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Treatment outcome in T-cell lymphoblastic lymphoma in adults - a population-based study from the Swedish Lymphoma Registry

Running head: Population-based study T-lymphoblastic lymphoma

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Abstract

Background. T-cell lymphoblastic lymphoma (T-LBL) is a rare neoplasm of precursor lymphoblast origin, for which there is no standard treatment for adults. Results of current treatment strategies in selected populations do exist but are largely unreported for unselected series. We aimed to investigate treatment outcome in a population-based cohort. *Materials and methods*. Patients were identified through the Swedish Lymphoma Registry and data was retrospectively collected for all adult (≥18 years) Swedish T-LBL patients diagnosed during 2000-2009. *Results*. A total of 39 patients with median age 40 years (range 18-78) were identified with females being significantly older than males (median age 66 versus 37, p=0.027). The 5-year overall survival for all patients was 42% with female gender was associated with shorter survival also when adjusted for treatment strategy and age (Hazard ratio (HR) 4.29; p=0.002). Thirty patients received intensive chemotherapy, otherwise used for treatment of acute lymphoblastic leukemia (ALL), which resulted in an overall response rate of 97% and a 5-year progression-free survival (PFS) of 49%. In this group only CNS involvement at diagnosis predicted shorter PFS (HR 13.3; p=0.030). Among patients treated with hyper-CVAD the addition of mediastinal irradiation resulted in longer time to progression compared to patients receiving only chemotherapy (p=0.047). The major reason for treatment failure was relapse and in this series 18-fluoro-deoxyglucose positron emission tomography (PET) did not predict this risk. *Conclusions*. This population-based study indicates that all fit T-LBL patients should be considered for intensive treatment. Our results also suggest a beneficial effect of mediastinal irradiation in combination with hyper-CVAD treatment. Relapsing patients have a dismal outcome irrespective of salvage treatment.

Introduction

T-cell lymphoblastic lymphoma (T-LBL) is a rare disease of precursor T-cell origin representing a lymphoma variant of T-cell acute lymphoblastic leukemia (T-ALL). T-LBL is most common in children and young adults with a male preponderance and it typically presents with a large mass in the anterior mediastinum. Pleural and pericardial effusion is common and the disease has a high risk of central nervous system (CNS) involvement. Morphologically and immunophenotypically T-LBL and T-ALL are very similar and classified as one entity in the WHO classification. The distinction of T-LBL from T-ALL is usually made with respect to the degree of bone marrow involvement, naming cases T-LBL if there is 25 percent or less infiltration [1]. As for T-ALL, deregulation of NOTCH1-signaling in many cases seem to be important for the evolution of T-LBL[2] but at gene expression level there are indications of differences between T-LBL and T-ALL[3, 4] .

Initial therapeutic strategies based on CHOP-like chemotherapy yielded poor long term survival [5]. Following reports of improved results in children treated with intensive ALL-type chemotherapy [6] this strategy has been adopted also for the treatment of adults. Due to the rarity of the disease there are few prospective trials specifically for T-LBL in adults and most data originates from retrospective reports on the specific outcome of T-LBL-patients enrolled in large LBL/ALL-studies.

ALL-type treatment typically consists of an induction treatment followed by a consolidation phase with re-inductions. In some protocols maintenance treatment with chemotherapy for up to two years is part of the consolidation. High-dose chemotherapy and autologous stem cell transplantation (SCT) instead of maintenance chemotherapy has been reported in a retrospective material to improve survival [7] but a prospective trial resulted in a similar outcome between the two strategies [8]. Allogeneic stem cell transplantation has

retrospectively not showed a clear benefit over autologous SCT with regard to long term survival [9]. The role of mediastinal irradiation has also been investigated without a definite answer [10, 11]. With ALL-type treatment long term survival between 50-70% has been reported [10, 12, 13] but no standard treatment strategy has been established. The major concern with current treatment strategies is relapse, since recurrent disease has a very poor prognosis [14]. Unfortunately, risk factors for relapse after ALL-type treatment have been hard to establish.

To our knowledge, there are no reports on the outcome for adult T-LBL with T-ALL excluded, in an unselected population with the current treatment strategies. We therefore aimed to investigate the outcome in a Swedish population-based cohort.

