial diagnosis were included: 66% of patients in this subgroup received an anthracycline-containing regimen. Even if data on consolidation in the subpopulation with FL transformed at initial diagnosis are not reported, we can speculate that the transplanted proportion of patients was very low, since only 2% of the entire study population underwent ASCT. This therapeutic approach resulted in a 66% 5-year PFS and 88% 5-year OS, and these results are close to those obtained in the present study. Survival outcome of the largest published series of composite or discordant lymphomas, which consists in 98 patients from the British Columbia database, is very close to that here reported (Kansara *et al,* 2016). Interestingly, in the Canadian experience the addition of rituximab maintenance after R-CHOP did not result in any advantage in terms of both PFS and OS, while in our survey we observed an improvement of 5-year PFS for those patients in Group 1 who received rituximab maintenance compared to observation (94% vs 83%, p=0.024). This analysis confirms an excellent outcome for the “transformed at initial diagnosis” group in the rituximab era;

nevertheless, no plateau appears in the survival curves, showing that composite and discordant lymphomas behave similarly to FL and prompting a potential role for maintenance. Our data, with the limits of a retrospective assessment, suggest a potential role for rituximab maintenance in transformed at initial diagnosis lymphomas, that nonetheless needs to be confirmed in a prospective setting. At present, the role for ASCT as consolidation for HT at initial diagnosis has not been clearly established. In Group 1 we did not detect any advantage for any consolidation, and our data suggest that ASCT can be safely omitted in transformed lymphoma at initial diagnosis, accordingly with recently published recommendations (Godfrey *et al*, 2018). This data is in keeping with the previously reported excellent outcome for composite/discordant lymphoma with standard rituximab-chemotherapy: 34 patients with composite/discordant lymphoma obtained similar survival rate at 5 years, irrespectively to ASCT as consolidation (Madsen *et al,* 2015). Excellent outcome with standard anthracycline-containing immuno-chemotherapy induction for composite lymphoma without ASCT consolidation has been confirmed by recent studies (Magnano *et al,* 2017; Behad *et al*, 2017). Group 2 includes 85 patients in which HT occurred after a previous FL diagnosis, treated in a large proportion with rituximab in combination with different chemotherapy regimens, containing anthracycline in only 45% of cases. Looking at Group 2 as a whole, outcome in terms of response and survival is inferior to the one reported in Group 1, pointing out that transformation after an overt history of FL is a worse condition than transformation at initial diagnosis. Group 2 population is considerably heterogeneous, since it includes both treatment-naïve and heavily pre-treated patients before transformation. Our analysis shows that a shorter interval between FL diagnosis and HT determines a worse survival outcome, thus confirming a worse prognosis for earlier transformation (Link *et al,* 2013). Notably, Group 2 survival outcome is superimposable to that of the unfavorable subgroup of not-transformed FL patients who experienced an early event after R-CHOP first-line (Casulo *et al,* 2015). Five-years PFS and OS, 33% and 51% respectively, are superior to survival data reported in the pre-rituximab era (Al-Tourah *et al*, 2008; Montoto *et al,* 2007) and do not significantly differ from those reported in the majority of studies conducted in the rituximab era (Conconi *et al,* 2012; Link *et al*, 2013; Ban-Hoefen *et al*, 2013; Guirguis *et al*, 2014; Madsen *et al*, 2015; Gleeson *et al*, 2016). In the present analysis, the number of therapies received for FL prior to HT emerges as a crucial prognostic factor for post-transformation outcome. Indeed, we demonstrated a significant survival difference between treatment-naïve patients at time of transformation (Group 2A) compared to patients who received a single therapeutic line pre-HT (Group 2B) and to patients who received at least 2 therapeutic lines for FL pre-HT (Group 2C). Complete remission rate and survival in Group 2A are superimposable to those we described in Group 1 and superior to those observed in Group 2B and 2C, thus confirming, in keeping with previous reports, a better post HT outcome for treatment-naïve patients (Ban-Hoefen *et al*, 2013; Lerch *et al*, 2015; Madsen *et al*, 2015; Wagner-Johnston *et al*, 2016). Group 2A survival curve showed a clear and early plateau, connotating transformation in the treatment-naïve setting as a highly curable condition. Post-HT treatment with rituximab and anthracycline was beneficial, in terms of CR achievement and survival, for most Group 2 patients. Post-HT prognosis of the entire Group 2C is significantly inferior respect to Group 1, 2A and 2B. Prognosis inside Group 2C was poorer in the subgroup of patients who received more than two pre-HT therapeutic lines, with a median OS inferior to 12 months in this subgroup; this dismal survival outcome is not dissimilar to that reported in the DLBCL refractory setting (Crump *et al*, 2017). These data confirm the previous finding that, in the pre-treated setting, the number of therapeutic lines for FL inversely correlates with prognosis after transformation (Madsen *et al*, 2015). Group 2B patients, for which HT occurred at first event after a single therapeutic line for FL, achieved a long-term outcome, superior to the one described in a similar subgroup in the PRIMA trial; in the prospective international trial 40 patients experienced biopsy proven transformation after immuno-chemotherapy and rituximab maintenance. Notably, the most frequent schedule for induction phase was R-CHOP, and HT occurred during the first year of follow-up in the majority of patients: both these characteristics confer an unfavorable prognosis to the transformed population. In this setting, CR rate was 50.3% and median survival after transformation was 3.8 years; a significant survival advantage was obtained by consolidation with ASCT (median OS not reached

