Original Article

Transformed Lymphomas: Is It Really Rare?

Transforme Lenfomalar: Gerçekten Nadir mi?

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ABSTRACT

Objective: In our study, we aimed to evaluate the factors that affect the prognosis of patients with transformed lymphoma who are followed up in our clinic.
Materials and Methods: Forty-five patients with transformed lymphoma who were eligible for our study were retrospectively analyzed. The preparations of the patients were confirmed by experienced pathologists with second look.
Results: The majority of the primary diagnosis of the patients was follicular lymphoma. The most common type of transformed lymphoma was diffuse large B-cell lymphoma (DLBCL). The time to transformation was measured as 31 months (2-312). The number of patients who responded to the first rescue treatment after transformation was 32 (71%), and the number of refractory patients was 9 (20%). Median survival in transformed patients was 4.5 months (1-102).
Conclusion: The time to transformation was measured as 31 months. In addition, heterogeneity in the diagnosis type of primary diseases and the treatments received are other reasons that may explain the difference in transformation times between studies. More studies are needed for more accurate prognostic assessment.

Keywords: Clinical response, Prognostic factors, Targeting Therapy, Survival

ÖZET

Giriş ve Amaç: Çalışmamızda kliniğimizde takipli olan transforme lenfoma hastalarının prognozunda etkili olan faktörleri değerlendirmeyi amaçladık.
Yöntem ve Gereçler: Çalışmamıza uygun olan 45 transforme lenfoma hastası retrospektif olarak incelendi. Hastaların preparatları deneyimli patologlar tarafından yeniden değerlendirilerek doğrulandı.
Bulgular: Hastaların primer tanısının büyük çoğunluğunu folliküler lenfoma oluşturmaktaydı. En sık transforme lenfoma çeşidi diffüz büyük B hücreli lenfoma (DBBHL) olarak gözlendi. Transformasyona kadar geçen süre 31 ay (2-312) olarak ölçüldü. Hastalarda transformasyon sonrası ilk kurtarma tedavisine yanıt veren kişi sayısı 32 (%71), refrakter hasta sayısı ise 9 (%20)'du. Transforme hastalarda median sağ kalım 4,5 ay (1-102) olarak ölçüldü.
Tartışma ve Sonuç: Transformasyona kadar geçen süre 31 ay olarak ölçüldü. Primer hastalıkların tanılarındaki heterojenlik ve alınan tedavilerdeki farklılıklar çalışmalar arası transformasyon sürelerinin farklılığını açıklayabilecek nedenlerden olabilir. Daha sağlıklı prognostik değerlendirme için daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Klinik yanıt, Prognostik faktörler, Hedefe Yönelik Tedavi, Sağkalım

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Introduction

Lymphomas are the most common hematological malignancies. In classification, lymphomas are divided into two as Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL). Hodgkin lymphomas are most common between the ages of 20 and 40, but after the age of 55, there is a second increased incidence. The incidence of Hodgkin lymphomas in the community is 2.3/100,000. NHL is the 7th most common malignancy and accounts for 4.3% of all cancer cases. NHL ranks 5th in cancer-related deaths. Its incidence is 19.6 per 100,000 [1-3]. Advanced age and stage are among the factors thought to affect prognosis in DLBCL, which is one of the most frequently transformed lymphoma types [4,5].

In addition to standard conventional chemotherapy and radiotherapy, targeted therapy agents improved prognosis. Especially with the initiation of rituximab treatment, great progress has been made in the treatment of lymphoma. With the improvement of both treatment and care conditions, the life expectancy after treatment was prolonged and contributed to the occurrence of transformed lymphomas in patients [6]. In some studies, it has been shown that a bulky mass, which is thought to have a poor prognostic effect in the pre-rituximab period, is not as effective as thought on the prognosis in the post-rituximab period [7]. Rescue treatments used in patients with transformed lymphoma vary by center, and inter-clinical response rates vary according to treatment regimens [8].

Autologous transplantation is among the treatment options for suitable lymphoma patients who are considered to be at high risk after transformation. Considering the effects of the preparation regimens used before autologous transplantation on the prognosis, it may be necessary to perform autologous transplantation with a preparation regimen that is thought to be suitable for the patient profile [9].

