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Research Article

Clinical Characteristics, Treatment Pattern and Outcome of Histologic Transformed Lymphoma, a Single Institution Experience

Bolanle Gbadamosi[1*], Yifan Pang[2], Daniel Ezekwudo[1], David Macari[1], John Khoury[1], Anish Konde[1], Nwabundo Anusim[1], Michael Stender[1], Ishmael Jaiyesimi[1], Susanna Gaikazian[1]

[1]Department of Hematology and Oncology, Beaumont Hospital Oakland University School of Medicine, Royal Oak, MI, USA

[2]Department of Internal Medicine, Beaumont Hospital Oakland University School of Medicine, Royal Oak, MI, USA

[*]**Corresponding Author:** Dr. Bolanle Gbadamosi, Department of Hematology and Oncology, Beaumont Hospital Oakland University School of Medicine, Royal Oak, MI, USA, Tel: 347-272-9793, E-mail: gbadamosi.bm@gmail.com

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Abstract

Indolent lymphomas may transform into intermediate or high-grade lymphoma, a diagnosis that is usually made reached by tissue biopsy, with unfavorable prognosis. A retrospective study was performed of the clinical characteristics, treatment patterns and outcomes of 73 patients with histologic transformed lymphoma originating as follicular lymphoma (FL), chronic lymphocytic leukemia/small cell leukemia (CLL/SCL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), or low grade B cell lymphoma not otherwise specified (NOS). The median time to transformation was 55 months (range 1-258) and Diffuse Large B Cell Lymphoma (DLBCL) constituted the majority of HTL diagnosis diagnoses. There was a statistically significant longer time to the development of HTL in patients with CLL and LPL compared to other indolent lymphoma types (FL, MZL and low-grade B cell lymphoma NOS); however, overall survival (OS) at histologic transformation was similar regardless of the indolent lymphoma type preceding HTL. Treatment with Rituximab-containing regimens have increased overall survival in HTL compared with the pre-rituximab era. In the 63 treated cases of HTL, PET showed complete remission (CR) in the majority of patients (55%) with 15% achieving partial remission (PR) and 15% having progressive disease (PD). OS at two years was approximately 60%, and 41% of patients remained alive at 5 years. Univariate analysis identified that treatment with RCHOP conferred better OS when compared to regimens with less or greater intensity than RCHOP, p=0.001. Multivariate analysis confirmed that achievement of CR and LDH level

within the normal range statistically predicted better OS. On-going clinical trials may suggest novel therapeutics and provide for more evidence-based management of HTL.

Keywords: Lymphoma; Histological transformation; Chemotherapy; Overall survival; Rituximab; Clinical trials

1. Introduction

Despite the known favorable prognosis of indolent lymphomas (IL), histologic transformation (HT) to intermediate or high-grade lymphoma is a potential and significant event. Histologic transformed lymphoma (HTL) is rarely an end point in trials of indolent lymphomas and most of the transformations are to Diffuse Large B Cell Lymphoma (DLBCL). The PRIMA trial reported a 4.1% risk of HTL at six years in follicular lymphoma patients with high tumor burden [1]; there is paucity of data on HT in other types of indolent lymphomas. Diagnosis of HTL is ideally made by tissue biopsy, cellular morphology and immunohistochemistry with or without cytogenetics [2]. Others have defined HTL using clinical criteria [3] such as rapid progression of adenopathy, laboratory abnormalities and/or new onset of constitutional symptoms. Radiographic evidence, especially positron emission tomography (PET) scan, may be used in situations where adequate tissue diagnosis is not feasible. Current information on and the management of HTL are mostly extrapolated from retrospective studies of HTL or from prospective trials of DLBCL, despite known heterogeneity of DLBCL and exclusion of HTL patients from most trials of DLBCL [4]. Our study aims to contribute to the existing literature on the clinical characteristics, treatment pattern and outcomes of patients with HTL.