Material and methods

The Swedish Cancer Registry (SCR) is a national registry to which pathologists and clinicians are obliged to report every case of malignancy diagnosed. However, at the level of specific lymphoma classification the SCR contains limited information. Due to this the Swedish Lymphoma Group in January 2000 launched the Swedish Lymphoma Registry (SLR) containing more detailed information, covering all lymphoma patients from the age of 18 years. When receiving a lymphoma diagnosis the SCR notifies the appropriate Regional Cancer Center that in their turn sends the SLR form to be completed by the clinician responsible for the patient. In 2007 information contained in the SLR was extended to include information on treatment and response. Since the start of the SLR the coverage has been at the level of 95-97 % compared to the SCR.

Study population

All Swedish patients diagnosed with T-LBL between 1 January 2000 and 31 December 2009 were identified through the SLR. In total, 46 patients were initially registered in the SLR as having a diagnosis of T-LBL during this time period but seven patients had an infiltration >25% of bone marrow cellularity and were re-classified as T-ALL and excluded from this study. The diagnosis of T-LBL was established in routine clinical care by histology and immunohistochemistry and followed the 2001 edition of the WHO classification of lymphoid neoplasms [1]. Basic data was collected from the SLR and after informed consent further data was collected retrospectively from the individual patient record. Out of the remaining 39 patients one individual declined further participation and one patient´s record could not be retrieved and thus, only basic data from the registry was available. For surviving patients the median follow up was 6.5 years.

CSF cytology was examined for all patients in the intensive treatment group. Evaluation of treatment response included computed tomography (CT) -scanning and bone marrow examination for the patients in the intensive treatment group. At the discretion of the physician PET-scan was included in the post-induction evaluation. These examinations were performed at variable time point from the start of treatment but all patients were evaluated before the start of consolidation treatment. The present study was approved by the Regional Ethical Board, Lund, Sweden.

Statistics

Treatment response was classified according to the International Harmonization Criteria [15]. OS was defined as time from diagnosis to death or latest follow up. PFS was defined as time from diagnosis to relapse/progression or death from any cause. Time to progression was defined as time from diagnosis to relapse/progression or lymphoma-specific death. All analyses were made on an intention to treat basis. Distribution differences of clinical

characteristics between groups were analyzed with chi-square test and age differences with Mann-Whitney U test. Survival curves were estimated with the Kaplan-Meier method, groups were compared using log rank test and risk factor analysis was made using Cox proportional hazard ratios. Factors were analyzed in univariable analysis and all factors with $p \leq 0.1$ were retained in the multivariable analysis. All p-values were two sided and values were regarded statistically significant if $p \leq 0.05$. All statistics were performed with SPSS version 19.

Results

Patient characteristics

The median age for the entire cohort was 40 years (range 18-78) with a male: female ratio of 1.6 : 1. Eleven patients were 60 years or older and females were older than males (median age 66 *versus* 37, p=0.027). Clinical characteristics at diagnosis are listed in Table I. Almost half of the patients presented with stage IV disease either with bone marrow infiltration or with extensive involvement of one or more extra-lymphatic organs. Two patients presented with a vena cava superior syndrome and two patients had CNS involvement at diagnosis. Patients older than 60 years had significantly less often bulky disease (> 10 cm) compared to younger patients (36% *versus* 82%, p=0.007) as well as less often pericardial and pleural effusions (p=0.032 respectively p=0.008). Two patients had a history of myasthenia gravis and underwent surgery for thymic tumors. One patient had a prior diagnosis of hematologic malignancy (indolent B cell lymphoma). Pathology review results included one patient with negative staining for terminal deoxynucleotidyl transferase (TdT). This patient showed histologic, immunophenotypic and clinical characteristics that in all other aspects were typical of T-LBL. One patient was not tested for TdT-staining and the diagnosis of T-LBL was established based on immunophenotypic and histologic findings. The remaining patients all had TdT-positive lymphomas.

Treatment

Active treatment was given to all patients. The choice of treatment was made according to the physician's decision and was for analysis purpose grouped into intensive or non-intensive regimens as listed in Table II. Patients treated with non-intensive regimens (median 74 years, range 55-77) were significantly older ($p<0.001$) but with a similar WHO performance status compared to patients receiving intensive treatment (median 37 years, range 18-66).