There are various publications on the incidence of transformed lymphoma in patients with relapsed/refractory lymphoma. In their study, Bolanle Gbadamosi et al. reported that 73 of 617 patients examined between 2007 and 2015 were diagnosed with transformed lymphoma [10]. In other studies, the rate of transformation in lymphomas varies between 10 and 70% [11]. In addition, the rate of transformation varies according to the type of primary lymphoma [12]. Risk scoring used in lymphomas can be useful in predicting the formation of transformation. For example, there are studies showing that disease stage, FLIPI score at diagnosis, presence of lactate dehydrogenase (LDH) and B symptoms are associated with the risk of transformation in follicular lymphoma [13,14]. One reason why the rate of transformed lymphoma varies so much in the literature is that there are few studies. In addition, the incidence of lymphomas may vary depending on gender, race, age, some infectious factors (HHV-8, HIV, HCV, HBC, EBV, H.Pylori, Chlamydia, Borrelia, etc.).

The factors that cause the formation of transformed lymphomas are not yet fully understood. It is thought that radiotherapy and chemotherapeutic agents exposed during the treatment process contribute to the process. Unfortunately, the clinical course is worse in transformed lymphomas than in de novo lymphoma, and the response to treatment is worse [10,15-17]. While making the treatment decision in transformed lymphomas, the type of transformed lymphoma, its stage and the general clinical condition of the patient are important parameters that determine the treatment decision. There are studies in the literature suggesting that post-transformation rescue chemotherapy should be given in patients with a diagnosis of primary follicular lymphoma, considering the patient's anthracycline exposure, and then autologous

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stem cell transplantation should be performed [18]. In lymphoma patients, both in primary diagnosis and after transformation, follow-up can be life-saving by providing early diagnosis of relapsed, refractory or newly developed transformed lymphoma. Therefore, patients should be followed up in routine follow-up. Periodic laboratory and imaging examinations should be performed, and if suspicious lesion is encountered, biopsy should be performed again [19].

In our study, we aimed to evaluate the factors contributing to prognosis, risk factors, clinical features and response to treatment, considering the data gap in the literature in transformed lymphomas. Transformed lymphomas are often an exclusion criteria when conducting randomized controlled trials. Therefore, there are insufficient data on this patient group. Our research aims to close this information gap.

Materials and Methods

This study by Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital ethics committee approval was obtained. (Ethics committee no: 2021-12/16). This study was conducted under the ethical principles of Helsinki.

The records of all lymphoma patients admitted to the lymphoma outpatient clinic were reviewed retrospectively. Patients admitted to the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Hematology clinic between March 2002 and April 2021 were evaluated.

In the study, in which approximately 600 patients were evaluated, 45 patients who met the criteria were included in the study. Transformed lymphoma diagnosis of the patients was confirmed histopathologically by hematopathologists.

The primary and transformed lymphoma diagnoses of the patients were made by experienced pathologists and confirmed by second look.

Patients older than 18 years of age with a diagnosis of transformed lymphoma were included in the study. Transformed lymphoma was not proven by second look and patients under the age of 18 were not included in the study. The primary diagnoses of the patients were DLBCL, Mantle cell lymphoma, Hodgkin lymphoma, Chronic lymphocytic leukemia (CLL), Burkitt lymphoma, Marginal zone lymphoma, Follicular lymphoma, Peripheral T-cell lymphoma (PTCL), Angioimmunoblastic T-cell lymphoma.

Patients with low-grade lymphoma with no indication for treatment were followed up using a wait-and-see strategy. Patients with indications for treatment were treated in line with the recommendations of current guidelines. After the primary diagnosis, patients were screened with PET-CT to evaluate treatment response or when recurrence was suspected. Histopathological sampling was performed from the patients with suspicious lesions.

Statistical analyzes were performed using the IBM Statistical Package for the Social Sciences (SPSS) V26 (Armonk, NY). The general characteristics of the patients were presented with descriptive statistics. Numerical data were given as median (min.-max.), categorical data as ran. Factors predicting treatment response were analyzed by logistic regression, and factors predicting survival were analyzed by cox regression. $P<0.05$ was considered statistically significant.

Results

The median age of the patients was 54.5 (18-85). The number of women was 20 (44.4%) and the number of men was 25 (55.6). The incidence, stages of primary diagnoses and laboratory datas are shown in Table-1.