vs 1.7 years) (Sarkozy *et al*, 2016). More recently, an international study analyzed 439 biopsy proven transformation occurring at first event in a large cohort of FL, and survival after transformation was 41% at 5 years (Federico *et al,* 2018). Outcome of Group 2B is consistent with both previous reports on HT as first event. In the entire Group 2, the delivery of any consolidation strategy versus observation after post-HT treatment was associated with a survival advantage, while ASCT as consolidation strategy led to superior survival only in the subgroup of patients who did not receive an anthracycline-containing post-transformation treatment. On the other hand, patients who did not receive anthracycline at transformation were in large part exposed to the drug for FL treatment, and probably represent an unfavorable subgroup that can benefit from autologous transplant. The role of ASCT in tFL after a previous FL diagnosis in the rituximab era is debated, since some of the available reports demonstrated a survival advantage for transplanted patients (Alonso-Alvarez *et al,* 2017; Sarkozy *et al*, 2016; Villa *et al*, 2013) while others did not (Link *et al*, 2013; Lerch *et al*, 2015). Notably, some studies clearly identified a favorable subset of tFL patients, mainly treatment- or antrachycline-naïve patients at HT, with excellent outcome without transplantation (Ban-Hoefen *et al*, 2013; Madsen *et al*, 2015). Different definitions of transformation and inhomogeneous criteria for ASCT eligibility might bias comparison between studies, not enabling to draw definitive conclusions on the role of transplantation.

In conclusion, outcome of tFL in the rituximab era confirms to be better than reported in historical series, also in a large real-life experience, and strongly differs according to time to transformation and to number of pre-HT treatment lines. Time to transformation and number of pre-HT treatment lines are two simple and always accessible clinical variables that should be considered when defining a treatment strategy for tFL, which, while reliable data from prospective trials are still lacking, should be tailored and individualized. Transformed FL at initial diagnosis showed an excellent outcome with standard immuno-chemotherapy; a longer follow-up would be necessary to clarify a pattern of late relapses in this subpopulation. Rituximab maintenance versus observation in the transformed FL at initial diagnosis allowed to obtain a PFS advantage, and its role should be investigated in a prospective manner. With the limits of a retrospective data collection, our analysis suggests that ASCT should be avoided in treatment-naïve tFL patients and strongly considered if transformation occurred in a short interval from initial diagnosis and after at least one therapeutic line for FL, especially if anthracycline-containing. Finally, transformation after more than 2 two previous lines for FL showed a dismal prognosis, with a post-HT median survival less than one year, and clearly represents an unmet clinical need that might benefit from novel therapeutical approaches, such as CAR-T.

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Authorship contributions

CR, GR, MF conceived the study, assisted by AA, AC and LA. AA, AC, FC, SR, BB, AF, LN, CP, EM were responsible of recruitment of patients and collection of clinical data. LM performed the statistical analyses. CR and GR prepared the initial version of the paper. Final approval of manuscript was given by all authors.