2. Methods and Statistical Analysis

Electronic medical records at Beaumont Hospital were retrospectively queried for patients with a diagnosis of intermediate or high-grade non-Hodgkin's lymphoma which includes DLBCL, Mantle cell lymphoma (MCL), Burkitt Lymphoma, or High-grade B cell lymphoma, type not otherwise specified (NOS) [5] from January 2007 to December 2015. This Study was approved by the William Beaumont Hospital Institutional Review Board and a waiver of individual informed consent was granted for this retrospective review. Patients having a tissue diagnosis of HTL were then identified for analysis. Baseline characteristics were reported as median (range) or mean (standard deviation) for continuous variables as appropriate, whereas categorical variables were reported as frequency (%). The Shapiro-Wilk test was used to assess the normality of continuous variables. Baseline characteristics of the different indolent lymphoma types were compared using the Kruskal-Wallis H-test for continuous data, and Chi-square test for categorical data. Survival was estimated using the Kaplan-Meier method. Univariate analysis of overall survival (OS) was performed with the log-rank test. A multivariate Cox proportional hazard model was constructed for OS using a limited backward elimination process. Candidate predictors for multivariate analysis were chosen to have a $P < 0.20$ in univariate analysis. The statistical significance level (P) was set at less than 0.05 for a two-tailed test. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0.

3. Results

Among the 617 patients identified with a diagnosis of intermediate or high-grade non-Hodgkin's lymphoma, 82 (13%) had pathologic diagnosis of HTL during the study period. Seventy-three patients had sufficient data to be included for analysis. Fifty-four of the 73 patients had diagnosis of HTL that was preceded by a period of indolent lymphoma diagnosis, while the remaining 19 patients were diagnosed with HTL based on tissue pathology showing intermediate or high-grade lymphoma at the same time as the initial diagnosis of indolent lymphoma. All patients had the tissue diagnosis confirmed by a hematopathologist.

The median age at diagnosis of HTL was 71 years (range 35-90); 34 (47%) patients were male and 39 (53%) were female. The majority of patients, 65 of 73 (89%), were Caucasian; 3 (4%) were African American and 5 (7%) were identified as other races. The types of indolent lymphoma diagnosed were: grade 1-2 follicular lymphoma (FL) in 33 patients (45%), Chronic lymphocytic leukemia/ small lymphocytic leukemia (CLL/SLL) in 17 patients (23%), marginal zone lymphoma (MZL) in 10 patients (14%), lymphoplasmacytic lymphoma (LPL) in 8 patients (11%), low grade B cell lymphoma NOS in 5 patients (7%). The median time to transformation was 55 months (range 1-258) in the fifty-four patients whose diagnosis of HTL had been preceded by a period of indolent lymphoma. DLBCL constituted the majority of HTL diagnoses 70 (96%); there were 2 (3%) cases of mantle cell lymphoma and 1 (1%) case of Burkitt lymphoma (Table 1).

Characteristic	n =73
Male	34 (46.6)
Age, years*	71 (35, 90)
Time to HTL, months*	19 (0, 258)
Ki67, %*	72.5 (10, 95)
LDH, U/L*	281 (107, 5403)
Uric acid, mg/dL*	5.6 (2.0-11.3)
Albumin, g/dL*	3.8 (1.9, 4.7)
WBC, bil/L*	6.7 (0.9, 81.8)
Hb, g/dL*	11.6 (4.6, 71.5)
Plt, bil/L*	201 (13, 627)
Low grade lymphoma treatment	
Observation	17 (23.3)
Treatment	37 (50.7)
Concurrent diagnosis with HTL	19 (26.0)
HTL treatment	
RCHOP	43 (58.9)
<RCHOP	
Rituximab + Bendamustine (BR)	4 (5.5)
Rituximab + Reduced Dose CHOP (R-mini-CHOP)	4 (5.5)

Rituximab + Cyclophosphamide, Vincristine, and Prednisone (R-CVP)	1 (1.4)
Rituximab only	1 (1.4)
Splenectomy only	1 (1.4)
>RCHOP	
RCHOP + high dose therapy followed by autologous stem cell transplant (HDT-ASCT)	1 (1.4)
Rituximab, Ifosfomide, Cyclophosphamide and Etoposide (R-ICE)	4 (5.5)
Rituximab, Etoposide, Prednisolone, Vincristine, Cyclophosphamide, Doxorubicin (R-EPOCH)	1 (1.4)
Rituximab, hyper fractionated Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone alternating with high dose methotrexate (R-Hyper-CVAD)	2 (2.7)
Rituximab + high dose methotrexate	1 (1.4)
Supportive only	8 (11.0)
Unknown	2 (2.7)
HTL response to treatment (n=63)	
CR	40 (54.8)
PR	11 (15.1)
PD	11 (15.1)
Unknown	1 (1.4)
Data are presented as n (%) or *median (range). Abbreviations: HTL, histologically transformed lymphoma; LDH, lactate dehydrogenase; WBC, white blood cell count; Hb, hemoglobin; PLT, platelet count; R-CHOP, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone; CR, complete remission; PR, partial response; PD, progressive disease.	