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Table 1. Demographics and clinical data of the patients

Parameters	N, %
Age (median, min-max)	54,5 (18-85)
Gender (M/F)	25 (55.6%) / 20 (44.4%)
Initial Diagnosis	
Follicular lymphoma	16 (35.6%)
Hodgkin lymphoma	11 (24.4%)
Chronic lymphocytic leukemia	5 (11.1%)
Marginal zone lymphoma	5 (11.1%)
Diffuse large B cell lymphoma	4 (8.9%)
Mantle cell lymphoma	1 (2.2%)
Burkitt lymphoma	1 (2.2%)
Peripheral T cell lymphoma	1 (2.2%)
Angioimmunoblastic T cell lymphoma	1 (2.2%)
Stage (early/late)	15 (33.3%) / 30 (66.7%)
Laboratory	Median (min-max)
LDH (u/L)	228 (144-821)
Uric acid (mg/dL)	5,7 (2,7-10,7)
Albumin (g/L)	4,1 (2,6-5)
WBC (cells/uL)	5210 (3500-59320)
Hb (g/dL)	12,8 (5,9-16)
Plt (cells/uL)	220.000 (46.000-485.000)
Initial Treatment	
R-CHOP	17 (37.8)
ABVD	11(24,4%)
WATCH&WAIT	9 (20%)
CHOEP	2(4,4%)
CHOP	1 (2,2%)
CODOX M	1 (2,2%)
CVP	1 (2,2%)
R-EPOCH	1 (2,2%)
R-HYPER CVAD	1 (2,2%)
R-FC	1 (2,2%)
RT (received)	13 (28.9)

LDH: lactate dehydrogenase; WBC: white blood cells; Hb: Hemoglobin; Plt: Platelets.
R: Rituximab, CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone,
ABVD: Adriamycin Bleomycin Vinblastine Dacarbazine, CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone, CODOX M: Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate, Cytarabine, CVP: Cyclophosphamide, Vincristine,
Prednisolone, EPOCH: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, HYPER CVAD: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, FC: Fludarabine, Cyclophosphamide, RT: Radiotherapy

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Table 2. Histological Transformed Lymphoma Clinical Data

Parameters	N, %
Time to histologic transformation (median, min-max)	31 (2-312) months
Stage (early/late)	11 (24.4%) / 34 (75.6%)
Ki67 (median, min-max)	80 (7-95)
HTL Diagnosis	
Diffuse large B cell lymphoma	31 (68.9%)
Hodgkin Lymphoma	4 (8.9%)
Marginal zone lymphoma	4 (8.9%)
Follicular lymphoma	3 (6.7%)
Angioimmunoblastic T cell lymphoma	1 (2.2%)
Peripheral T cell lymphoma	1 (2.2%)
Chronic lymphocytic leukemia	1 (2.2%)
HTL first treatment	
R-CHOP	20 (44,4%)
Watch&Wait	8 (17,8%)
R-GDP	4 (8,9%)
GDP	3 (6,7%)
ABVD	2 (4,4%)
ASHAP	1 (2,2%)
CVP	1 (2,2%)
Obinutuzumab+lenalidomid	1 (2,2%)
Rituksimab+bendamustin	1 (2,2%)
Rituksimab+CHOEP	1 (2,2%)
Rituksimab+deksametazon	1 (2,2%)
Missing	1 (2,2%)
Salvage CT line ≥2	7 (15.6%)
RT	8 (7.8%)
HTL first salvage treatment response	
Chemosensitive	32(71%)
Chemorefractory	9(20%)
N/A	4(8,9%)
Mortality	9 (20%)
Time from HTL diagnosis to mortality (median, min-max)	4,5 (1-102) months

HTL, histologically transformed lymphoma; CT: chemotherapy RT: radiotherapy
N/A: not applicable.R: Rituximab, CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, GDP: Gemcitabine, Dexamethasone, Cisplatin, ABVD: Adriamycin Bleomycin Vinblastine Dacarbazine, CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone, ASHAP: Adriamycin, Solumedrol, High-dose Ara-C, cisplatinum, CVP: Cyclophosphamide, Vincristine, Prednisolone

Table 3- Factors Affecting Response- Refractory to Initial Rescue Therapy Evaluated*.

Parameters	Univariate Analysis	
	HR (%95-CI)	P Value
Age	1,02 (0,98-1,06)	0,29
Gender (female based)	0,6 (0,16-2,16)	0,43
1. Lymphoma Stage	2,06 (0,97-4,38)	0,06
Kİ-67	1,02 (0,99-1,05)	0,20
Time to histologic transformation	0,99 (0,98-1,01)	0,39
LDH (u/L)	1 (0,99-1,01)	0,96
Uric acid (mg/dL)	1,25 (0,83-1,88)	0,28
Albumin (g/L)	2,13 (0,46-9,94)	0,33
Hb (g/dL)	0,94 (0,70-1,26)	0,68

LDH: lactate dehydrogenase; Hb: Hemoglobin
*In the parameters examined, no parameter that had a significant relationship with the response was found.

