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Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database

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Summary

Histological transformation (HT) is a major cause of morbidity and mortality in patients with indolent non-Hodgkin lymphoma (NHL). The multicentre National Cancer Comprehensive Network database for NHL provides a unique opportunity to investigate the natural history of HT in the rituximab era. 118 patients with biopsy-confirmed indolent lymphoma and subsequent biopsy-confirmed HT were identified. Treatments for HT included autologous stem-cell transplant (auto-SCT) ($n = 50$), allogeneic SCT (allo-SCT) ($n = 18$), and treatment without transplant ($n = 50$). The 2-year overall survival (OS) for the entire cohort was 68%. For auto-SCT patients aged ≤60 years ($n = 24$), the 2-year OS was 74%. For non-transplanted patients aged ≤60 years ($n = 19$), the 2-year OS was 59%. The 2-year OS of patients naïve to chemotherapy prior to HT was superior to patients who were exposed to chemotherapy prior to HT (100% vs. 35%, $P = 0{\cdot}03$). In this largest prospective cohort of patients of strictly defined HT in the rituximab era, the natural history of HT appears more favourable than historical studies. Younger patients who were not exposed to chemotherapy prior to HT experienced a prolonged survival even without transplantation. This study serves as a benchmark for future trials of novel approaches for HT in the Rituximab era.

Keywords: rituximab era, non-Hodgkin lymphoma, histological transformation, stem-cell transplantation, diffuse large B-cell lymphoma.

The natural history of indolent non-Hodgkin lymphoma (NHL) is variable, but generally characterized by prolonged survival that has been recently increasing since the introduction of rituximab as part of standard therapy (Fisher *et al*, 2005a; Swenson *et al*, 2005). A major cause of morbidity and mortality of indolent NHL is histological transformation (HT), which is the evolution of indolent NHL to diffuse large B-cell lymphoma (DLBCL). Transformation occurs at a

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rate of approximately 3% per year, and arises from all subtypes of indolent B cell lymphoproliferative disorders (Bastion *et al*, 1997; Al-Tourah *et al*, 2008). In the pre-Rituximab era, the prognosis of transformation was generally poor, with a median survival after histological conversion of approximately 1 year for patients with follicular lymphoma (FL) (Montoto *et al*, 2007).

For younger patients with a favourable performance status, high-dose therapy with autologous stem cell transplantation (auto-SCT) results in a prolonged progression-free survival (PFS) for a substantial subset of patients with transformed NHL, based upon retrospective single and multi-institutional experiences (Bernstein & Burack, 2009). Auto-SCT has offered 2-year overall survival (OS) rates ranging between 40% and 74% (Foran *et al*, 1998; Friedberg *et al*, 1999; Chen *et al*, 2001; Williams *et al*, 2001; Andreadis *et al*, 2005; Sabloff *et al*, 2007; Ramadan *et al*, 2008; Eide *et al*, 2011). Data on the impact of rituximab on outcome of transformation are quite limited. A preliminary presentation of an experience of patients with HT from Vancouver, British Columbia suggested that R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) results in a superior OS compared to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) for treatment of HT (Al-Tourah *et al*, 2007). Bains *et al* (2013) studied outcomes in 34 patients with limited-stage FL treated with radiotherapy who developed HT. They found that the addition of rituximab for the treatment of HT improved the 3-year post-transformation OS compared with combination chemotherapy alone (87% vs. 38·5%, $P < 0{\cdot}00001$).

We used the multicentre National Cancer Comprehensive Network (NCCN) prospective registry to define the prognosis of HT in the rituximab era. In this study, we describe the experience of 118 patients with transformed lymphoma in the rituximab era. Survival outcomes for various treatment modalities including stem cell transplant (autologous, allogeneic, or both), standard chemotherapy without transplant, and other more conservative measures were examined. Finally, for the patients who were not transplanted for HT, we compared the outcomes of those who were treatment-naïve prior to HT *versus* those who were treatment-exposed prior to HT.