Non-intensive treatments consisted of CHOP, COP and VACOP-B. The only patient younger than 69 years treated with CHOP was a 55 year old male with a history of myasthenia gravis. After complete resection of a thymic tumor, with the diagnosis of T-LBL, a kidney tumor that proved to be a renal clear cell cancer was found. No manifestation of T-LBL was found and after nephrectomy he was treated with six courses of CHOP-21.

In the intensive treatment group all patients were treated at large centers experienced with the treatment of ALL. Patients received an array of ALL-type induction treatments as listed in Table II. The choice of regimen was to some extent center-related and with patients receiving LSA2L2 induction being older compared to patients treated with other induction regimens ($p=0.002$). Patients receiving the pediatric protocols Euro LB-02, NOPHO-ALL-92 HR and VSTB-95 as a group were not significantly younger than patients treated with other protocols ($p=0.597$). Details for the various regimens has been described earlier, [16-21] except for the VSTB -95 regimen. This very intensive protocol was developed for the treatment of pediatric lymphoma patients by VSTB (Swedish working group for the treatment of solid tumors in children) and consists of an induction phase, re-induction, three CNS oriented blocks and a late re-induction maintenance followed by maintenance therapy with 6-mercaptopurine and oral methotrexate.

For the two patients with CNS involvement at diagnosis treatment consisted of hyper-CVAD with alternate intrathecal injections of methotrexate and cytarabine twice weekly until disease clearance from the CSF after which they received additional intrathecal methotrexate prophylaxis but no CNS irradiation. For all other intensively treated patients intrathecal prophylaxis but no CNS irradiation therapy was administered. This prophylaxis consisted of single methotrexate in most cases.

Mediastinal irradiation was given on an individual basis at the discretion of the physician, with none of the induction treatments precluding this option. Four patients (stage I-IV), all treated with hyper-CVAD, had mediastinal irradiation as part of their primary treatment. One patient presenting with a superior vena cava syndrome received immediate radiation therapy at a dose of 21 Gy before chemotherapy was initiated while three patients, 1 in CR and 2 in PR, received irradiation, at doses between 30 and 36 Gy, after induction chemotherapy.

Consolidation treatment was given to 25 of the 30 intensively treated patients as listed in Table III. Reasons for not giving consolidation were toxicity during induction treatment in three patients, early relapse in one patient and unknown cause in one patient. Two patients were treated with high-dose chemotherapy followed by autologous SCT and two patients underwent allogeneic SCT after induction treatment. The remaining 21 patients had maintenance chemotherapy for up to two years. Maintenance treatment for patients given hyper-CVAD was 6-mercaptopurine once daily and oral methotrexate once weekly, with re-inductions every second month the first year and every third month the following year.

Adverse events and treatment related deaths

In the group of patients treated with non-intensive regimens (n=7), three patients died during treatment; one from septicemia, one by unknown cause shortly after the first chemotherapy course and one patient started on VACOP-B had quickly deteriorating health and died soon

after the start of palliative irradiation. Post-mortem exam revealed pulmonary aspergillosis and a concurrent epithelial cancer in the mediastinum. The remaining patients in this group had no major complications to treatment.

No treatment-related deaths occurred during induction treatment in the intensive treatment group. Febrile neutropenia was common, resulting in minor treatment delays. Fourteen out of 19 patients (74%) treated with hyper-CVAD received the planned number of treatments without major complications. One patient treated with VSTB-95 developed severe hepatic toxicity shortly after treatment initiation and subsequently received less intensive second-line therapy. A 43-year old patient started on the pediatric protocol NOPHO-ALL-92 HR was switched to LSA2L2 maintenance already after the early intensification treatment and never received HD Mtx.

Treatment outcome

Evaluation of treatment response was performed at variable time point before the start of consolidation treatment. Thirteen patients were evaluated with the addition of PET but no pre-treatment PET had been performed in any of these patients.

