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Supplement Article

XI. How to treat children and adolescents with relapsed non-Hodgkin lymphoma?

Wilhelm Woessmann*

Department of Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany

**Correspondence to:*
W. Woessmann, Department of Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany.
E-mail: wilhelm.woessmann@paediat.med.uni-giessen.de

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Introduction

Treatment for childhood and adolescent non-Hodgkin lymphoma (NHL) has been optimised within the major biological subgroups for the last 30 years. Event-free survival rates reach almost 90% for mature B-cell NHL (B-NHL), 80% for lymphoblastic lymphomas (LBL) and 70% for anaplastic large cell lymphomas (ALCL). The efficacy of the front-line treatment leaves highly refractory relapsed disease, and few patients are available to study re-induction and consolidation approaches. With the exception of few phase II studies and one ongoing prospective trial, therefore, data on children with relapsed NHL are limited to retrospective analyses. Most of these analyses include low patient numbers and summarise patients over more than 10 years during which time first line therapies often changed.

The influence of front-line therapy efficacy on outcome in relapse can be highlighted by two examples: The Japanese group reported survival of 43% of 48 LBL-relapse patients, altogether 89% of 260 LBL patients survived [1]. Only 14% of 34 LBL relapse patients survived in a Berlin-Frankfurt-Muenster (BFM) series, leading to a comparable survival of 91% of all 324 LBL patients [2]. A second example with potential future implications for paediatric relapsed mature B-NHL is the dismal outcome of adult diffuse large B-cell lymphoma (DLBCL) relapse patients who received rituximab in first-line therapy compared to those who did not get rituximab first-line [3].

Outcome in relapse further differs according to the NHL subtype. Both retrospective data and an unpublished NHL-BFM analysis suggest that patients with relapsed ALCL or DLBCL have a fair chance to survive (40–60%), whereas survival of patients with relapsed Burkitt lymphoma (BL) and LBL stays less than 30%. Based on these observations, the questions which re-induction therapy and what kind of consolidation therapy to chose—autologous, allogeneic blood stem cell transplantation (SCT) or maintenance chemotherapy—need to be asked within each NHL subtype and with known and best identical first-line therapy.

Relapsed or refractory lymphoblastic lymphoma

From the available four retrospective analyses in the literature, only limited conclusions are possible regarding efficacious re-induction therapy, the role of SCT and local therapy modalities, prognostic factors in relapse and novel treatment options (Table 1). The BFM group reports an unselected series of 34 children and adolescents with refractory or relapsed T-cell (T)-LBL ($n = 28$) or precursor B-cell (pB)-LBL ($n = 6$) after uniform BFM type front-line protocols but with various salvage regimen [2]. Mitsui *et al*. summarise a series of eight refractory and 40 relapsed patients with various front-line and second-line therapies [1]. Data from European Organisation for Research and Treatment of Cancer (EORTC) studies are confined to eight patients with relapsed pB-LBL [4]. The survival rate of relapsed patients was only 14% at 3 years in the BFM group studies and was zero for the relapsed pB-LBL patients in the EORTC studies [2,4], whereas a 43% survival rate at 3 years was reported in the Japanese series [1]. However, the minimal follow-up time of patients was as short as 5 months in some patients. Furthermore, front-line therapies differed, and the relapse rate after front-line therapy was 18% compared to 11% in the BFM studies. Progressive disease was the predominant cause of death. Due to the retrospective nature and divers terminologies, interpretation and comparison of data are limited.