Figure 1

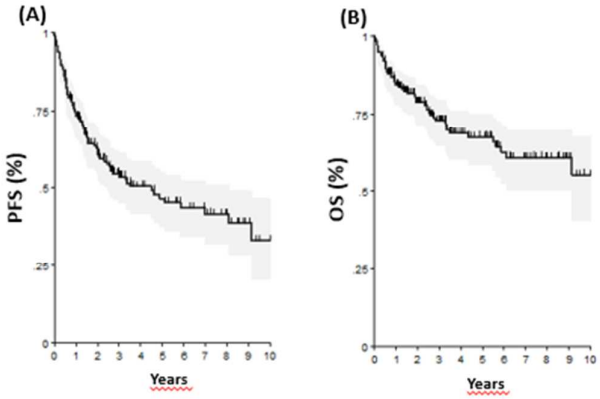

Fig 1. Survival after transformation of the entire study population.

(A) 5-year PFS was 47%. (B) 5-year OS was 67%.

Figure 2

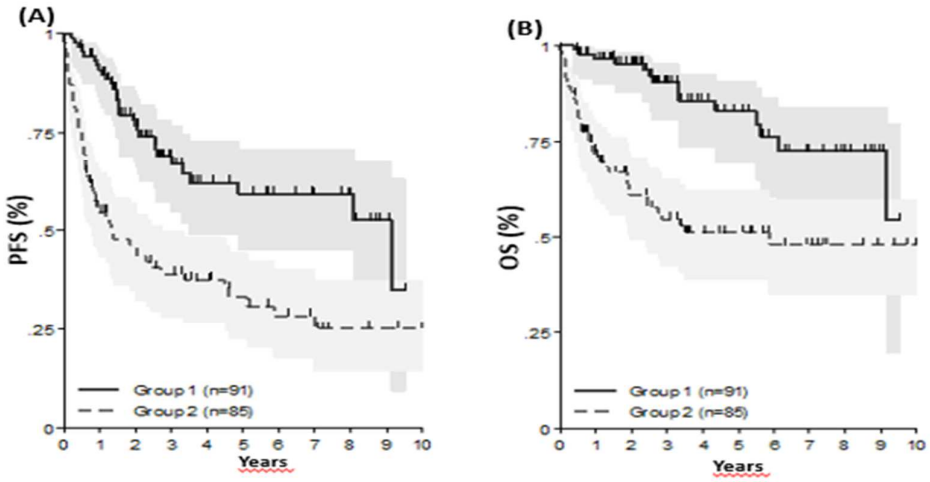

Fig 2. Survival after transformation in patients with HT at initial diagnosis (Group 1) and with HT after a previous FL diagnosis (Group 2).

(A) 5-year PFS was superior in Group 1 vs Group 2 (59% vs 33%, p<0.001). (B) 5-year OS was increased in Group 1 vs Group 2 (83% vs 51%, p<0.001).

Figure 3

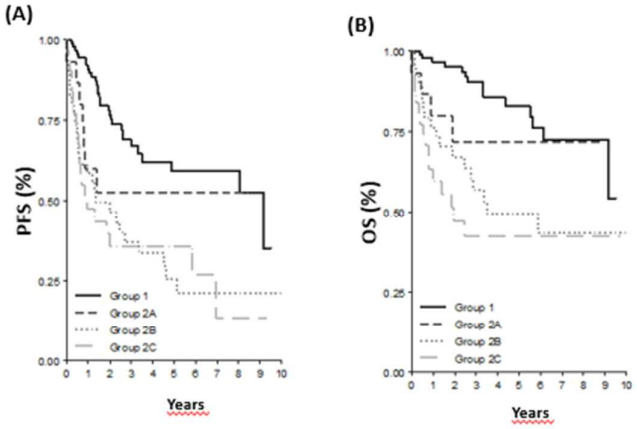

Fig 3. Survival after transformation according to the number of previous therapies.