Table 1: Baseline characteristics of patients with histologically transformed lymphoma.

Among the 54 patients in whom diagnosis of indolent lymphoma preceded diagnosis of HTL, management of indolent lymphoma was by observation only in 17 (31.5%) patients and active treatment was prescribed for the remaining 37 (68.5%) patients (Table 1). Treatment strategies included: Rituximab only in 2 (3.7%) patients, 1-4 lines of a rituximab-containing regimen in 22 (40.7%) patients that included Bendamustine (BR); Fludarabine (FR); Fludarabine and Cyclophosphamide (FCR); or Chlorambucil (CR), Cyclophosphamide, Vincristine, and Prednisone (RCVP); non- rituximab containing systemic therapy in 3 (5.6%) patients (2 Chlorambucil and 1 ibrutinib); radiation therapy alone in 4 (7.4%) patients, and splenectomy only in 3 (5.6%) patients . Details of indolent lymphoma treatment were not available for the remaining 3 patients.

Treatment following diagnosis of HTL included Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP) in the majority of patients. Eleven (15.1%) patients were treated with a less intense regimen

than R-CHOP (<R-CHOP) and 9 (12.3%) patients received more intense regimen than R-CHOP (>R-CHOP) (See Table 1 for treatment details). Eight (11%) patients received supportive care only as they were not suitable candidates for treatment with chemotherapy, and treatment information was not available for the remaining 2 (2.7%) patients. In the 63 treated cases of HTL, PET showed complete remission (CR) in the majority of patients (55%) with 15% achieving partial remission (PR) and 15% having progressive disease (PD). No details of response were available for one patient.

Of the two patients diagnosed with double-hit DLBCL, the original diagnosis of both was follicular lymphoma and they both had elevated proliferative index Ki67 of 80% and 90%. One of the patients had progressive disease with RCHOP and received second line R-Hyper-CVAD without a durable response and died of progressive disease 18 months after diagnosis of HTL. The second patient had initial CR to first line R-CHOP but unfortunately developed CNS relapse shortly after and died of progressive disease 7 months after diagnosis of HTL.

Patient laboratory characteristics included median (range)levels of: lactate dehydrogenase (LDH) at 281 U/L (range: 107-5403 U/L); uric acid 5.6 mg/dL (range: 2.0-11.3 mg/dL), albumin 3.8 g/dL (range 1.9-4.7g/dL), white blood cell count 6.7 bil/L(0.9-81.8 bil/L), hemoglobin 11.5 g/dL (4.6-17.5 g/dL), and platelet count 201 bil/L (13- 627 bil/L). Proliferative index (Ki67) was reported in 64 patients; the median was 72.5% (range: 10-95) and 54 (84.3%) of these had a proliferative index of 50% or greater. Of the 34 patients that had cytogenetics and fluorescent in situ hybridization (FISH) performed, 2 (6%) met criteria for double-hit DLBCL, chromosomal rearrangement involving translocation of the c-myc gene located on chromosome 8q24 with the BCL2 and/or BCL6 genes (t 14:18) [5]. Extranodal involvement was present in 58 (79%) patients at the time of HTL diagnosis, with the number of extranodal sites being 1 site in 38 patients and 2 sites in 14 patients; 6 patients had 3 or more extranodal site involvement. At the time of diagnosis of HTL, the age of the patient, sex, Ki67, LDH, albumin, number of extranodal sites, response to treatment and OS were similar regardless of the type of indolent lymphoma. However, patients with Richter's transformation tended to have more leukocytosis and thrombocytopenia while those with HTL from MZL were more likely to have normal hemoglobin at diagnosis relative to others. There was a statistically significant difference in the median (range) time in months to transformation among the different indolent lymphoma histologies, with FL, MZL and low-grade lymphoma NOS progressing in a shorter time period than CLL and LPL; p=0.035 (Table 2).