Patients and methods

We used the NCCN NHL database (http://www.nccn.org/network/business_insights/outcomes_database/outcomes.asp), a multicentre prospective registry of comprehensive clinical, treatment, and outcome data for patients with NHL, to evaluate the natural history of HT (LaCasce *et al*, 2008). All patients with indolent NHL or HT presenting to participating NCCN centres between 1 July 1 2000 and 29 February 2011, were eligible for inclusion in this cohort. Patients were identified based on transformation, and included both newly and previously diagnosed NHL. Some of the patients were enrolled prior to HT. The seven participating NCCN member institutions included: City of Hope Comprehensive Cancer Center, Dana-Farber Cancer Center, Fox Chase Cancer Center, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Roswell Park Cancer Institute, The University of Texas M.D. Anderson Cancer Center, and The University of Michigan Comprehensive Cancer Center. The institutional review boards at all participating centres approved the data collection protocol for the NCCN-NHL outcomes database.

Patients were required to meet the following definition of HT for inclusion: (i) confirmed documentation of initial pathological diagnosis of indolent NHL, and (ii) biopsy proven transformation to DLBCL more than 6 months from the initial diagnosis of the indolent histology. We required a minimum of 6 months between the diagnosis of indolent and aggressive histologies in order to ensure that the study excluded composite and discordant histologies. All pathology was reviewed at NCCN institutions by experienced haematopathologists. Patients not meeting these criteria were excluded, as were those with discordant histologies on presentation. Furthermore, patients with grade 3b FL were excluded. Eligible patients were divided into the following groups, based upon their treatment for histological transformation: any stem cell transplant (SCT) and no SCT for treatment of HT. Patients who had SCT prior to HT were not included. Patients who received SCT for HT were further subdivided into autologous (auto-SCT) and allogeneic stem cell transplant (allo-SCT). If more than one SCT was received during follow up, type of first transplant received following HT was used for classification. Patients in the allo-SCT group never received auto-SCT. Primary comparisons were made between patients who received SCT *versus* those who did not (no-SCT). Subgroup analyses were performed on the cohort of patients aged ≤60 years. Baseline demographic and clinical characteristics were examined, including: age at initial diagnosis, age at HT, gender, ethnicity, disease histology at diagnosis, type of therapy received prior to HT as well as number of therapy lines prior to HT and time from initial diagnosis to HT. For patients not receiving SCT, type of therapy received for HT was reported. The primary endpoint sought was OS, defined as time from HT to death. Median follow-up time was defined as the time (in years) starting from the diagnosis of HT to their last quality visit date with an NCCN institution, using a reverse censoring method. Baseline demographic and clinical characteristics were compared between any SCT and no-SCT cohorts, auto-SCT and allo-SCT cohorts, and auto-SCT *versus* allo-SCT *versus* no-SCT cohorts using chi-square or Fisher's exact test for categorical variables and Kruskal-Wallis test for medians. OS was estimated using the Kaplan-Meier method. P values $< 0{\cdot}05$ were considered statistically significant. All analyses were performed using SAS v9·2 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics

A total of 118 patients were eligible for analysis after exclusion. Their clinical characteristics are outlined in Table I. 71 (60%) were male and the median age at diagnosis of HT was 59 years (range: 37 ~ 88 years). Histologies at diagnosis of indolent lymphoma were: 102 (86%) FL (grades 1 ~ 3a, 3 not otherwise specified [NOS], or NOS); 12 (10%) marginal zone lymphoma; and 4 (3%) small lymphocytic lymphoma. Prior to HT, 23 (19%) were treatment-naïve while 95 (81%) had been exposed to treatment for their indolent lymphoma. 83 (70%) were treated with rituximab-containing regimens and 60 (51%) were exposed to anthracyclines. Median number of therapeutic lines given prior to HT was one (range 0–8). Median time from indolent NHL to HT was 30 months (range: 6–184 months).

