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Original Research Article

Dismal outcome of t-cell lymphoma patients failing first-line treatment: results of a population-based study from the Modena Cancer Registry

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Abstract

We conducted a population-based study to establish the outcome of T-cell lymphoma (TCL) patients failing systemic first-line therapy. All TCL patients failing first-line systemic therapy in the province of Modena were identified from Modena Cancer Registry between 1997 and 2010. A total of 53 patients were analysed. Regarding the type of failure, 18 patients relapsed, and 35 progressed during first treatment. Among relapsed patients, the median time from date of response to relapse after first treatment was 6.2 months (range 1.87–102). A total of 18 patients (34%) died before receiving salvage treatment, 21 received platinum or gemcitabine-containing regimens (7 addressed to autologous stem cell transplant (ASCT)), 12 other CT regimens; 2 received radiotherapy (RT). The median survival after relapse (SAR) was 2.5 months. After a median follow-up for living patients after failure of 35 months (range 8–111 months), 44 patients died, and the cause of death was found to be lymphoma progression in all (98%) but one of them. The median SAR was 2.5 months. The 3-year SAR was 19%. Univariate and multivariate Cox regression analyses for SAR were performed. In multivariate analysis, performance status and type of failure were associated with a higher risk of death after relapse. The outcome of TCL patients failing first-line therapy is poor. Only a few cases that could receive ASCT had promising chances of long remission. There is urgent need for novel agents for patients requiring second-line treatment.

Keywords: **T-cell lymphoma; treatment; prognosis; salvage therapy**

Introduction

The mature or peripheral T-cell lymphomas (TCLs) are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of post-thymic lymphocytes. TCL represent 10–15% of lymphoid malignancies according to the most recent from the World Health Organization (WHO) classification, both T cell neoplasms (T) and natural killer cell neoplasm (NK) neoplasms are considered together regarding their straight correlation in terms of immunologic characteristics and function [1].

In general, patients with TCL, excluding those with anaplastic lymphoma kinase-positive anaplastic large cell lymphoma, exhibit a 5-year survival of about 30% [2–4].

Several studies have been performed to assess the contribution of a number of clinical and biological factors to the prognosis of TCL. In most of them, adverse prognostic features such as poor performance status (PS), advanced stage, presence of extranodal sites, bulky disease and high lactate dehydrogenase (LDH) levels were significantly correlated with shorter survival. The usefulness of the Prognostic Index for TCL (PIT) has also been investigated and confirmed by several authors [5,6].

Current treatment strategies are largely ineffective. cyclophosphamide, doxorubicin, oncovin, prednisone (CHOP) remains the most commonly used first-line regimen, able to achieve a remission rate of 50% [7–9]. These poor results led to the development of a number of studies on intensification with high-dose chemotherapy and autograft with conflicting results [10,11]. Moreover, patients failing to obtain a remission with first-line therapy are expected to have a dismal outcome, but there is a lack of studies focusing on this subset of patients.

The purpose of this population-based study was to establish the outcome of patients with TCL progressing or relapsing after first-line therapy.

Patients and methods

All TCL patients diagnosed in the province of Modena, Italy between 1 January 1997 and 31 December 2010 were identified from the archives of the Modena Cancer Registry (MCR) that covers a population of approximately 600 000 people. Among them patients progressing or relapsing after first-line systemic treatment were selected for the present study. The MCR was established in 1988 and is located in the Comprehensive Cancer Center of the University of Modena and Reggio Emilia. This registry obtains cancer diagnoses for all persons living in the Modena province via local pathology departments (registry of nodal, extranodal and bone marrow biopsies), from both local and national reports of hospital admissions and death certificates. The coverage achieved by the MCR can be considered excellent because of the very low rate of case included on the basis of death certificate only (0.1%) [12].

For each case included in the present study, the MCR provided data on patient demographics, histological type and primary cancer site. Histology was coded according to the third revision of the International Classification of Diseases for Oncology, which is based upon the World Health Organization classification of lymphoid neoplasms and reviewed by MA and GB [13]. Also, additional data on disease characteristics, treatment modalities, together with response assessments and outcome were actively retrieved and collected.