Type	**CLL n=17**	**FL n=33**	**LPL n=8**	**MZL n=10**	**NOS n=5**	**p**
Age, years*	71.41 (43-88)	67.45 (40-90)	71.00 (62-84)	68.00 (35-86)	71.80 (62-80)	0.753
Sex	M 10, F 7	M 14, F 19	M 4, F 4	M4, F 6	M2, F3	0.817
Time to HTL, months†	59.5 (22.1-97.0), max 258	29.24 (15.0-43.5), max 129	84.63 (33.8-135.5), max 223	25.40 (1.1-49.7), max 85	23.6 (0.0 -83.7), max 110	**0.035**
IDL treatment	Obs:8	Obs:8	Obs:0	Obs:0	Obs:1	**0.018**

	Treat: 7	Treat: 14	Treat: 8	Treat: 6	Treat: 2	
Median Ki67, %*	63.85% (10%-90%)	66.07% (30%-90%)	71.62% (55%-85%)	64% (30%-95%)	75% (60%-90%)	0.824
Extranodal involvement	No:4 Yes:13	No:7 Yes: 26	No:1 Yes:7	No: 3 Yes:7	No:0 Yes:5	0.688
LDH, U/L	325.5 (135-1113)	533.76 (174-5403)	244.5 (107-484)	321.5 (130-800)	570.75 (281-1149)	0.804
Alb, g/dL	3.556 (1.9-4.7)	3.85 (2.8-4.7)	3.441 (2.2-4.2)	3.87 (2.8-4.5)	3.54 (2.2-4.0)	0.313
WBC, bill/L	22.231 (1.8-81.8)	7.136 (1.7-20.6)	4.625 (0.9-6.6)	8.81 (4.5-25.1)	16.04 (3.9 -55.3)	**0.002**
Hb, g/dL	11.1 (7.4 -14.9)	11.77 (4.6-15.0)	9.888 (6.9-12.5)	13.16 (10.2-17.5)	10.64 (9.6-11.5)	0.018
Plt, bill/L	149.94 (16-357)	224.91 (13-403)	171.13 (14-328)	291.60 (132-627)	209.20 (66-388)	**0.029**
Response	CR 8, PR 2, SD/PD 3	CR 21, PR 5, SD/PD 5	CR 3, PR 2, SD/PD 2	CR 5, PR 2, SD/PD 1	CR 3, PR 0, SD/PD 0	0.870
HTL survival time, months*	34.29 (0-85)	44.82 (0-130)	19.88 (0-38)	40.50 (1-158)	27.00 (0-92)	0.421

Data are presented as n (%);*median (full range); or †median (25th, 75th percentiles), maximum.

Abbreviations: HTL, histologically transformed lymphoma; M, male; F, female; IDL, indolent lymphoma; Obs, observation; Treat, treatment; LDH, lactate dehydrogenase; Alb, albumin; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet count; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table 2: Clinical characteristics of indolent lymphoma types in patients with HTL.

The median OS in the entire cohort of 73 patients from the time HTL was diagnosed was 31.0 months (range: 6.3 to 55.7 months). Survival at two years was approximately 60%, and about 41% of patients remained alive at 5 years (Figure 1). Univariate analysis identified that treatment with RCHOP conferred better OS when compared to regimens with less or greater intensity than RCHOP, p=0.001. Age less than 70 years (p=0.004), attainment of CR (p=0.001), LDH less than 422 U/L (p=0.001), albumin greater than 3.7g/dl (p=0.041) and hemoglobin greater than 11.5g/dl (p=0.001) also conferred better OS by univariate analysis (Table 3). Multivariate analysis confirmed attainment of CR and LDH within normal range (100-238 U/L) to have a statistically significant association with superior OS. Prior treatment with rituximab or other anti-CD 20 monoclonal antibody as indolent lymphoma had no statistically significant association with OS after diagnosis of HTL, p=0.65.