(A) 5-year PFS was similar in treatment naïve patients at transformation, considering patients with transformation at initial diagnosis (Group 1) and patients with transformation after a watch and wait policy (Group 2A) (59% vs 52%, p=0.248), and inferior in patients who transformed at first relapse or progression (Group 2B: 25%, HR: 2.89, p<0.001) and in patients who received at least two therapeutic lines pre-transformation (Group 2C, 36% , HR: 3.15, p<0.001) (B) 5-year OS was similar in treatment naïve patients at transformation, considering patients with transformation at initial diagnosis (Group 1) and patients with transformation after a watch and wait policy (Group 2A) (83% vs 72%, p=0.310), and inferior in patients who transformed at first relapse or progression (Group 2B: 50%, HR: 3.46, p=0.001) and in patients who received at least two therapeutic lines pre-transformation (Group 2C, 42% , HR: 4.94, p<0.001)

Figure 4

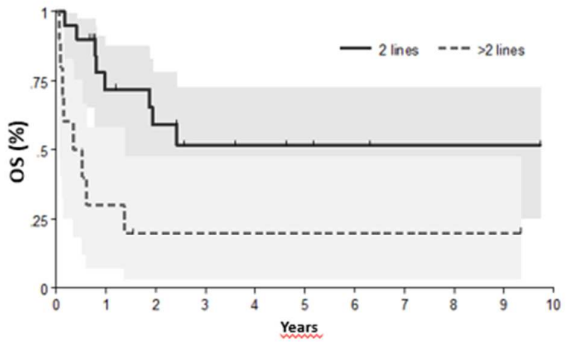

Fig 4. Overall survival after transformation in patients in which HT occurred after at least two therapeutic lines (Group 2C): patients who received more than two lines pre-HT had inferior outcome (5-year OS 20% vs 52%, p=0.004)

Figure 5

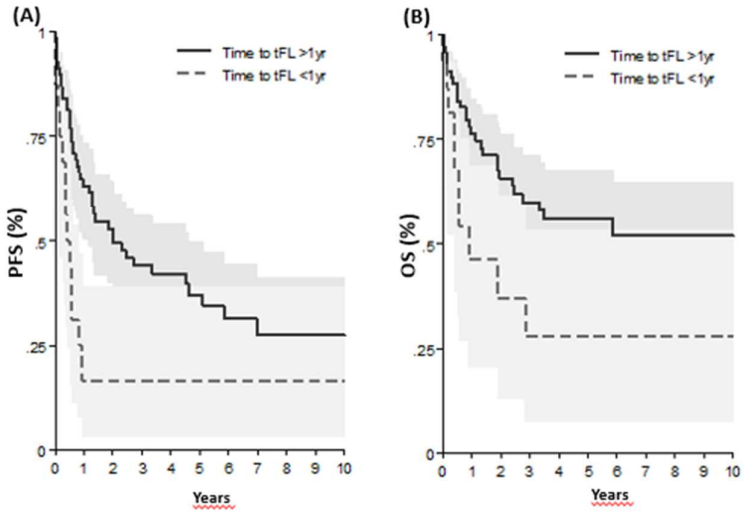

Fig 5. Survival after transformation according to the time to transformation in patients with HT after a previous FL diagnosis (Group 2).

(A) 5-year PFS was superior in patients with a time to transformation > 12 months vs ≤ 12 months (37% vs 17%, p=0.005). (B) 5-year OS was superior for patients with a time to transformation > 12 months vs ≤ 12 months (56% vs 29%, p=0.023).

Table I. Patient characteristics and subgroups according to the type of transformation

		Group 1 (n=91)	Group 2 (n=85)			
			Group 2A (n=15)	Group 2B (n=39)	Group 2C (n= 31)	p
Age, years	median (range)	62 (28-83)	51 (34-77)	64 (42-84)	68 (27-87)	0.053
		n (%)	n (%)	n (%)	n (%)	
Age	< 60	37 (41)	8 (53)	11 (28)	10 (32)	0.161
	≥ 60	54 (59)	7 (47)	28 (72)	21 (68)	
Sex	M	51 (56)	8 (53)	24 (62)	22 (70)	0.283
	F	40 (44)	7 (47)	15 (38)	9 (30)	
Symptoms	A	75 (82)	11 (73)	32 (82)	21 (68)	0.344
	B	16 (18)	4 (27)	7(18)	10 (32)	
Ann Arbor Stage	I-II	29 (32)	5 (33)	9 (24)	11 (37)	0.621
	III-IV	62 (68)	10 (67)	30 (76)	20 (63)	