Treatments for histological transformation

Treatment modalities for HT included auto-SCT ($n = 50$), allo-SCT ($n = 18$), and treatment without transplant (no-SCT; $n = 50$). Clinical characteristics of the patients treated with SCT for HT ($n = 68$) are depicted in Table II. At the time of transplant, 78% of auto-SCT and 67% of allo-SCT patients demonstrated a response to salvage treatment prior to their transplant. Patients in the auto-SCT group were older compared to the allo-SCT group (60 vs. 52 years, $P < 0{\cdot}0001$).

Clinical characteristics and treatments for HT of patients not treated with transplant for HT are depicted in Table III. 88% of these patients underwent chemotherapy at HT, of which an R-CHOP-based regimen was the most commonly used (56%). A salvage regimen (cytarabine- or platinum-based) was used in 19 (38%), a lenalidomide-based regimen was used in 2 (4%), and radioimmunotherapy was administered in 3 (6%). Six (12%) patients had neither chemotherapy nor any immunotherapy for HT and were observed only. The mean age for these untreated patients was 60 years (range: 48 ~ 71 years). All of these 6 patients had advanced stage disease (III/IV), were treatment-exposed prior to HT, and most succumbed to death via disease progression within months after the diagnosis of HT.

There were two significant differences that were detected between the SCT and no-SCT groups. First and expectedly, patients not transplanted were older than those transplanted (64 vs. 56 years, $P = 0{\cdot}002$). Secondly, a higher percentage of patients receiving any transplant for HT were exposed to an anthracycline-based regimen prior to HT compared to their non-transplanted counterparts (60% vs. 38%, $P = 0{\cdot}03$), and a lower percentage of patients transplanted for HT were chemotherapy-naïve compared to patients not transplanted for HT (10% vs. 32%, $P = 0{\cdot}005$).

Table I. Clinical characteristics of all 118 patients.

Characteristic	Number ($N = 118$)
Male, (%)	71 (60)
Median age at diagnosis of indolent disease (range), years	55 (31 ~ 85)
Median age at diagnosis of HT (range), years	59 (37 ~ 88)
Median time from diagnosis of indolent NHL to HT, months (range)	30 (6 ~ 184)
Ethnicity, (%)	
Caucasian (non-Hispanic)	104 (88)
Hispanic	6 (5)
African-American (non-Hispanic)	4 (3)
Asian Pacific Island (non-Hispanic)	3 (3)
Unknown	1 (1)
Histology prior to transformation, (%)	
Follicular	102 (86)
Grade 1	61 (52)
Grade 2	25 (21)
Grade 3a or 3 NOS	12 (10)
Grade NOS	4 (3)
Marginal Zone	12 (11)
MALT/Extranodal	8 (7)
Nodal	2 (2)
Splenic	2 (2)
Small Lymphocytic Lymphoma*	4 (3)
Therapy prior to HT, (%)	
Observation only	23 (19)
Any treatment	95 (81)
Rituximab-based	83 (70)
Anthracycline-based	60 (51)
Median number of therapeutic lines prior to HT (range)	1 (0 ~ 8)
Therapy for HT, (%)	
Autologous SCT	50 (42)
Allogeneic SCT	18 (15)
No transplant	50 (42)

NHL, non-Hodgkin lymphoma; HT, histological transformation; NOS, not otherwise specified; MALT, mucosa-associated lymphoid tissue lymphoma; SCT, stem cell transplantation.

*All patients with Small Lymphocytic Lymphoma had lymphocyte counts $<5{\cdot}0 \times 10^9$/l prior to HT.

Outcomes

All patients. For all 118 patients, the 20 and 5-year OS was 68% (95% confidence interval [CI]: 59–76%) and 49% (95% CI: 37–59), respectively, as depicted in the Kaplan–Meier curve (Fig 1A). With a median follow-up time of 3·4 years for all 118 patients, the median OS was 4·9 years. Of the 118 patients, 53 (45%) died: 58% of the no-SCT group, 30% of the auto-SCT group, and 50% of the allo-SCT group. The 2-year OS for patients transplanted for HT (auto- and allo-SCT) was 79% (95%CI: 69–89), while for the patients not transplanted for HT, it was 53% (95%CI: 39–68), as

Table II. Clinical characteristics of patients treated with stem cell transplantation for HT (n = 68).