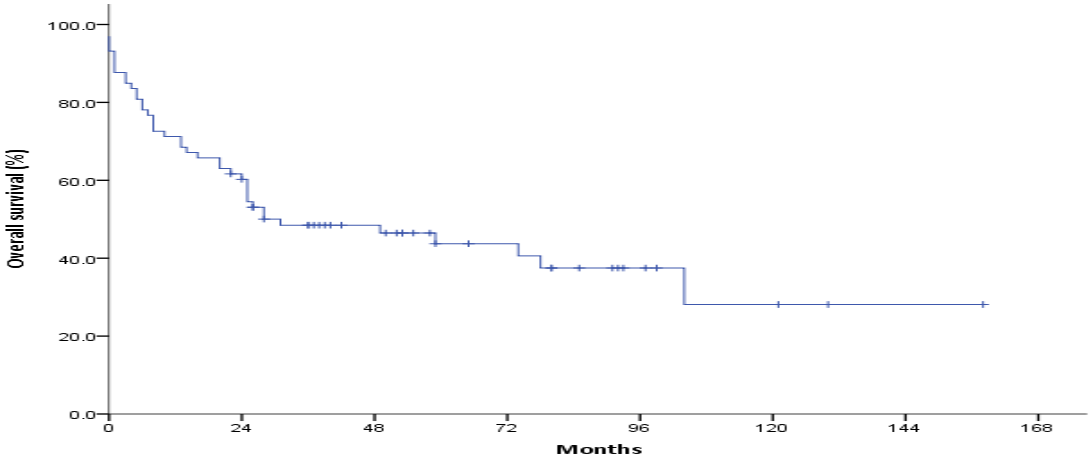

Figure 1: Kaplan Meier Curve of Overall Survival (OS) in the entire patient cohort with histologic transformed lymphoma. OS at two years was approximately 60%, and about 41% of patients remain alive at 5 years.

Variable	p	Directionality
Indolent lymphoma type	0.18	
Sex	0.759	
Indolent treated or observation	0.265	
HTL treatment	**0.001**	RCHOP is better than <RCHOP or >RCHOP
Extranodal presence or absence	0.56	
Response to treatment: CR, PR, SD/PD	**0.001**	CR the best
age <70 vs ≥70	**0.004**	<70 is better
Time to develop HTL	0.805	
Ki67, %	0.123	
LDH, U/L	**0.001**	LDH<422 better
Alb, g/dl	**0.041**	Alb>3.7 is better
WBC, bil/L	0.849	
Hb, g/dl	**0.001**	Hb>11.5 is better
Plt, bil/L	0.066	
Abbreviations: HTL, histologically transformed lymphoma; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; LDH, lactate dehydrogenase; WBC, white blood cells; Hb, hemoglobin; Plt, platelets.		

Table 3: Univariate analysis of variables associated with overall survival.

4. Discussion

Despite the favorable clinical course of most indolent lymphomas, histologic transformation to aggressive lymphoma remains a significant adverse event and in the pre-rituximab era was historically associated with worse outcome compared to patients with *de novo* aggressive lymphoma [2]. Published retrospective cohorts of HTL patients treated with chemotherapy alone without rituximab showed 5-year OS rates of 20% to 30%, and median OS ranging between 1 and 2 years [3, 6]. A more favorable prognosis has been shown for HTL since the introduction of rituximab. A study by Ban-Hoefen *et al.* reported 2-year OS of 68% [7], while 5-year OS survival of transformed lymphoma ranged from 40-70% [6-8]. These results are comparable to our study findings of 60% 2-year OS and 41% 5-year OS (Figure 1). However, a retrospective study of transformed DLBCL without prior RCHOP chemotherapy treatment for indolent lymphoma compared to *de novo* DLBCL treated with RCHOP showed no statistically significant difference in CR rate, PFS or OS between the *de novo* and transformed groups [8].

Follicular lymphoma is the most common subtype of indolent lymphoma and constitutes the most common indolent lymphoma to transform to aggressive lymphoma in the literature [3, 9, 10]. There are reports of HTL in other indolent lymphoma types such as CLL/SLL, MZL, and LPL [11-15]. Our institutional retrospective data also identified follicular lymphoma as the most common indolent lymphomas with HTL followed by CLL. Time to histologic transformation also varies among different types of indolent lymphoma; reported time to Richter's transformation in CLL ranged from 1.8 years to 4 years [16-18], from 2.75 years to 3.3 years in follicular lymphoma [2, 19], and 1.9 years to 2.6 years for marginal zone lymphoma [14]. Our study showed a statistically significant longer time to HTL in LPL and CLL compared to FL, MZL and low grade lymphoma NOS. Evaluating all indolent lymphomas with HTL, Villa et al reported a median time to transformation of 3.7 years in a retrospective study [20] similar to our findings of 3.4 years in the entire patient cohort.