All patients were staged according to the Ann Arbor system. The following baseline clinical characteristics were also recorded: gender, age B symptoms presence, performance status (Eastern Cooperative Oncology Group (ECOG) scale) [14], number of extranodal sites and LDH level. The PIT score was calculated as detailed by the 'Intergruppo Italiano Linfomi' [5]. Four variables were used to build up this score: age ($\leq$60 vs $>$60), performance status (ECOG $\leq$1 vs $>$2), LDH level (low versus high) and bone marrow involvement (negative versus positive). Depending on the number of adverse prognostic factors (0, 1, 2 or $\geq$3), patients were further classified into two risk groups. The study was approved by the institutional ethics committees.

Statistical analysis

Standard descriptive analyses were carried out. For a crude association analysis, categorical data were analysed using the chi-square or Fisher's exact test (two-sided) used for data analysis. Survival curves were estimated using the Kaplan–Meier method, and compared using the log-rank test. For patients who relapsed or progressed, survival after relapse (SAR) was calculated as the time from date of relapse or progression until last follow-up or death. All patients received follow-up examinations up to 31 December 2011.

Univariate and multivariate Cox regression analyses were conducted to identify prognostic factors associated with survival after progression or relapse. Variables yielding p-values < 0.2 in the univariate analysis were included in a forward multivariate regression analysis. Odds ratios with their 95% confidence intervals were computed. Two-tailed p-values < 0.05 were considered statistically significant. The SPSS version 17.0 software (Chicago, IL, USA) was used for data analysis.

Results

A total of 53 patients with relapsed or refractory peripheral T-cell lymphoma after initial systemic therapy were identified among 112 patients with systemic T-cell lymphoma patients from the MCR. Twenty-three patients (43%) were diagnosed with peripheral T-cell lymphoma not otherwise specified, 16 patients (31%) with anaplastic large T-cell lymphoma, seven (13%) with angioimmunoblastic T-cell lymphoma and seven (13%) with other subtypes.

The median age was 64 years (20–88), and 66% of patients were male. The majority of patients presented ECOG PS 0–1 (73%), advanced stage (79%) and 0–1 extranodal sites (70%). Abnormal LDH was found in 55% of patients, and bone marrow infiltration was found in 32%. A proportion of 62% of the patients were classified as high-risk PIT and 49% were classified as high-risk International Prognostic Index (Table 1). In general, patients failing first-line treatment presented more often abnormal LDH, high-risk PIT score and International Prognostic Index than patients who did not relapse (data not shown).

Regarding type of failure, 18 patients relapsed after complete remission, and 35 progressed during first treatment. Among relapsed patients, the median time from date of response to relapse after first treatment was 6.2 months (range 1.87–102).

Table 1. Clinical characteristics of patients failing first-line treatment

Clinical characteristics	*N* = 53 (%)
Age $>$60 years-old	33 (62)
PS $\geq$ 2	9 (17)
Stage III–IV	42 (79)
B symptoms	31 (58)
Abnormal LDH	29 (55)
BM infiltration	17 (32)
ENS $>$1	16 (30)
Non-anaplastic Lymphoma	37 (70)
PIT (high risk)	33 (62)
IPI (high risk)	26 (49)

LDH, lactate dehydrogenase; PS, performance status; BM, bone marrow; ENS, extranodal sites; PIT, Prognostic Index for T-cell lymphoma; IPI, International Prognostic Index.

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Treatment and outcome of patients failing first-line treatment

In total, 35 (66%) patients received active therapy at time of first relapse or progression: 14 patients received cisplatin, cytarabine and dexamethasone (DHAP) (five of whom were subsequently addressed to ASCT), seven received gemcitabine-containing regimens (two of whom were subsequently addressed to ASCT), five received doxorubicin-containing regimes and seven other CT regimens; and two patients were treated with RT only. The remainder 18 (34%) received supportive care only and died before receiving any salvage treatment.

A total of 18 (34%) patients died before receiving any salvage treatment with curative intend at the moment of relapse due to age, poor general health status and, also, aggressiveness of the disease.

Survival after relapse

After a median follow-up for living patients after relapse/progression of 35 months (range 8–111 months), 44 patients died, and the cause of death was found to be lymphoma progression in all (98%) but one of them. The median SAR was 2.5 months. The 3-year SAR was 19% (Figure 1).

Factors associated with survival after relapse

Among the 35 patients who received salvage treatment, 3-year SAR was 86% for those who underwent ASCT and was 14% for those who received conventional dose salvage treatment ($p = 0.002$). The median SAR for patients not undergoing ASCT was 4.56 months, and the median SAR for patients undergoing ASCT was not reached.