Nevertheless, some preliminary conclusions can be derived. Time and site of failure differ between T-LBL and pB-LBL. The median time from first diagnosis to relapse/progression was only 10 months for patients with T-LBL and often included the local site (50% isolated local recurrence, 75% local tumours involved) [2]. Quite different, the median time

Table 1. Retrospective analyses on relapsed or refractory lymphoblastic lymphoma (LBL)

All LBL-pts (n)	Relapse or progression (n)	Re-induction	Remission after re-induction (CR/PR)	T-LBL/ pB-LBL	Consolidation[a]			survival		
					Chemo.	Auto-SCT	Allo-SCT			
324	34	var.	9	28	–	–	9	4	14%	[2]
				6	–	–	3	1		
260	48	var.	26/9	32/9	12 (3)[a]	6 (2)	26 (12)	17	43%	[1]
53[b]	8[b]	var.	n.a.	8[b]	–	1	7	0	0	[4]
n.a.	n.a.	var.	n.a.	n.a.	n.a.	14 (4%)[a]	39 (40%)			[5]

T-LBL, precursor T-cell LBL; pB-LBL, precursor B-cell LBL; N.a., not available; Var., variable; Auto-SCT, autologous stem cell transplantation; Allo-SCT, allogeneic SCT; CR, complete remission; PR, partial remission.
[a]in brackets: in [1], number of patients alive at time of report (alive without SCT: 2/3 isolated central nervous system relapses, one late bone marrow relapse); in [5], event-free survival.
[b]only pB-LBL.

to failure was 19 months in patients with pB-LBL, and the bone marrow (BM) was the predominant site of relapse [2,4].

Regarding risk factors in relapse, the response to re-induction has major prognostic impact. With one exception, all patients with re-induction failure died [2]. The most frequently applied re-induction regimens were childhood acute lymphoblastic leukaemia front-line regimen for high-risk patients or acute lymphoblastic leukaemia relapse regimen (BFM, EORTC). The failure rate to this kind of re-induction was 27–50% [1,2]. The time to first failure remained an independent prognostic factor in the Japanese series but had no impact in the BFM series [1,2,4].

The performance of SCT was associated with significantly higher survival chance of 40–47% in both, the Japanese and the BFM series [1,2]. However, it remains unclear whether the improved survival of transplanted patients was due to SCT or was rather the expression of less resistant disease so that the patients reached SCT. Indicative of the latter is the observation in the BFM series that time from relapse to SCT was 4 months and time from relapse to deaths of the 29 patients who died was only 5.1 months. There were three survivors with chemotherapy alone in the Japanese series (Table 1) [1]. Data from the Centre for International Blood and Marrow Transplant Research (CIBMTR) suggest a clear benefit of allogeneic SCT over autologous SCT for children/adolescents with relapsed LBL pointing to a graft-versus LBL effect [5]. Another important observation in this study was that the remission status prior to SCT was the most important prognostic factor for the outcome of patients [5].

Based on these observations, the most important step towards better treatment outcome for children/adolescents with relapsed or refractory LBL is finding novel re-induction options to achieve sufficient response and a minimal disease status for successful administration of SCT.

Relapsed and refractory mature B-cell non-Hodgkin lymphoma

The limited reports on relapsed/refractory B-NHL are with one exception based on retrospective surveys and include different histologies. Generally, the reported survival rates are low. From the available data, the following conclusions can be derived. The chance to survive after failure to front-line therapy depends on histology: patients with DLBCL have survival rates of 40–50%, while the survival rate of patients with BL was only 15–30% [6,7] (BFM unpublished), the intensity of front-line therapy (better after less intensive front line) [8,9] and the time from first diagnosis to failure [8]. The chance to survive was almost zero for patients who were refractory to re-induction chemotherapy [6–8]. The rescue regimens used varied including, for example, course CYVE (high-dose cytarabin/etoposide) of the French Lymphome Malins de Burkitt, B-NHL high-risk courses of the BFM regimen, ifosfamid/carboplatin/etoposide (ICE), and others with or without rituximab. The failure rate to this kind of re-induction was in the range of 50% [6,8] and higher in BL compared to DLBCL [7]. In a prospective phase II study, the rate of complete remissions to ICE combined with rituximab was 4 of 14 children/adolescents with refractory/relapsed BLs compared to three of six patients with relapsed DLBCL [7]. The performance of SCT was reported to be a positive prognostic factor for survival [6,8]. However, this may likely reflect that SCT was considered mostly or only in case of a sufficient response to re-induction chemotherapy. In contrast to relapsed LBL data from the CIBMTR analysis showed no advantage of allogeneic over autologous SCT for the outcome of children/adolescents with relapsed B-NHL [5]. The administration of at least four doses of rituximab 375 mg/m^2,