	Any SCT N = 68	Autologous SCT N = 50	Allogeneic SCT N = 18
Median Age at HT (range)	57 (37 ~ 78)*	60 (44 ~ 78)	52 (37 ~ 57)
Median months from diagnosis of indolent NHL to HT (range)	1138 (37 ~ 184)**	1144 (6 ~ 184)	1138 (6 ~ 84)
Therapy Prior to HT, (%)			
Observation only	7 (10)*	5 (10)	2 (11)
Rituximab	52 (77)	37 (74)	15 (83)
Anthracycline	41 (60)**	30 (60)	11 (61)
Median Number of Prior Therapeutic Lines (range)	1 (0 ~ 8)	1 (0 ~ 4)	2 (0 ~ 8)
Median days from dx of HT to transplant	181 (63 ~ 1900)	174 (63 ~ 1900)	188 (75 ~ 565)
Disease status at SCT, (%)			
Any response	51 (75)	39 (78)	12 (67)
Resistant	7 (10)	2 (4)	5 (28)
Unknown	10 (15)	9 (18)	1 (6)

NHL, non-Hodgkin lymphoma; HT, histological transformation; SCT, stem cell transplantation; Dx, diagnosis.
*Statistically significant difference between patients who obtained any SCT *versus* no SCT with P = 0·002.
**Statistically significant difference between patients who obtained any SCT *versus* no SCT with P = 0·01.

Table III. Clinical characteristics of patients treated without transplantation for HT (n = 50).

	No transplant (N = 50)
Median age at HT (range), years	64 (38 ~ 88)
Median time from diagnosis of indolent NHL to HT (months) (range)	21 (6 ~ 118)
Therapy Prior to HT (%)	
Observation only	16 (32)
Rituximab	31 (62)
Anthracycline	19 (38)
Median Number of Prior Therapeutic Lines (range)	1 (0 ~ 4)
Treatment for Transformation Chemotherapy, (%)	44 (88)
R-CHOP variant	28 (56)
Salvage regimen	19 (38)
Lenalidomide-based	2 (4)
Radioimmunotherapy	3 (11)
Other	2 (7)
No therapy for Transformation, (%)	6 (12)

HT, histological transformation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

illustrated in Fig 1B. Of the patients receiving a transplant, the 2-year OS for the auto-SCT group was 83% (95%CI: 70–91), and 65% (95%CI: 39–83) in the allo-SCT group. In the auto-SCT group, there was no survival difference based on Rituximab exposure prior to HT. Of the no-SCT patients, those who were untreated prior to HT (no chemotherapy nor monoclonal antibody therapy; n = 16) experienced a superior survival compared to the no-SCT patients who were treatment-exposed prior to HT (81% vs. 39%, P = 0·003, Fig 1C). Although there was no survival difference detected between anthracycline exposure prior to HT when examining the entire cohort of 118 patients, this was not the case in the subgroup of non-transplanted patients. The non-transplanted patients who were naïve to anthracyclines prior to HT experienced a superior survival compared to those who were anthracycline-exposed (2-year OS of 61% vs. 38%, P = 0·05).

Patients aged ≤60 years. Of the patients aged ≤60 years (n = 61), the 2- and 5-year OS was: 67% (95%CI: 53–77) and 51% (95%CI: 34–65), respectively. For auto-SCT patients aged ≤60 years (n = 24), the 2-year OS was 74% (95%CI: 51–87). For allo-SCT patients aged ≤60 years (n = 18), the 2-year OS was 65% (95%CI: 39–83). For no-SCT patients aged ≤60 years (n = 19), the 2-year OS was 59% (95%CI: 32–78). These curves are depicted in the Kaplan-Meier curves in Fig 2A. In the non-transplanted younger (aged ≤60 years) patients, the 2-year OS of the 6 patients naïve to therapy prior to HT was superior to that of the 13 patients who were exposed to chemotherapy or Rituximab prior to HT (100% vs. 35%, P = 0·03, Fig 2B). The 5-year OS of these younger no-SCT patients that were treatment-naive prior to HT was 80% (95% CI: 20–97%). Of the 6 non-transplanted younger patients that were treatment-naïve prior to HT, two patients died (2·7 and 6·1 years after HT respectively) and the other 4 have thus far not experienced any other relapse or disease progression.