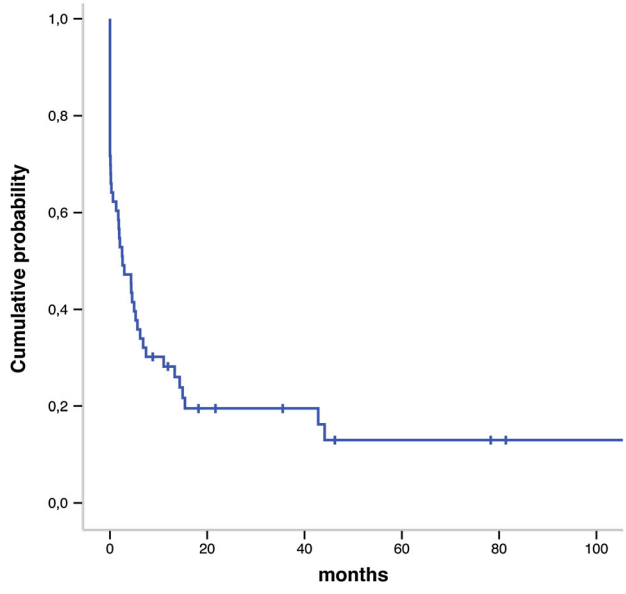

Figure 1. Survival after relapse

Univariate and multivariate Cox regression analyses for SAR were performed in order to identify prognostic factors among patients progressing or relapsing after first treatment. In multivariate analysis, PS and type of failure were associated with a higher risk of death after relapse (Table 2). Combining the information of PS and type of failure, patients who presented both bad prognostic factors had a dismal outcome, and no one was alive 6 months after failure (Figure 2). Among the subgroup of patients who received salvage therapy, the only factor that remained independent in the multivariate analysis was the number of extranodal sites more than 1 ($HR = 2.86$, 95% confidence interval 1.26–6.46, $p = 0.012$).

Discussion

Herein, we investigated the outcome of relapsed or refractory TCL patients using a population-based approach to describe the pattern of care and, also, to investigate factors influencing SAR. Overall, the current study confirmed that, in the general population, outside clinical trials, most patients with relapsed or refractory TCL have poor outcome and short survival [15]. We found a SAR rate of 19% at 3 years and median SAR of 2.5 months. These results are in keeping with recent analyses [16]. Of note, about 34% of this subgroup was not even able to obtain any further treatment mainly because of early death after failure. This picture clearly emphasizes the idea of the urgent need for new treatment approaches, but also highlights the high aggressiveness of the disease, which in a high proportion of cases limits the role of current, active therapy.

Our study provides a rare opportunity to analyse clinical features, treatment and outcome of patients failing first-line treatment. Patients failing first-line therapy presented poorer risk factors defined by PIT. Also, chemotherapy regimens at time of relapse or progression were heterogeneous with some patients treated with platinum-based or gemcitabine-based regimens. Of note, patients who had the best chance of cure were the ones for whom the high-dose chemotherapy with ASCT could be offered and completed. Even taking in consideration that these patients represent a high-selected subgroup of patients, the 3-year SAR was 86%. Nevertheless, standard ASCT could only be administered to remarkably few patients (seven patients at the first-line treatment and seven patients at the moment of failure). Recently, a similar study was conducted by the British Columbia Cancer Agency, in which they studied 208 patients identified as primary progressive or relapsed in their database between 1976 and 2010. Likewise, they also found an extremely poor outcome (median SAR of 7 months) with short remissions, and they confirmed that the outcome was far superior in patients able to receive a transplant. However, only 38 out of 53 planned for an auto or allo bone marrow transplant finally received it [16].