One patient had no measurable disease and one patient died from unknown reasons shortly after the first chemotherapy course (both treated with CHOP) and these two patients were excluded from the efficacy analysis leaving 35 of 39 patients available for evaluation of treatment response. The overall response rate (ORR) for the cohort was 30/35 (85%) with 12/35 (34%) achieving complete remission (CR) and 18/35 (51%) partial remission (PR). Among non-intensively treated patients none of the evaluable cases reached a CR. In the intensively treated group ORR was 97% with 57% CR and 40% PR, (Table II) and in this group only one patient in PR was switched to salvage treatment. The remainder of PR´s consisted of small residual masses and, with the exception of two patients receiving

mediastinal irradiation, did not influence therapy decisions. For all patients evaluated with PET after induction treatment the examination was assessed as normal.

In the entire series 22 patients died and among intensively treated patients 15 out of 30 patients died. In the latter group 12 patients experienced relapse, two patients developed secondary hematologic malignancies (one myelodysplastic syndrome and one pre-B-ALL), one patient developed complications related to allogeneic SCT in first complete remission and all of these patients subsequently died. This resulted in an estimated 5-year PFS and OS of 42 % for the entire cohort, Figure 1 A. For intensively treated patients the calculated 5-year PFS and OS was 49% and 48% respectively as shown in Figure 1 B and C. Among the 13 patients with a negative PET-CT at response evaluation 7 patients (54%) relapsed. CNS and mediastinum were the most common sites of relapse. Three patients experienced isolated CNS relapse, with one patient having CNS involvement at diagnosis, while another two had CNS relapse as part of a disseminated disease recurrence. No association to the number of intrathecal injections and CNS relapse could be detected, but notably 4 out of 5 patients did not complete induction treatment as planned. One patient had an isolated mediastinal relapse and further details are listed in Table IV. All relapses occurred within 27 months from diagnosis with 6 relapses during ongoing maintenance chemotherapy. There were no statistically significant associations between type of induction treatment and CNS-relapse (data not shown).

Among patients treated with hyper-CVAD there was a statistically significant difference ($p=0.047$, log-rank test) in time to progression between patients that received mediastinal irradiation as part of the primary treatment ($n=4$) or not ($n=15$). In the former group none of the patients experienced a relapse compared to 9 in the latter.

A wide range of salvage treatments were used and are listed in Table IV. Three patients proceeded to allogeneic SCT and 2 patients underwent an autologous SCT as part of the relapse treatment. One patient developed fatal complications after allogeneic SCT but all other relapsed patients eventually died from progressive lymphoma, Figure 2.

Prognostic factors

All clinical characteristics at diagnosis, listed in Table I, as well as intensive/non-intensive treatment were analyzed as predictors for OS and PFS (data not shown). For the entire cohort, age, female gender and non-intensive treatment were significant adverse factors for OS and PFS in univariable analysis, see Table V. In a multivariable analysis non-intensive treatment and female gender retained significance for a shorter OS while female gender was the only factor of significance for shorter PFS.

For the intensive treatment group age was not predictive for OS (HR= 0.998; p=0.930) or PFS (HR=0.997; p=0.856) or as a dichotomized variable with different age cut-offs. Three out of the four patients over 60 years of age who received intensive treatment are still alive in continuous remission. Only CNS disease at diagnosis showed statistically significance in predicting a shorter OS (HR=7.444; p=0.017) and PFS (HR= 13.310; p=0.005) in univariable analysis. In multivariable analysis CNS disease did not reach the level of significance for prediction of shorter OS but remained significant as a risk factor for shorter PFS (HR= 8.962; p=0.030) as shown in Table V.

Discussion

The outcome of adult T-LBL patients treated with ALL-type chemotherapy doubtlessly compares favorably to historical results with CHOP-based treatment. However, reports of this

strategy are mostly limited to highly selected patient populations from clinical trials or populations selected in other ways [22]. Population-based materials on adult T-LBL are scarce in the literature [23] and there is to our knowledge no published data focusing specifically on T-LBL outcome in a completely unselected population with the current treatment strategy.