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but not two doses was reported to improve outcome of children with relapsed B-NHL [8]. Again, the beneficial effect of rituximab remains unclear since only patients with more sensitive disease had a chance to receive more doses. Rituximab combined with ICE chemotherapy did not result in evidently higher response rates in the phase II study compared to historical data [7]. However, a recent report of CIBMTR data may point to a more complex role of rituximab [10]. The retrospective analysis suggests that rituximab given prior to or during allogeneic SCT may not only reduce the risk of acute graft-versus-host disease (GVHD) but also increase progression free survival of adult patients with B-NHL [10].

Based on these observations, it is of utmost importance for patients with early relapsing or refractory mature B-NHL to design effective re-induction regimens for rapid induction of complete remission which remain tolerable for these heavily pretreated children. Recent advances in transplant methodology, especially reduced intensity conditioning, improved host–donor matching and the use of monoclonal antilymphoma antibodies may open new treatment avenues in the future. Different approaches might be necessary for BL and DLBCL.

Relapsed of refractory anaplastic large cell lymphoma

Available data on therapy of patients with relapse of an ALCL are until now limited to retrospective analyses (Tables 2 and 3). A prospective stratified ALCL relapse trial of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) accrues patients since 2004. ALCL is usually chemosensitive at relapse. More than 80% of children and adolescents reached a second remission in reports from three national cohorts [11–13]. The response rate was independent from the types of first-line therapy and surprisingly also from the second-line regimens: re-inductions as different as vinblastine monotherapy, courses of CVA (CCNU, vinblastine and low-dose cytosine arabinoside) [11,14] and CC (high-dose cytosine arabinoside and etoposide) [13] achieved comparable response rates of 80%. Even the new targeted drug brentuximab vedotin led to 80% remissions in adults with anaplastic lymphoma kinase (ALK)-positive ALCL [15]. However, less than 50% of patients with progression during first-line therapy responded to re-induction in the retrospective BFM series [13]. These observation suggest that chemoresistance in ALCL is likely determined by the biology of the disease.

The survival chance for patients with relapsed ALCL reaches 50–70% with consolidation approaches as different as maintenance treatment with vinblastine, autologous or allogeneic SCT [5,11–14,16,17] (Table 2). The efficacy of these various consolidation therapies for relapsed ALK-positive ALCL cannot be compared between and within reported studies due to selection bias in patients receiving SCT, different strategies and the retrospective nature of the studies [5,11–14,16].

The French group reported long-term survival of ALCL relapse patients with 12 months CVA-chemotherapy and long-term vinblastine monotherapy even after failure of SCT [11]. Their updated experience on Vinblastine monotherapy for 36 ALCL relapse patients showed a 5-year

Table 3. Retrospective analyses on relapsed or refractory anaplastic large cell lymphoma (ALCL): efficacy of different consolidation approaches for relapsed ALCL

Patients (*n*)	CCR (*n*)	EFS or DFS (%)	
No SCT			
21	11	52%	[11]
10	6	53%	[12]
Auto-SCT			
6	2	—	[16]
15	9	45%	[11]
8	3	33%	[12]
39	22	58%	[13]
24	—	35%	[5]
Allo-SCT			
6	6	100%	[12]
16 + 5[a]	16	75%	[13]
12	—	46%	[5]

EFS, event-free survival; DFS, disease-free survival; CCR, continuous complete remission.
[a]Five secondary allo-stem cell transplantation (SCT).

Table 2. Retrospective analyses on relapsed or refractory anaplastic large cell lymphoma (ALCL): re-induction, consolidation and overall survival of cohorts of ALCL-relapse patients reported from four study groups

Patients (*n*)	Front-line therapy	Re-induction	Consolidation			Survival	
			No SCT	Auto-SCT	Allo-SCT		
13	Variable	Variable	7	6	—	Four alive	[16]
41	Variable	CVA[b]	21	15	1	69 ± 14%	[11]
26	Variable	Variable	10	8	6	61 ± 12%	[12]
74[a]	BFM-type	CC-AA[b]	19	39[a]	16	57 ± 6%	[13]

BFM, Berlin-Frankfurt-Muenster.
[a]strategy: autologous stem cell transplantation (SCT) for consolidation.
[b]chemotherapy courses: CVA (CCNU, Vinblastine, Cytosine-arabinoside); CC (high-dose Cytosine-arabinoside, Etoposide).