Survival has also been reported to be different in transformed lymphoma depending on the type of indolent lymphoma [12, 21]; contrary to this, we found no statistically significant different in OS following histologic transformation between the types of indolent lymphoma in our study. Treatment of low-grade lymphoma was thought to have affected outcome at histologic transformation. Yuen *et al.* showed better outcome at transformation in patients with indolent lymphoma managed with observation [22] in a retrospective study. Another report by Montoto *et al.* found a higher risk of transformation of indolent lymphoma with expectant management [23, 24] while the GELA trial did not find differing transformation risk between indolent lymphoma managed with expectant management or early treatment [25]. Our study did not find a statistically significant difference between OS after diagnosis of HTL and choice of indolent lymphoma treatment, i.e., observation or systemic therapy. Prior treatment of indolent lymphoma with rituximab or any anti CD-20 monoclonal antibody has not been reported to have any statistically significant relationship with patients' outcomes after histologic transformation [26], also consistent with our study findings.

ClinicalTrials.gov Identifier	Study Title	Study design	Status	Intervention	Population
NCT03837873	DLCL002 Protocol for Patients with High Risk Aggressive B-cell Lymphoma	Phase 2	Recruiting	R-DA-EPOCH + ASCT or R-DA-EPOCH then R-DHAP + ASCT	Transformed lymphoma no prior treatment
NCT02343536	Open-label Trial of Oral Azacitidine (CC-486) Plus RCHOP in Subjects with Large B-Cell Lymphoma or Follicular Lymphoma or Transformed Lymphoma	Phase 1	Active, not recruiting	Oral Azacytidine + R-CHOP	Transformed lymphoma allowed
NCT03352765	Rituximab, Bendamustine and Melphalan Chemo-immunotherapy Followed by Reinfusion of One's Own Stem Cell for Treatment of B-cell Lymphoma in Elderly Patients	Phase 1,2	Recruiting	Rituximab, Bendamustine & melphalan and ASCT	Transformed lymphoma allowed
NCT02051257	Memory Enriched T Cells Following Stem Cell Transplant in Treating Patients with Recurrent B-Cell Non-Hodgkin Lymphoma	Phase 1	Active, not recruiting	CD19CAR-CD28-CD3zeta-EGFRt-expressing TCM-enriched T cells	Transformed recurrent non-Hodgkin lymphoma
NCT01665768	Maintenance Rituximab With mTor Inhibition After High-dose Consolidative Therapy in Lymphoma	Phase 2	Active, not recruiting	Everolimus and Rituximab	Transformed lymphoma allowed
NCT03133221	1630GCC: Zydelig Maintenance in B-Cell Non-Hodgkin's Lymphoma After Autologous Stem Cell Transplantation	Phase 2	Recruiting	Zydelig	Transformed after ASCT
NCT03147885	Selinexor Plus Combination Chemotherapy in Treating Patients with	Phase 1,2	Recruiting	Selinexor	Transformed recurrent non-Hodgkin lymphoma

	Advanced B Cell Non-Hodgkin Lymphoma				
NCT02652715	Salvia Hispanica Seed in Reducing Risk of Disease Recurrence in Patients with Non-Hodgkin Lymphoma	N/A (Pilot)	Active, not recruiting	Dietary Supplement: Salvia Hispanica Seed	Transformed recurrent non-Hodgkin lymphoma
NCT02924402	Study to Evaluate Safety and Tolerability of XmAb13676 in Patients with CD20-expressing Hematologic Malignancies	Phase 1	Recruiting	XmAb13676	Transformed lymphoma allowed
NCT03349450	DPX-Survivac and Checkpoint Inhibitor in DLBCL (SPiReL)	Phase 2	Recruiting	DPX-Survivac vaccine, Pembrolizumab and Cyclophosphamide	Transformed lymphoma allowed
NCT02207062	Ibrutinib in Treating Patients with Relapsed or Refractory Transformed Indolent B-cell Non-Hodgkin Lymphoma	N/A (pilot)	Active, not recruiting	Ibrutinib	Transformed lymphoma allowed
NCT03321643	Atezolizumab, Gemcitabine, Oxaliplatin, and Rituximab in Treating Patients with Relapsed or Refractory Transformed Diffuse Large B-Cell Lymphoma	Phase 1	Recruiting	Atezolizumab, Gemcitabine, Oxaliplatin, and Rituximab	Recurrent transformed non-Hodgkin lymphoma
NCT03884998	Copanlisib and Nivolumab in Treating Participants with Richter's Transformation or Transformed Indolent Non-Hodgkin's Lymphoma	Phase 1	Recruiting	Copanilisib in Combination With PD-1 Antagonist Nivolumab	Richter's transformation or transformed indolent non-Hodgkin's lymphoma
NCT00924326	CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma	Phase 1, 2	Active, not recruiting. Has results	Fludarabine, Cyclophosphamide, Anti-cluster of differentiation 19 (CD19)-CAR , Aldesleukin	Transformed follicular lymphoma