We here report the results for all Swedish adult T-LBL patients during a 10 year period, from 2000 to 2009. During the studied time period there were no national guidelines for the treatment of adult T-LBL patients in Sweden, nor any clinical trials that enrolled patients. Thus, reflecting the lack of a standard treatment for adult T-LBL patients, many different treatment regimens were used. These facts in combination with the low number of patients are of course major limitations of the present study and make comparisons between intensive treatment strategies difficult. Another limitation of this study is the lack of central pathology review and we have included one patient with negative TdT-staining, but with histologic and clinical characteristics typical for T-LBL, as this has been described previously [24]. The clinical characteristics of the patients in our material largely fit into previous descriptions [1]. The median age in our cohort is higher than in clinical trials since T-LBL, although very rarely, still occurs among elderly patients who may not be reported in series with uniform treatment. As expected and well described before, there was a male predominance among the patients. Somewhat surprisingly we found a significant difference in the age between genders, with females being older than males. It cannot be excluded that this reflects a true difference since the age cut-off in clinical trials eliminates the possibility to detect such difference. Older patients (age $\geq$ 60 years) also less often had bulky disease, pleural and pericardial effusions while there was no difference between age groups with respect to mediastinal involvement, which was present in almost all patients.

Long-term survival in LBL in recent reports from clinical trials has varied between 51 and 72% [7, 10, 12, 13]. Since our cohort included patients that received CHOP-like treatment the 5-year OS of 42 % for the whole cohort is, not surprisingly, inferior to these results. Neither age nor classic lymphoma risk factors, e.g. IPI predicted outcome in our study. The factors that predicted a shorter overall survival in multivariable analysis were non-intensive treatment and female gender. The inferior outcome among females was not expected, and cannot fully be explained by the fact that among older patients receiving non-intensive treatment, most patients were females. The group of non-intensively treated patients was too small for a separate multivariable risk factor analysis but among intensively treated patients there was no significant difference in outcome between genders.

In our material there were 30 patients known to receive ALL-type treatment and also in this group the estimated 5-year OS of 48% is inferior to what has been reported from clinical trials, probably explained by the population-based nature of our cohort including patients with different comorbidities.

There were several complications to treatments but the overwhelming problem was relapsing disease. As reported earlier, prognosis after relapse was extremely poor [14]. In our series none of 12 relapsed patients survived, 11 whom died from progressive disease, despite three of them undergoing allogeneic SCT in second remission. Factors that predict the risk of relapse after ALL-type treatment have been hard to establish and not consistent between studies [7, 10, 12]. In our material only CNS-involvement at diagnosis predicted a shorter PFS. This must be cautiously interpreted, since there were only 2 patients with CNS-involvement in our series. However, both patients in our study were treated with hyper-CVAD and our finding is the same as in the study by Thomas et al [13], where CNS-involvement at diagnosis was the only predictor for a shorter PFS among T/B-LBL patients treated with hyper-CVAD. The study by Thomas et al is the only other recent study including

patients with CNS-involvement not receiving cranial irradiation or undergoing SCT. In combination with our results it suggests that hyper-CVAD without cranial irradiation might not be a sufficient treatment for patients presenting with CNS-disease.

Since bulky disease is a common feature of T-LBL many patients ended up with a residual mass after treatment, most commonly, in the mediastinum. This clinical challenge has been approached with the addition of mediastinal irradiation in earlier studies. In the study by Thomas et al [13] patients treated with prophylactic mediastinal irradiation (30 to 39 Gy) after hyper-CVAD induction had lower incidence of mediastinal relapse compared to patients that received no irradiation. Although none of the regimens precluded mediastinal irradiation only four patients received this treatment as part of the primary treatment in our series. All four patients were treated with hyper-CVAD, and when comparing time to relapse/progression with non-irradiated patients treated with hyper-CVAD there was a statistically significant difference in favor of irradiated patients. The benefits of mediastinal irradiation might however be related to specific induction treatments or irradiation dose since in a study by Hoelzer et al [10] no beneficial effect was seen. In that study, patients treated with GMALL-protocols received prophylactic mediastinal irradiation at a lower dose (24 Gy) but still the majority of relapses occurred in the mediastinum. Although the number of patients are low our results supports the notion that there may be a beneficial effect of mediastinal irradiation at least for patients treated with hyper-CVAD chemotherapy.