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Table 2. Univariate and multivariate analysis of factors associated with survival after relapse

Clinical characteristics	Univariate analysis			Multivariate analysis*		
	HR	95% CI	P	HR	95% CI	P
Gender						
Female	1					
Male	0.86	0.46–1.6	0.64			
Age *						
<60	1					
≥60	2.34	1.2–4.56	0.01			
PS*						
0–1	1			1		
2–4	2.82	1.29–6.18	0.009	2.6	(1.17–5.8)	0.019
Stage						
I–II	1					
III–IV	1.2	0.59-2.44	0.61			
B symptoms						
No	1					
Yes	0.76	0.42–1.39	0.37			
LDH						
Normal	1					
Abnormal	1.2	0.65–2.28	0.54			
BM						
Negative	1					
Positive	1.37	0.73–2.58	0.32			
EN sites*						
0–1	1					
>1	1.72	0.91–3.26	0.09			
Histologic subtype*						
Anaplastic	1					
Non-anaplastic	1.86	0.94–3.6	0.07			
Type of failure*						
Relapse	1			1		
Progression	2.92	1.47–5.82	0.002	2.4	1.19–4.8	0.01

LDH, lactate dehydrogenase; PS, performance status; BM, bone marrow; ENS, extranodal sites; 95% CI, 95% confidence interval.
*Variables yielding *p*-values < 0.2 in the univariate analysis were included in a forward multivariate analysis. The variables that remained in the final model were performance status and type of failure.

Taken together, current efforts should be made in order to avoid relapse and to increase the number of patients eligible for the only current curative treatment.

Reliable prognostic scores are needed to further evaluate novel treatment strategies based on risk. In the present analysis, patients identified as having a higher risk of failure are those with poor PS and type of failure and the presence of both identified a subgroup of high-risk profile. Even though the high aggressiveness of the disease limits the role of prognostic stratification at this setting, the results of our study and previous studies corroborate the suggestion that these prognostic scores should be calculated and also included in new prospective trials.

We are aware that one limitation of the present study was its retrospective nature. Nevertheless, the population-based approach should grant for the lack of selection biases. Another limitation could be the inclusion of multiple T-cell histologies in a single group, because they are biologically different and it would be expected to have different outcomes. However, given the rarity of these entities, and also that we included only failing patients, we think that this procedure is acceptable.

Advances in understanding the biology, immunophenotype and genetics of lymphoma have led to the identification of a number of potential therapeutic targets. The development of new drugs targeting CD30 represents a substantial improvement and might be useful also in T-cell lymphoma given the high frequency of CD30 in these subtypes. Besides, new agents such as histone deacetylase inhibitors (e.g. romidepsin and vorinostat), antifols (e.g. pralatrexate), monoclonal antibodies (e.g. CD25 and CD4) and immunotoxins (e.g. denileukindiftitox) are under investigation in T-cell lymphomas, in general.

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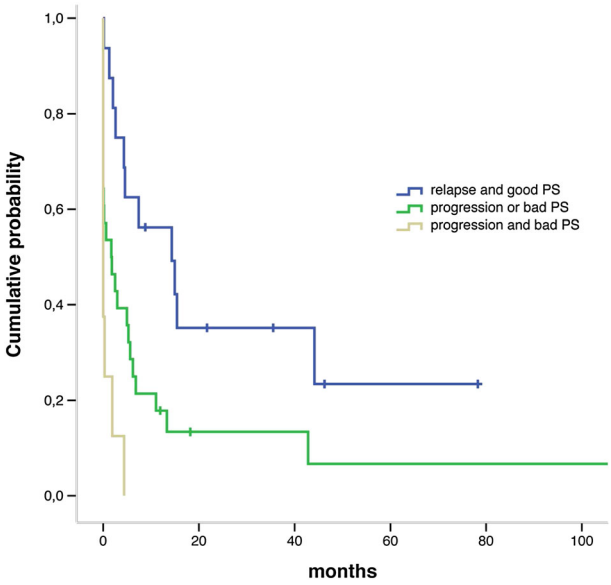

Figure 2. Survival after relapse according to performance status and type of failure

In conclusion, the outcome of TCL patients is poor and is dramatically poor for patients failing first-line therapy. A high proportion of refractory/relapsed patients do not receive any kind of therapy and, even for those able to receive it, present a very dismal outcome. Only a few cases who could receive ASCT after relapse had promising chances of long-lasting remission. On the basis of the results of this population-based study, it is evident that there is urgent need for novel agents to be offered to TCL patients to reduce the risk of failure after first-line treatment and improve the efficacy of first-line treatment requiring second-line treatment. Additional studies are needed to determine the relative value of novel therapies in development. The therapeutic challenges are the assessment of the potential benefit of combining these new drugs with the existing ones, including conventional chemotherapy and autologous or allogeneic transplantation.

Conflict of interest

The authors have no competing interest.

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