Cause of Death

Causes of death, stratified by treatment for HT, are outlined in Table IV. Cause of death was due to disease progression in 59% of the no-SCT patients, 60% of the auto-SCT patients, and 44% of the allo-SCT patients. Death due to treatment-related toxicity occurred in 17% of the no-SCT

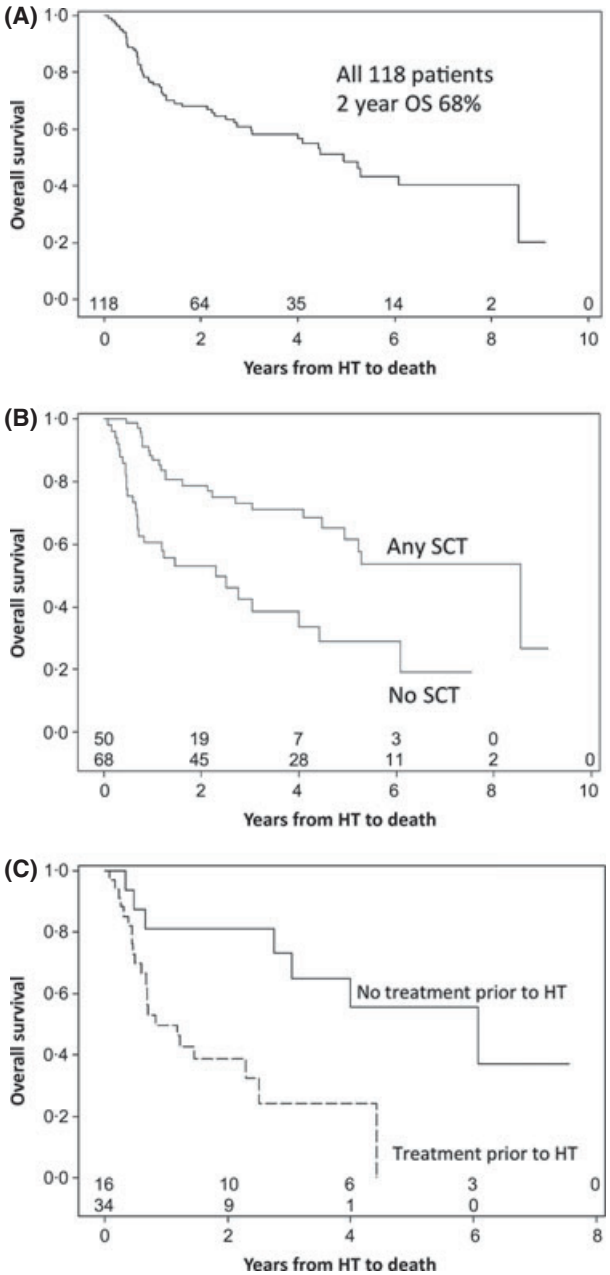

Fig 1. Overall survival. (A) For all 118 patients, the 2- and 5-year overall survival (OS) was 68% (95% confidence interval [CI]: 59–76%) and 49% (95%CI: 37–59%), respectively. (B) 2-year OS for the non-stem cell transplantation (SCT) patients was 53% (95%CI: 39–68%) and for any SCT (auto-SCT and allo-SCT) group it was 79% (95%CI: 69–89%). (C) All non-transplanted patients (n = 50), treatment prior to histological transformation (HT; n = 34) *versus* no treatment prior to HT (n = 16). Among the no-SCT patients (n = 50), those who were not exposed to chemotherapy nor monoclonal antibody therapy prior to HT (n = 16) experienced a superior survival compared to that of the 34 patients who were treatment-exposed prior to HT (81% vs. 39%, P = 0·003).

group, 7% of the auto-SCT group, and 44% of the allo-SCT group. The median age of the 17% of no- SCT patients that died of treatment-related mortality was 69 years (range:

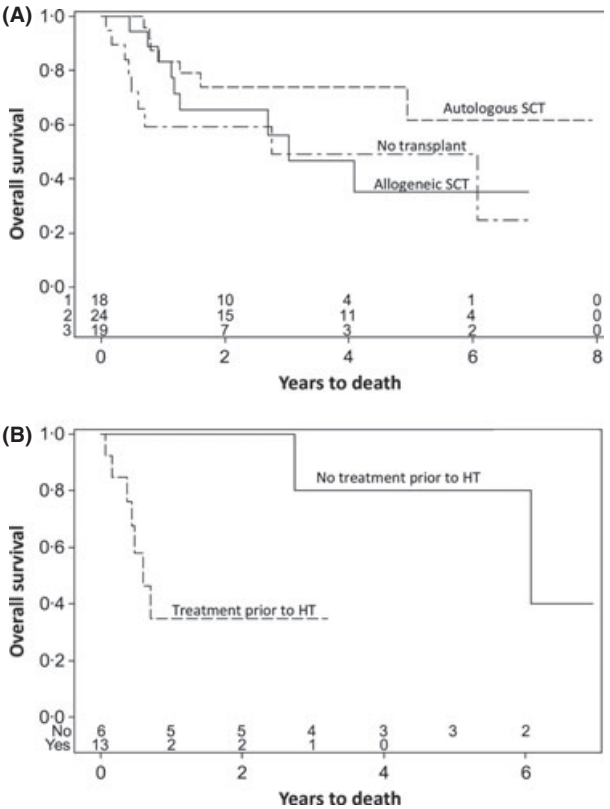

Fig 2. Patients aged ≤60 years (n = 61). (A) Overall Survival (OS) in years from histological transformation (HT) by treatment for HT. For autologous stem cell transplantation (SCT) patients aged ≤60 years (n = 24), the 2-year OS was 74% (95%CI: 51–87%). For allogeneic SCT patients aged ≤60 years (n = 18), the 2-year OS was 65% (95%CI: 39–83%). For no-SCT patients aged ≤60 years (n = 19), 2-year OS was: 59% (95%CI: 32–78%). (B) Non-transplanted patients aged ≤60 years (n = 19), no treatment prior to HT (n = 6), *versus* treatment prior to HT (n = 13), (P = 0·03).

59 ~ 80 years). Specific aetiologies for the treatment-related toxicity for the allo-SCT group included fungal and bacterial infections as well as hepatic veno-occlusive disease. Death due to a secondary malignancy occurred in 2 patients in the no-SCT group (both died from pancreatic cancer), a single individual in the auto-SCT group (colon cancer), and a single patient in the allo-SCT group (myelodysplastic syndrome).

Discussion

Our study of 118 patients is the largest cohort of patients with HT in the rituximab era. Importantly, we limited the study to include only patients meeting stringent criteria for histological transformation. We observed 3 main findings in this study: (i) Outcomes for HT are improving, with higher OS compared to historical data from the pre-rituximab era, (ii) Autologous stem cell transplant continues to yield favourable survival outcomes despite previous rituximab exposure, and (iii) There is a potential subgroup of patients,

Table IV. Cause of death.

Total number of patients who died	Allo-SCT (n = 9)	Auto-SCT (n = 15)	No-SCT (n = 29)	All (n = 53)
Death due to disease progression, (%)	4 (44)	9 (60)	17 (59)	30 (57)
Treatment-related toxicity, (%)	4 (44)	1 (7)	5 (17)	10 (19)
Failure to recover blood counts	–	–	1	
Fungaemia	1	–	1	
Bacterial infection	2	–	2	
Airway obstruction	–	–	1	
Hepatic veno-occlusive disease	1	–	–	
Multi-organ failure post-transplant	–	1	–	
Secondary malignancy, (%)	1 (11)	1 (7)	2 (7)	4 (8)
	MDS	Colon Cancer	Both pancreatic Cancer	
Motor Vehicle Accident, (%)	0	0	1 (3)	1 (2)
Unknown, (%)	0 (0)	4 (27)	4 (14)	8 (15)

SCT, stem cell transplantation; MDS, myelodysplastic symdrome.

specifically those that are naïve to any chemotherapy or rituximab prior to HT, who experience a prolonged survival without undergoing transplantation.