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Table 4- Factors Affecting Survival After Transformation*

Parameters	Univariate Analysis	
	HR (%95-CI)	P Value
Age	1,04 (0,99-1,08)	0,12
Gender (female based)	1,14 (0,57-2,29)	0,70
2. Lymphoma Stage	4,93 (0,76-31,88)	0,09
Kİ-67	1 (0,97-1,03)	0,95
Time to histologic transformation	0,99 (0,98-1,01)	0,54
LDH (u/L)	0,99 (0,99-1,01)	0,65
Uric acid (mg/dL)	1,27 (0,85-1,91)	0,25
Albumin (g/L)	0,95 (0,20-4,56)	0,95
Hb (g/dL)	0,90 (0,67-1,22)	0,52

LDH: lactate dehydrogenase; Hb: Hemoglobin
*Parameters thought to be associated with survival after transformation were examined by Cox regression analysis, but again, no significant difference was found due to diagnostic heterogeneity and the limitation of the study population.

While 36 (80%) of the primary diagnosed patients received active chemotherapy, 9 (20%) were followed without medication. The initial treatments of the patients are shown in Table-1.

The median time to transformation was observed as 31 months (2-312). The majority of the transformed patients, such as 31 (68.9%), were diagnosed with DLBCL (Table 2). When the patient was restaged after transformation, the number of early stage patients was 11 (24.4%), while the number of late stage patients was 34 (75.6%). The median Ki67 proliferation index value of the transformed patients was 80% (7-95%).

The treatments given in patients with transformed lymphoma are shown in Table-2. The number of patients who received more than two lines of treatment was seven (15.6%). In the post-treatment evaluation, 32 (71%) of the patients transformed in PET-CT were responsive to treatment. nine (21%) were considered as refractory. Treatment response of four (8.9%) patients could not be reached. Mortality was observed in nine (20%) patients. Post-transformation mortality time was 4.5 months (1-102).

Cases refractory to first salvage therapy in logistic regression analysis are analyzed in Table 3. In the parameters examined, no parameter that had a significant relationship with the response was found. The limited number of cases examined here and the lack of a homogeneous diagnosis group seem to play a role.

In Table 4, parameters thought to be associated with survival after transformation were examined by Cox regression analysis, but again, no significant difference was found due to diagnostic heterogeneity and the limitation of the study population.

Discussion

Although it is clinically rare, high-grade and low-grade lymphomas can transform into each other after treatment. However, due to the large number of lymphoma types, a heterogeneous study group is formed, making it difficult to obtain meaningful statistical data. However, limited studies have shown that the prognosis in transformed lymphomas is worse than in de novo lymphomas. Addition of additional mutations to primary lymphoma and previous treatment agents play a role in this. In addition, the fact that the treatments given differ according to the centers and years makes it difficult to make comparisons between studies. For example, pre-rituximab data and current stem cell transplant

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preparation regimens are just some of the reasons for these differences.

Especially since many studies were conducted in the pre-rituximab period, different results can be obtained in terms of treatment responses and overall survival. In the study of Link BK et al., OS was worse in patients who were transformed before 18 months than those with late transformation, and additionally, it was seen that taking rituximab beforehand did not make a difference in terms of survival with de novo DLBCL [18]. No significant difference was found in our study.

When the literature is examined, follicular lymphoma is the most common first diagnosis in transformed lymphomas in many studies [11,12,15]. In our study, we observed that 16 (35.6%) of our patients had a diagnosis of follicular lymphoma, consistent with the literature.

The time to transformation was measured as 31 months. During this time Villa et al. 44 months, Gbadamosi et al. In his study, it was shown as 40 months [10,20]. The type of diagnosis of the primary diseases and the treatments received are among the reasons that may explain the difference in transformation times between studies.

Conclusion

Despite new treatment agents such as rituximab, immunomodulators, Bruton tyrosine kinase inhibitors, BCL-2 inhibitors and CAR-T cell therapy, desired curative treatment responses still have not been achieved in transformed lymphomas. For this reason, many clinical studies are still ongoing. Due to the heterogeneous nature of transformed lymphomas, reaching a sufficient number of patients and conducting randomized controlled studies create difficulties.

Improvement of treatment success in transformed lymphomas can be achieved by conducting extensive studies including new treatment agents in this area.

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