Legend Table I:

Group 1: transformation at initial diagnosis; Group 2: transformation after FL diagnosis; Group 2A: transformation after watch and wait; Group 2B: transformation after a single therapeutic line for FL; Group 2C: transformation after at least two therapeutic lines for FL

Table II. First line treatment for Follicular Lymphoma in Group 2 patients with transformation after FL diagnosis (Group 2)

	Therapy	Group 2A	Group 2B	Group 2C
		n (%)	n (%)	n (%)
First line treatment	W&W	15 (100)	1 (3)	1 (3)
	CHOP/CHOP-like		14 (36)	20 (64)
	Radiotherapy		3 (7)	3 (10)
	CVP		4 (10)	6 (20)
	Fludarabine		14 (36)	
	Bendamustine		1 (3)	1 (3)
	Others		2 (5)	
First line Rituximab			21 (54)	16 (52)
Rituximab maintenance			2 (5)	4 (13)
First line consolidation	Radiotherapy		3 (50)	2 (67)
	ASCT		1 (17)	1 (33)
	Others		2 (33)	
Total		15	39	31

Legend Table II:

ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; Group 2: transformation after FL diagnosis; Group 2A: transformation after watch and wait; Group 2B: transformation after a single therapeutic line for FL; Group 2C: transformation after at least two therapeutic lines for FL; W&W: watch and wait

Table III. Treatment modalities for HT

		Group 1	Group 2		
	Therapy		2A	2B	2C
		n (%)	n (%)	n (%)	n (%)
Chemotherapy for tFL	CHOP/CHOP-like	75 (82)	9 (60)	17 (44)	12 (38)
	Platinum-based	10 (11)		7 (18)	8 (26)
	Sequential therapy	3 (3.5)	5 (33)	6 (15)	
	CVP			2 (5)	
	Lenalidomide				1 (3)
	Bendamustine				3 (10)
	Radiotherapy alone				1 (3)
	Palliative care				3 (10)
	Others	3 (3.5)	1 (7)	7 (18)	3 (10)
Rituximab for tFL		85 (93)	14 (93)	28 (72)	19 (61)
Rituximab maintenance post tFL		19 (22)	4 (27)	3 (8)	3 (10)
Consolidation post-tFL	Radiotherapy	15 (53)	1 (17)	3 (20)	1 (13)
	ASCT	13 (46)	3 (49)	9 (60)	4 (50)
	AlloTx				1 (13)
	Radioimmunotherapy		1 (17)	3 (20)	2 (24)
	Others		1 (17)		
Total		91	15	39	31

Legend Table III:

ASCT: autologous stem cell transplantation; Allotx: allogeneic transplantation; CHOP: cyclophosphamide, daunorubicin, vincristine, prednisone; CVP: cyclophosphamide, vincristine, prednisone; Group 1: transformation at initial diagnosis Group 2: transformation after FL diagnosis; Group 2A: transformation after watch and wait; Group 2B: transformation after a single therapeutic line for FL; Group 2C: transformation after at least two therapeutic lines for FL; Platinum-based regimens: dexamethasone, Ara-C, cisplatinum (DHAP), etoposide, dexamethasone, Ara-C, cisplatinum (ESHAP), ifosfamide, carboplatinum, etoposide (ICE); sequential therapy: anthracycline based short induction, CVP, intermediate dose Ara-C

Alonso-Alvarez, S., Magnano, L., Alcoceba, M., Andrade-Campos, M., Espinosa-Lara, N., Rodriguez, G., Mercadal, S., Carro, I., Sancho, J.M., Moreno, M., Salar, A., Garcia-Pallarols, F., Arranz, R., Cannata, J., Terol, M.J., Teruel, A.I., Rodriguez, A., Jimenez-Ubieto, A., Gonzalez de Villambrosia, S., Bello, J.L., Lopez, L., Mansalvo, S., Novelli, S., de Cabo, E., Infante, M.S., Pardal, E., Garcia-Alvarez, M., Delgado, J., Gonzalez, M., Martin, A., Lopez-Guillermo, A. & Caballero, M.D. (2017) Risk of, and survival after, histological transformation in follicular lymphoma in the rituximab era. A retrospective multicenter study by the Spanish GELTAMO group. *British Journal of Hematology*, **178**, 699-708.