The use of PET-CT as part of the evaluation and risk of relapse is not very well described in T-LBL. In our material PET-CT was part of the induction response evaluation for 13 of the intensively treated patients, mostly because of residual masses. All the examinations were interpreted as normal, but still more than half of the patients relapsed. The PET-CT was not performed in a uniform manner, as exact time point for evaluation varied between patients and there was no central review or centralized protocol. These facts limits conclusions to be

drawn from the results but point to that PET-CT must be interpreted with caution and might not be safely used for directing therapeutic decisions and should be further investigated in clinical trials.

In conclusion our results shows the beneficial effect of ALL-type treatment compared to CHOP-like therapy also in a completely unselected patient cohort. The results strongly suggests that all reasonably fit patients, including patients above 60 years of age, should be considered for intensive treatment as age had no impact on the risk for shorter survival. Also the addition of mediastinal radiation therapy should be considered for patients treated with hyper-CVAD. Relapse was the main reason for treatment failure and with the lack of targeted therapy, the role of even more intensified treatment for the youngest adult patients warrants further investigation.

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Declaration of interest

The authors report no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Figure legends

Figure 1

Kaplan-Meier estimates of Overall (OS) and Progression-free Survival (PFS) among T-cell lymphoblastic lymphoma patients.

Figure 1A

OS (solid line) and PFS (dashed line) for the entire cohort.

Figure 1B

OS, intensive treatment group (solid line) and non-intensive group (dashed line).

Figure 1C

PFS, intensive treatment group (solid line) and non-intensive group (dashed line).

Figure 2

Overall survival curve of T-cell lymphoblastic lymphoma patients calculated from the time of relapse.

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Table I

Patients' clinical characteristics at diagnosis.

Clinical characteristics		Number (%)
Age > 60 years		11 (28)
Male		24 (62)
Female		15 (38)
B-symptoms		14 (36)
Ann Arbor stage	I	12 (31)
	II	9 (23)
	III	0 (-)
	IV	18 (46)
Bulky disease (>10cm) *		26 (67)
BM involvement		9 (23)
Mediastinal tumor †		35 (90)
CNS involvement		2 (5)
Pleural effusion ‡		20 (51)
Pericardial effusion ‡		9 (23)
LDH > UNL		28 (72)
Extranodal involvement > 1		8 (21)
WHO performance status >1		2 (5)
IPI	0-1	18 (46)
	2-3	19 (49)
	4-5	2 (5)

* data for one patient missing † data for two patients missing ‡ data for three patients missing, BM indicates bone marrow; LDH, lactate dehydrogenase; UNL, upper normal level; IPI, international prognostic index

Table II

Induction treatment

		N	Treatment response				
Intensive treatments			CR	PR	SD	PD	NE
	Hyper CVAD *	19	8	10	1		
	LSA2L2	4		4			
	NOPHO-ALL-92 HR	2	1	1			
	VSTB -95	2	1	1			
	Euro LB-02	1	1				
	GMALL 06/99	1	1				
	ABCDV	1		1			
Non-intensive treatments							
	VACOP-B	1			1		
	CHOP	5		1	1	1	2
	COP	1			1		

* One patient had mediastinal irradiation prior to chemotherapy, CR indicates Complete Remission; PR, Partial Remission; SD, Stable Disease; PD, Progressive Disease; NE, Not Evaluable.

Table III

Maintenance and consolidation therapy

		N	Alive in CCR (N)
Chemotherapy maintenance	6-MP/Mtx	3	1
	hyper-CVAD *	15	8
	LSA2L2	3	3
	GMALL 06/99	1	1
Autologous SCT		2	2
Allogeneic SCT		2	0
None		4	0

* 3 patients had mediastinal irradiation before starting maintenance treatment. CCR indicates continuous complete remission; 6-MP, 6-mercaptopurine; Mtx, methotrexate; hyper-CVAD, 6-mercaptopurin po, methotrexate po, daunorubicin iv, vincristine iv, prednisone po, cytarabine sc, thioguanine po; LSA2L2, thioguanine po, cyclophosphamide iv, hydroxy-urea po, daunorubicine iv, methotrexate it, methotrexate po, carmustin iv, cytarabine iv, vincristine iv, prednisone po; GMALL 06/99, dexamethasone po, methotrexate it, cytarabine it, dexamethasone it, high-dose methotrexate iv, vindesine iv, etoposide iv, high-dose cytarabine iv, PEG-asparaginase iv, 6-mercaptopurine po, prednisone po, doxorubicin iv, cyclophosphamide iv, thioguanine po, tenisposide iv.