NCT02348216	Safety and Efficacy of KTE-C19 in Adults with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)	Phase 1,2	Recruiting	Axicabtagene Ciloleucel (KTE-C19), Fludarabine, Cyclophosphamide	Transformed follicular lymphoma
NCT02420912	Nivolumab and Ibrutinib in Treating Patients with Relapsed, Refractory, or High-Risk Untreated Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Richter Transformation	Phase 2	Active, not recruiting	Nivolumab, Ibrutinib	Richter syndrome
NCT02747732	Study of Ibrutinib in Combination with Bendamustine and Rituximab for Patients with Relapsed/Refractory Aggressive BCL	Phase 2	Recruiting	Ibrutinib, Bendamustine, Rituximab	Transformed indolent lymphoma
NCT03277729	A Phase I/II Study to Evaluate the Safety of Cellular Immunotherapy Using Autologous T Cells Engineered to Express a CD20-Specific Chimeric Antigen Receptor for Patients with Relapsed or Refractory B Cell Non-Hodgkin Lymphomas	Phase 2	Recruiting	CD20 CAR T cell IV	Recurrent/refractory transformed B-cell non-Hodgkin lymphoma
NCT02499003	GOAL: GA101 Plus Pixantrone for Relapsed Aggressive Lymphoma	Phase 2	Active, not recruiting	Obinutuzumab, Pixantrone	Transformed indolent non-Hodgkin's lymphoma
NCT02628405	R-ICE and Lenalidomide in Treating Patients with First Relapse/Primary Refractory Diffuse Large B-Cell Lymphoma	Phase 1,2	Recruiting	R-ICE and Lenalidomide	Recurrent/ refractory transformed non-Hodgkin lymphoma

NCT01897571	Open-Label, Multicenter study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects with Adv. Solid Tumors or With B-cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With DLBCL	Phase 1,2	Active, not recruiting	Tazemetostat	Transformed follicular lymphoma
NCT02572453	Onalespib in Treating Patients with Relapsed or Refractory Anaplastic Large Cell Lymphoma, Mantle Cell Lymphoma, or Diffuse Large B-Cell Lymphoma	Phase 2	Recruiting	Onalespib	Recurrent/ refractory transformed non-Hodgkin lymphoma
NCT03440567	Avelumab, Utomilumab, Rituximab, Ibrutinib, and Combination Chemotherapy in Treating Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma	Phase 1	Recruiting	Avelumab, Utomilumab, Rituximab, Ibrutinib, and Combination Chemotherapy	Transformed follicular lymphoma to diffuse large B-cell lymphoma
NCT03583424	Venetoclax, Carmustine, Etoposide, Cytarabine, and Melphalan Before Stem Cell Transplant in Treating Participants with Relapsed or Refractory Non-Hodgkin Lymphoma	Phase 1,2	Recruiting	Venetoclax, Carmustine, Etoposide, Cytarabine, and Melphalan	Refractory transformed indolent non-Hodgkin lymphoma
NCT03103971	huJCAR014 CAR-T Cells in Treating Adult Patients with Relapsed or	Phase 1	Recruiting	Autologous Human Anti-CD19CAR-4-1BB-CD3zeta-	Recurrent transformed non-Hodgkin lymphoma