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event-free survival (EFS) of 30% and a survival of 65% [14]. The patients were not a selection of good-risk relapse patients as 15 patients had re-relapsed after SCT, and several patients presented with early first relapse. Based on the French data, vinblastine monotherapy for 24 months was chosen as therapy for patients with a low-risk relapse in the ALCL relapse trial.

The efficacy of autologous SCT for consolidation varied widely between reported series from national groups and a CIBMTR analysis (Table 3) [5,11–13,16]. This variation may be explained by different consolidation approaches to ALCL relapse. In the French series, autologous SCT was preferentially used for patients who had relapsed after more intensive front-line therapy compared to those who did not receive SCT [11]. In the BFM group, the strategy for all patients was re-induction followed by autologous SCT after Total Body Irradiation (TBI)-based conditioning from 1990 on [13]. Therefore, those who received the autologous SCT were a selection of good-risk relapse patients compared to those who did not reach SCT or received allogeneic SCT. The efficacy of an autologous SCT was tested for patients with a medium risk of relapse in the ALCL relapse trial of the EICNHL.

Data on the use of allogeneic SCT for relapsed ALCL are limited to the Japanese and BFM series as well as the CIBMTR analysis (together 38 patients) and case reports [5,12,17]. Taken together, there is a very low further relapse rate after allogeneic SCT for relapsed ALCL (0–20%) suggesting that a graft-versus ALCL effect may exist. The failure rate does not seem to be associated with donor type [17]. Additionally, allogeneic SCT was even effective in some patients with actively growing lymphoma [17]. The high efficacy of allogeneic SCT together with the risk of late effects was the basis to choose allogeneic SCT for consolidation of high-risk relapse patients in the ALCL relapse study.

Considering the general efficacy of the highly variable consolidation therapies, identification of risk factors for treatment stratification upon relapse is warranted. The time from initial diagnosis to relapse or progression has been described as major risk factor in children and adolescents with relapsed ALCL [11–13]. In the French series of 41 children and adolescents with ALCL relapse, 24 patients relapsing within 12 months from initial diagnosis had a significantly lower disease-free survival of 28% compared to 17 patients with later relapse (68%) [11]. The BFM group report on 74 ALCL patients relapsing after comparable first-line therapy showed that only 4 of 16 patients ($25 \pm 11\%$) with progression during initial therapy survived compared to 38 of 58 patients with later relapse ($66 \pm 6\%$) [13]. Among patients with progression during first-line therapy, survivors have only been reported after allogeneic SCT with very few exceptions [12,13,16].

About 15% of children and adolescents present with bone marrow or central nervous system involvement in relapse [11,13] which correlated with reduced survival in one analysis [13]. Expression of the T-cell antigen cluster of differentiation 3 (CD3) was associated with a high risk of failure in patients consolidated by autologous SCT in the retrospective BFM series. The prognostic impact of CD3 positivity, however, needs to be interpreted cautiously due to low patient numbers and CD3 expression data taken retrospectively from pathology reports. Based on these data, patients in the prospective EICNHL ALCL relapse trial are stratified primarily according to the time of relapse and further according to the immunophenotype.

SGN35 (brentuximab vedotin) and crizotinib are new targeted treatment options emerging for CD30-positive and ALK-positive malignancies [15,18]. Initial data regarding the safety profile and response rates are promising. However, given the high response rate to and efficacy of vinblastine monotherapy for relapsed ALCL almost without risk of late effects, clinical trials are necessary to define the role of these new agents in the therapeutic management for ALCL.

Conflict of interest

The author reports no potential conflict of interest.

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