Although the underlying biology of transformation is not fully understood, there is increasing data that HT may occur by both divergent evolution from a common progenitor cell and/or by a direct evolution from the indolent lymphoma clone (Carlotti *et al*, 2009). Gene expression profiling (GEP) of 20 paired samples of FL and HT performed by Davies *et al* (2007) noted two pathways by which HT may evolve: one that is similar in proliferation rate to the antecedent FL and the other that has a higher proliferation rate and is characterized by the presence of recognized oncogenic abnormalities. The acquisition of novel mutations via somatic hypermutations has also been implicated in the pathogenesis of HT (Martinez-Climent *et al*, 2003; Rossi *et al*, 2006; Lawrie *et al*, 2009). In addition, it has been suggested that the tumour microenvironment may also play a critical role. In one study, GEP signatures were performed on FL samples of patients who developed HT later on and compared to those who did not develop HT (Glas *et al*, 2007). The GEP of patient samples who did not transform had a down-regulation of the immune related genes, therefore implying that HT may be mediated by an 'immune signature.' Rituximab therapy may be altering the underlying biology of transformation by interfering with any of the aforementioned mechanisms, contributing to our observed favourable outcomes. For example, Rituximab may affect genetic stability or tumour proclivity for acquiring novel oncogenic mutations, alter the tumour microenvironment, or change the regulation of immune related genes.

In the current literature, data regarding outcomes for HT are predominantly from the pre-Rituximab era. Studies from the Rituximab era are only recently emerging. Reddy *et al* (2012) studied patients who received either auto-SCT or allo-SCT for early HT (within 1 year of FL). These patients experienced a 5-year OS of 80%. This was compared to 15 patients in the same study who obtained SCT for late transformation (>1 year of FL), whose 5-year OS was significantly less at 34%. Recently, a Canadian study with 172 patients was published, where 22 patients were treated with allo-SCT, 97 with auto-SCT, and 53 with rituximab-containing chemotherapy. The 5-year OS after HT was 46% for allo-SCT, 55% for auto-SCT and 40% for no-SCT patients obtaining rituximab-containing chemotherapy (Villa *et al*, 2013). However, this trial included patients treated since 1994, which was prior to Rituximab approval.

In this present study, patients who obtained autologous SCT (n = 50) for HT experienced a 2-year OS of 83%, which appears more favourable compared to not only the historical controls from the pre-Rituximab era, but also to the Canadian study as well. Although there are caveats to making historical comparisons, similar survival data from the pre-Rituximab era range between 40% and 74% (Foran *et al*, 1998; Friedberg *et al*, 1999; Chen *et al*, 2001; Williams *et al*, 2001; Andreadis *et al*, 2005; Sabloff *et al*, 2007; Ramadan *et al*, 2008; Eide *et al*, 2011). There are a number of possible explanations for improved outcomes for auto-SCT for the treatment of HT in the Rituximab era, which include refinement and increased adherence to supportive care, changing eligibility for transplantation, and pretreatment rituximab improving outcomes in ASCT. Interestingly, the outcome of salvage therapy and auto-SCT for the treatment of *de novo* DLBCL failing first-line therapy has been shown in the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study (Gisselbrecht *et al*, 2010) to be inferior in those exposed to Rituximab therapy. However, we did not observe this phenomenon with transformed lymphoma in our study, with improved survival seen with auto-SCT compared to historical controls from the pre-Rituximab era. This reinforces the concept that there is a distinct biology between *de novo* DLBCL in first relapse and transformed DLBCL.