Al-Tourah, A.J., Gill, K.K., Chhanabhai, M., Hoskins, P.J., Klasa, R.J., Savage, K.J., Sehn, L.H., Shenkier, T.N., Gascoyne, R.D. & Connors, J.M. (2008) Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **26**, 5165-5169.

Ban-Hoefen, M., Vanderplas, A., Crosby-Thompson, A.L., Abel, G.A., Czuczman, M.S., Gordon, L.I., Kaminski, M.S., Kelly, J., Millensone, M., Nademanee, A.P., Rodriguez, M.A., Zelenetz, A.D., Niland, J., LaCasce, A.S. & Friedberg, J.W. (2013) Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. *British Journal of Hematology*, **163**, 487-495.

Bastion, Y., Sebban, C., Berger, F., Felman, P., Salles, G., Dumontet, C., Bryon, P.A. & Coiffier, B. (1997) Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. *Journal of Clinical Oncology*, **15**, 1587-1594.

Behad, A., Boddy, C., Fought, A., Taxter, T., Falkiewickz, M., Landsburg, D.J., Winter, J.N., Pro, B., Gordon, L.I., Karmali, R. & Kaplan, J. (2017) Diffuse Large B-Cell Lymphomas Transformed from or with Concurrent Follicular Lymphoma Demonstrate Similar Clinical Outcomes As De-Novo Diffuse Large B-Cell Lymphomas, Except for Cases Harboring Double Hit Rearrangements. *Blood*, **130**, Suppl 1, 828.

Blaker, Y.N., Eide, M.B., Liestol, K, Lauritzen, G.F., Kolstad, A., Fossa, A., Smeland, E.B. & Holte H. (2014) High dose chemotherapy with autologous stem cell transplant for patients with transformed B-cell non-Hodgkin lymphoma in the rituximab era. *Leukemia & Lymphoma*, **55(10)**, 2319-2327.

Bouska, A., Zhang, W., Gong, Q., Iqbal, J., Scuto, A., Vose, J., Ludvigsen, M., Fu, K., Weisenburger, D.D., Greiner, T.C., Gascoyne, R.D., Rosenwald, A., Ott, G., Campo, E., Rimsza, L.M., Delabie, J., Jaffe, E.S, Braziel , R.M., Connors, J.M., Wu, C.I., Staudt, L.M., D'Amore, F., McKeithan, T.W. & Chan, W.C. (2016) Combined copy number and mutation analysis identifies oncogenic pathways associated with transformation of follicular lymphoma. *Leukemia,* **31(1),** 83-91.

Brotkorb, M., Linjiaerde, O.C., Huse, K., Troen, G., Hystad, M., Hilden, V.I., Myklebust, J.H., Leich, E., Rosenwald, A., Delabie, J., Holte, H. & Smeland, E.B. (2014) Whole-genome integrative analysis reveals expression signatures predicting transformation in follicular lymphoma. *Blood*, **123(7)**, 1051-1054.

Casulo, C., Burack, W.R. & Friedberg J.W. (2015) Transformed follicular non-Hodgkin lymphoma. *Blood*, **125**, 40-47

Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stoobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V. (2007) Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*, **25**, 579-586.

Conconi, A., Ponzio, C., Lobetti-Bodoni, C., Motta, M., Rancoita, P.M.V., Stathis, A., Moccia, A.A., Mazzuchelli, L., Bertoni, F., Ghielmini, M., Cavalli, F. & Zucca, E. (2012) Incidence, risk factors and outcome of histological transformation in follicular lymphoma. *British Journal of Hematology*, **157**, 188-196.

Crump, M., Neelapu, S.S., Farooq, U., Van Den Nesten, E., Kuruvilla, J., Westin, J., Link, B.K., Hay, A., Cerhan, J.R., Zhu, L., Boussetta, S., Feng, L., Maurer, M.J., Navale, L., Wiezorech, J., Go, W.J. & Gisselbrecht, C.