Table IV

Relapse treatment and site of relapse

Salvage chemotherapy	Site of relapse	Survival after relapse (months)	Cause of death
ICE x 2 , EPOCH x 2 + Alemtuzumab	m, bm	3	Progressive lymphoma
multiagent chemotherapy, nelarabine, multiagent chemotherapy + vincristine and asparaginase, prednisone + interferon	bm	5	Progressive lymphoma
ICE, HD Mtx, FLAG-Asp, 6-mercaptopurine	ln,bm, breast	5	Progressive lymphoma
FLAG-Asp, alemtuzumab	ln, pl, CNS	4	Progressive lymphoma
FLAG-Asp, nelarabine	m, pl	2	Progressive lymphoma
FLAG-Asp + allogenic SCT, ICE	m, CNS	22	Progressive lymphoma
ICE x 4 + BEAC and autologous SCT	m	11	Progressive lymphoma
HD cytarabine, CNS & spinal radiation + BEAM and autologous SCT, liposomal cytarabine	CNS	13	Progressive lymphoma
Idarubicine/cytarabine + allogeneic SCT	CNS	5	Progressive lymphoma
ICE, gemcitabine/cisplatin, ICE, fludarabine/cytarabine, fludarabine/etoposide + allogeneic SCT	ln, m, bm	8	Treatment related death
MEA + mediastinal irradiation, ABCDV/VABA + LSA2L2-maintenance	kidney, liver	25	Progressive lymphoma
ICE x 5, liposomal cytarabine, HD cytarabine	CNS	5	Progressive lymphoma

m indicates mediastinum; bm, bone marrow; ln, lymph node; pl, pleura; CNS, central nervous system; ICE (ifosfamide, carboplatin and etoposide); EPOCH (etoposide,prednisone,vincristine,doxorubicine and cyclophosphamide); HD indicates high-dose; FLAG-Asp (fludarabine, cytarabine, GCS-F and asparaginase); BEAC (carmustine,

etoposide, cytarabine and cyclophosphamide); BEAM (carmustine, etoposide, cytarabine and melphalan); MEA (mitoxantrone, etoposide and cytarabine); ABCVD (cytarabine, betamethasone, cyclophosphamide, daunorubicine and vincristine); VABA (vincristine,cytarabine, betamethasone and amsacrine)

Table V

Risk factor analysis for overall survival (OS) and progression-free survival (PFS)

	Factor	**OS**			**PFS**		
Total cohort		N	Univariable, HR (95 % CI); p	Multivariable, HR (95 % CI);p	N	Univariable, HR (95 % CI);p	Multivariable, HR (95 % CI);p
	age	39	1.04 (1.01-1.06) ; p=0.007	1.01 (0.98-1.05); p=0.432	37	1.03 (1.01-1.06); p=0.021	1.01 (0.97-1.04); p=0.773
	female gender	39	4.67 (1.96-11.1); p=0.001	4.29 (1.68-11.0); p=0.002	37	4.18 (1.74-10.0); p=0.001	3.71 (1.47-9.37); p=0.006
	non-intensive treament	37	5.63 (2.11-15.0); p=0.001	4.09 (1.04-16.1); p=0.002	37	5.18 (1.96-13.7); p=0.001	3.90 (0.97-15.7); p=0.056
Intensive treatment group	female gender	30	2.55 (0.90-7.24); p=0.078	1.94 (0.59-6.31); p=0.273	30	2.37 (0.84-6.68); p=0.103	1.71 (0.52-5.55); p=0.375
	CNS involvement	30	7.44 (1.42-39.0); p=0.017	4.59 (0.74-28.6); p=0.103	30	13.3 (2.18-81.4); p=0.005	8.96 (1.23-65.1); p=0.030

Only factors with $p \leq 0.1$ in univariable analysis are shown.