As expected in our registry study, there were distinct differences between the group that was received transplant and those not transplanted for HT. Transplanted patients tended to be more heavily pre-treated, yet were also younger than

their non-transplanted counterparts. Therefore, outcome comparisons between these groups cannot be made without strong caveats. In an effort to minimize age as a confounding factor for comparison, we performed a subgroup analysis that was limited to patients aged ≤60 years. This analysis yielded at least two major observations. First, given favourable OS for the entire ASCT group, auto-SCT should still be considered for treatment of HT.

Another notable observation was that the 2- and 5-year OS of the younger non-transplanted patients who were naïve to any chemotherapy or monoclonal therapy prior to HT were favourable, at 100% and 80% respectively. Disease progression as a cause of death was similar between patients who obtained auto-SCT (60%) and the non-transplanted group (59%). These results suggest that younger patients who are treatment-naïve prior to HT may still enjoy prolonged survival even without high-dose chemotherapy with SCT. This is consistent with older data from Stanford in the pre-rituximab era that demonstrated a superior OS in a cohort of patients with transformed lymphoma, for patients who were chemotherapy naïve at the time of transformation compared with those patients who were previously treated (Yuen *et al*, 1995). More recently, in a series of 60 patients that transformed in the rituximab era, survival after HT was also shown to be superior in patients who were initially observed compared to those patients who were initially treated with chemotherapy for their indolent disease (Link *et al*, 2012). Although radioimmunotherapy was approved in the United States for treatment of HT during our study (Gordon *et al*, 2004; Fisher *et al*, 2005b; Wondergem *et al*, 2012), and recent data suggests lenalidomide has substantial single-agent activity in transformed lymphoma (Czuczman *et al*, 2011), only three patients in our study were treated with radioimmunotherapy and two patients were treated with lenalidomide at transformation. Therefore, the impact of these novel regimens cannot be ascertained in our database.

Existing data regarding the use of allogeneic transplantation for HT are also limited, with the number of patients in these series ranging between 5 and 25 patients. In one series of 16 patients who underwent alloSCT for HT, there were 8 deaths related to transplant complications, 4 patients died of disease relapse, and the remaining 4 patients were alive and disease-free at <2 years post-SCT (Doocey *et al*, 2005). In another study of 16 patients with HT undergoing reduced-intensity conditioning (RIC) with allo-SCT, the 3-year OS was 21% (Rezvani *et al*, 2008), and in a series of 18 patients receiving RIC allo-SCT, the 4-year OS was 60% (Thomson *et al*, 2009). In our study, we report the OS of 18 patients undergoing allogeneic transplant for the treatment of HT in the Rituximab era. These patients experienced a 2-year OS of 65%. Similar to the other studies, cause of death in our study for the patients after an allo-SCT were mostly attributed to either disease progression (44%) or transplant-related mortality (44%), which included fungal and bacterial infections as well as hepatic veno-occlusive disease.

We acknowledge that comparisons between the various subgroups in this study as well as to historical controls cannot be adequately validated without a randomized controlled trial. However, it is unlikely that a randomized trial evaluating transplantation *versus* no transplantation will ever be completed due to accrual barriers. An intergroup study attempting to evaluate the role of radioimmunotherapy in HT closed after 3 years due to lack of accrual. Nevertheless, from our data, it appears that several treatment approaches individualized to patient factors are efficacious. Future studies need to explore the impact of molecular and immunological factors on treatment outcomes. For example, it is clear from studies in DLBCL that double hit features (BCL2- and MYC-positive disease) portend very poor outcomes (Friedberg, 2012); this is likely to be the case in HT as well.

In conclusion, compared with historical series, the natural history of histologically-defined HT appears more favourable in our multicentre, prospective cohort in the rituximab era. Long-term survival is seen with a variety of treatment strategies. In particular, patients who are therapy-naïve prior to transformation may experience favourable outcomes with Rituximab-containing therapy alone without transplant. Future studies should evaluate predictive biological factors and validate our results to determine which patients may benefit from a conservative approach to treatment of HT. We believe that the present study serves as an important benchmark for future trials of novel approaches for HT.

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Author contributions

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Conflict of interest disclosure

A.D.Z. is an advisor to Roche/Genentech. Otherwise, there are no potential conflicts of interest to disclose for all authors in this manuscript.

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