(2017) Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood,* **130**, 1800-1808

Cunningham, D., Hawkes, E.A., Jack, A., Quian, W., Smith, P., Mouncey, P., Pocock, C., Ardeshna, K.M., Radford, J.A., McMillan, A., Davies, J., Turner, D., Kruger, A., Johnson, P., Gambell, J. & Linch, D. (2013) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*, **381**, 1817-1826.

Federico, M., Caballero, M.D., Marcheselli, L., Tarantino, V., Manni, M., Sarkozy, C., Alonso-Alvarez, S., Wondergem, M., Cartron, G., Lopez-Guillermo, A., Issa, D, Morschhauser, F., Alcoceba, M., Kimby, E., Rusconi, C., Chamuleau, M., Holter, H., Lockmer, S., Montoto, S., da Silva, M.G., Aurer, I., Zucca, E., Paszkiewicz-Kozik, E., Minoia, C.,Skrypets, T., Blaker, Y.N., Salles, G. & Coiffier, B., for the Aristotle Consortium(2018) Rituximab and the risk of transformation of follicular lymphoma: a retrospective pooled analysis. *Lancet Haematol,* **5**, e359-67.

Federico, M., Luminari, S., Dondi, A., Tucci, A., Vitolo, U., Rigacci, L., Di Raimondo, F., Carella, A.M., Pulsoni, A., Merli, F., Arcaini, L., Angrilli, F., Stelitano, C., Gaidano, G., Dell'olio, M., Franco, V., Galimberti, S., Sacchi, S. & Brugiatelli, M. (2013) R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. *Journal of Clinical Oncology*, **31**, 1506-1513.

Ghesquieres, H., Berger, F., Felman, P., Callet-Bauchu, E., Bryon, P.A., Traverse-Glehen, A., Thieblemont, C., Baseggio, L., Michallet, A.S., Coiffier, B. & Salles, G. (2006) Clinicopathologic characteristics and outcome of diffuse large B-cell lymphomas presenting with an associated low-grade component at diagnosis. *Journal of Clinical Oncology*, **24**, 5234-5241.

Gleeson, M., Hawkes, E.A., Peckitt, C., Wotherspoon, A., Attygalle, A., Sharma, B., Du, Y., Ethell, M., Potter, M., Dearden, C., Horwich, A., Chau, I. & Cunningham, D. (2016) Outcomes of transformed follicular lymphoma in the rituximab era: the Royal Mardsen experience 2003-2013. *Leukemia & Lymphoma*, **58(8)**, 1805-1813.

Godfrey, J., Leukam, M.J.& Smith, S.M. (2018) An update in treating transformed lymphoma. *Best Practice & Research Clinical Hematology,* **31, 251-261**

Guirguis, H.R., Cheung, M.C., Piliotis, E., Spaner, D., Berinstein, N.L., Imrie, K., Zhang, L. & Buckstein, R. (2014) Survival of patients with transformed lymphoma in the rituximab era. *Annals of Hematology*, **93**, 1007-1014.

Kansara, R., Connors, J.M., Savage, K.J., Gerrie, A.S., Scott, D.W., Slack, G.W., Gascoyne, R.D., Sehn, L.H., & Villa, D. (2016) Maintenance rituximab following induction R-CHOP chemotherapy in patients with composite or discordant, indolent and aggressive, B-cell non-Hodgkin lymphomas. *Haematologica,* **101(10),** 411-414.

Kim, H., Hendricskon, R. & Dorfman, R.F. (1977) Composite lymphoma. *Cancer,* **40**, 959-976.

Lerch, K., Meyer, A.H., Stroux, A., Hirt, C., Keller, U., Viardot, A., Marks, R., Schreiber, S., Pezzuto, A. & Scholz, C.W. (2015) Impact of prior treatment on outcome of transformed follicular lymphoma and relapsed de novo diffuse large B cell lymphoma: a retrospective multicentre analysis. *Annals of Hematology,* **94**, 981-988.

Link, B.K., Maurer M.J., Nowakowski, G.S., Ansell, S.M., Macon, W.R., Syrbu, S.I., Slager, S.L., Thompson, C.A., Inwards, D.J., Johnston, P.B., Colgan, J.P., Witzig, T.E., Habermann, T.M & Cerhan, J.R. (2013). Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the

University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *Journal of Clinical Oncology*, **31**, 3272-3278.