	Refractory B-Cell Non-Hodgkin Lymphoma or Acute Lymphoblastic Leukemia			EGFRt-expressing CD4+/CD8+ T-lymphocytes, Cyclophosphamide, Fludarabine	
NCT03704714	Nivolumab and Combination Chemotherapy in Treating Participants with Diffuse Large B-Cell Lymphoma	Phase 1,2	Recruiting	Cyclophosphamide, Doxorubicin , Hydrochloride, Nivolumab, Prednisone, Rituximab, Vincristine Sulfate	Transformed follicular lymphoma to diffuse large B-cell lymphoma
NCT03484702	Trial to Determine the Efficacy and Safety of JCAR017 in Adult Subjects with Aggressive B-Cell Non-Hodgkin Lymphoma (TRANSCENDWORLD)	Phase 2	Recruiting	JCAR017	Transplant-ineligible transformed follicular lymphoma
NCT03833180	A Phase 1 Dose-Escalation and Cohort-Expansion of VLS-101 in Hematologic Malignancies	Phase 1	Recruiting	VLS-101	Richter transformation lymphoma

Abbreviations: N/A, not applicable.

Search performed on clinicaltrials.gov on 7/10/2019, using search criteria of transformed lymphoma, interventional studies, adult patients 18 and above, recruiting or active but not currently recruiting, available in all countries, all funders included. (Search algorithm) https://clinicaltrials.gov/ct2/results?cond=Transformed+Lymphoma&term=&type=Intr&rslt=&recrs=a&recrs=d&age_v=&age=1&age=2&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= . Thirty-one results were generated but three studies are not included in the above table (one excluded transformed lymphoma, another only included CD30 expressing-lymphoma utilizing brentuximab vedotin, while the third is a study of topical treatment in CD30 positive lymphoma).

Table 4: Clinical Trials of Histologic Transformed Lymphoma.

Double hit DLBCL is historically known to be resistant to chemoimmunotherapy and has a higher incidence of CNS disease. Aside from its occurrence in *de novo* DLBCL, it has also been reported in HTL, particularly when t (14;18) in follicular lymphoma acquires c-myc translocation [27], as also identified in our study. Jonathan W. Friedberg proposed considering dose-adjusted R-EPOCH similar to what is prescribed for *de novo* double-hit lymphoma, for those patients with double-hit lymphoma in the setting of transformed follicular lymphoma without prior anthracycline exposure or salvage chemotherapy followed by ASCT in those with prior anthracycline treatment [28]. Treatment and survival of patients with HTL continues to evolve particularly in the era of targeted therapies. Data on timing and role of HDT-ASCT in HTL continues to be debated in the rituximab era, with some studies suggesting better outcome with HDT-ASCT in CR-1 [29-31] and others finding no significant impact on survival [26]. Silvia Montoto proposed that consolidation with HDT-ASCR may be considered in patients with transformed lymphoma who received lines of chemotherapy for indolent lymphoma and treatment with R-CHOP at transformation, or for those who received RCHOP prior to HTL, required salvage chemotherapy at the time of transformation, and had good response and performance status [7]. Only one of our study patients received ASCT in CR-1.

There are a number of on-going clinical trials of DLBCL enrolling patients with HTL that are evaluating the role of targeted therapies upfront and in the relapsed-refractory setting, and utilizing novel therapies such as immunomodulatory drugs (IMiDs), Bruton's tyrosine kinase (BTK) inhibitors, B-cell lymphoma 2 (BCL-2) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, Programmed T cell death-1 (PD-1) inhibitors, HDT-ASCT, and Chimeric Antigen Receptors T cell (CAR-T) therapy (Table 4). Many of these studies are in early stages and thus optimal treatments for DLBCL HTL will likely remain unresolved for the foreseeable future.

5. Conclusion

Despite improved outcome in the rituximab era, the outcome of HTL particularly in the relapsed-refractory setting remains unsatisfactory. Our retrospective study identified achievement of CR and LDH level within the normal range to statistically predict better OS. We found a statistically significant longer time to the development of HTL in patients with CLL and LPL compared to other indolent lymphoma types (FL, MZL and low-grade B cell lymphoma NOS; however, OS at histologic transformation was similar regardless of the indolent lymphoma type preceding HTL. Future directions will depend on the outcome of on-going clinical trials, the results of which will suggest novel therapeutics and provide for more evidence-based management of HTL

Conflicts of Interest

All authors declare no conflict of interest.

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