Madsen, C., Pedersen, M.B., Vase, M.O., Bendix, K., Moller, M.B., Johansen, P., Jensen, B.A., Jensen, P., Munksgaard, L., Brown, P.D., Segel, E.K. & d'Amore, F.A. (2015) Outcome determinants for transformed indolent lymphomas treated with or without autologous stem cell transplantation. *Annals of Oncology*, **26**, 393-399.

Magnano, L., Balaguè, O., Dhlouy, I., Rovira, J., Karube, K., Pinyol, M., Rivas-Delgado, A., Costa, D., Martinez-Trillos, A., Gonzalez-Farre, B., Martinez-Pozo, A., Giné, E., Colomer, D., Delgado, J., Villamor, N., Campo, E. & Lopez-Guillermo, A. (2017) Clinicobiological features and prognostic impact of diffuse large B-cell component in the outcome of patients with previously untreated follicular lymphoma. *Annals of Oncology,* 28, 2799-2805

Mokthar, N.M. (2007) Composite lymphoma. *Journal of Egyptian National Cancer Institute,* **19,** 171-175

Montoto, S. (2015) Treatment of patients with transformed lymphoma. *Hematology. American Society of Hematology. Education Program*, **2015**, 625-630.

Montoto, S., Davies, A.J., Matthews, J., Calaminici, M., Norton, A.J., Amess, J., Vinnicombe, S., Waters, R., Rohatiner, A.Z. & Lister, T.A. (2007) Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *Journal of Clinical Oncology*, **25**, 2426-2433.

Pasqualucci, L., Khiabanian, H., Fangazio, M., Vasishtha, M., Messina, M., Holmes, A.B., Ouillette, P., Trifonov, V., Rossi, D., Tabbò, F., Ponzoni, M., Chadburn, A., Murty, V.V., Baghat, G., Gaidano G., Inghirami, G., Malek, S.N., Rabadan, R. & Dalla-Favera, R. (2014) Genetics of Follicular Lymphoma Transformation. *Cell Reports*, **6**, 130-140.

Sarkozy, C., Trneny, M., Xerri, L., Wickham, N., Feugier, P., Leppa, S., Brice, P., Soubeyran, P., Da Gomes, S.M., Mounier, C., Offner, F., Dupuis, J., Caballero, M.D., Canioni, D., Paula, M., Delarue, R., Zachee, P., Seymour J., Salles, G. & Tilly, H. (2016) Risk factors and outcomes for patients with follicular lymphoma who had an histologic transformation after response to first-line immune-chemotherapy in the PRIMA trial. *Journal of Clinical Oncology*, **34**, 2575-2582.

Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (2008) WHO classification of tumors of haematopoietic and lymphoid tissues. IARC Press, Lyon, International Agency for Research on Cancer

Villa, D., Crump, M., Panzarella, T., Savage, K.J., Toze, C.L., Stewart, D.A., MacDonald, D.A., Buckstein, R., Lee, C., Alzharani, M., Rubinger, M., Foley, R., Xenocostas, A., Sabloff, M., Muccilli, A., Chua, N., Couture, F., Larouche, J.F., Cohen, S., Connors, J.M., Ambler, K., Al-Tourah, A., Ramadan, K.M. & Kuruvilla, J. (2013) Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. *Journal of Clinical Oncology*, **31**, 1164-1171.

Vitolo, U., Trněný, M., Belada, D., Burke, J.M., Carella, A.M., Chua, N., Abrisqueta, P., Demeter, J., Flinn , I., Hong, X., Kim, W.S., Pinto, A., Shi, Y.K., Tatsumi, Y., Oestergaard, M.Z., Wenger, M., Fingerle-Rowson, G., Catalani, O., Nielsen, T., Martelli, M. & Sehn, L.H. (2017) Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *Journal of Clinical Oncology*, **35**, 3529-3537.

Wagner-Johnston, N.D., Link, B.K., Byrtek, M., Dawson, K.I., Hainsworth, J, Flowers, C.R., Friedberg, J.W. & Bartlett, N.I. (2015). Outcomes of transformed follicular lymphoma in the modern era: a report from the National LymphoCare Study (NLCS). *Blood*, **126**, 851-857.