VPDL Chemotherapy for T-cell Lymphoblastic Lymphoma (T-LBL) in Adults: Comparison with Upfront Autologous Stem Cell Transplantation in a Single Center

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Background: Treatment of T-cell lymphoblastic lymphoma (T-LBL) with CHOP or CHOP-like chemotherapy has resulted in poor long-term outcomes. High-dose chemotherapy followed by ASCT has been applied for this dreaded disease. However, the efficacy is still controversial. T-LBL is considered the nodal/extranodal presentation of acute lymphoblastic leukemia. Favorable results with VPDL chemotherapy have been reported in the setting of adult lymphoblastic leukemia. We, therefore, treated T-LBL patients with modified VPDL chemotherapy and compared the outcomes with those achieved using upfront ASCT.

Methods: We retrospectively reviewed the outcomes of 24 T-LBL patients treated either with upfront ASCT (n=11) or VPDL chemotherapy without ASCT (n=13) between January 1996 and October 2005.

Results: The median follow-up duration for surviving patients was 17 months (range, 5～109 months). The two-year event-free survival (EFS) rates were 83.1% in the VPDL group and 27.3% in the upfront ASCT group (P=0.008). The two-year overall survival (OS) rates were 83.9% in the VPDL group and 27.3% in the upfront ASCT group (P=0.006).

Conclusion: This study suggests that VPDL chemotherapy is very effective and may be superior to upfront ASCT in the treatment of T-LBL patients. ***(Korean J Hematol 2008;43:138-144.)***

Key Words: T-cell lymphoblastic lymphoma, Chemotherapy and autologous stem cell transplantation

INTRODUCTION

Lymphoblastic lymphoma (LBL) is an uncommon malignancy accounting for less than 2% of non-Hodgkin's lymphomas (NHL).[1)] About 80% of LBLs are of T-cell immunophenotype (T-LBL), with the remainder being B cell type (B-LBL). In the World Health Organization classification, LBL is considered a precursor B-cell/T-cell neoplasm and the nodal/extranodal presentation of acute lymphoblastic leukemia (ALL).[2)]

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Treatment with CHOP or CHOP-like chemotherapy protocols has resulted in poor long-term outcomes.[3-6] Attempts to improve long-term outcomes have resulted in chemotherapy programs that integrate consolidation with stem cell transplantation (SCT).[5,7-9] A prospective study comparing chemotherapy alone and upfront autologous SCT (ASCT), however, failed to show better efficacy of ASCT in the treatment of T-LBL.[10] A treatment program using intensive, cyclical chemotherapy using alternating courses of non-cross-resistant drugs including L-asparaginase was introduced to treat adult ALL and produced high response rate and prolonged disease-free survival.[11] We applied the regimen, VPDL chemotherapy to treat T-LBL patients and compared the results with the outcome of upfront ASCT.

MATERIALS AND METHODS

1. Study group

From January 1996 to October 2005, 28 adult patients presented with T-LBL at Asan Medical Center. Four patients who underwent ASCT for relapse of disease were excluded. Follow-up data were collected until April 20, 2007. Eligibility criteria included age ≥15 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, adequate renal and hepatic functions, and absence of HIV infection.

2. Diagnosis

Diagnosis was based on morphological and immunohistochemical examination of materials from lymph nodes or bone marrow using routine techniques, all of which were reviewed by a pathologist (JH). Histopathological classification was based on the World Health Organization (WHO) criteria for T-LBL.[2]

3. Staging

Clinical, laboratory, and radiological evaluations included physical examination, CT scans of the thorax, abdomen and pelvis, bilateral bone marrow aspiration and biopsy, complete blood cell count with differential, liver and kidney function tests, and serum lactate dehydrogenase (LDH). Patients were staged according to the Ann Arbor staging classification.[12] The age-adjusted International Prognostic Index (IPI) was based on performance status, tumor stage and serum LDH.[13]

Table 1. Prior chemotherapy regimens in the ASCT arm

	No. of patients (n=11)	Percent
First-line chemotherapy		
VPDL*	5	45.5%
CODOX-M/IVAC	5	45.5%
Vanderbilt	1	9.1%
Second-line chemotherapy		
CODOX-M/IVAC	3	27.3%
DHAP	1	9.1%
CVPD	1	9.1%
ESHAP	1	9.1%
Vanderbilt	1	9.1%
None	4	36.0%

*Patients who underwent VPDL induction treatment (See Table 2).
Abbreviations: CODOX-M, cyclophosphamide, doxorubicin, vincristine, cytarabine and methotrexate (iv and intrathecal); CVPD, cyclophosphamide, vincristine, dexamethasone, and doxorubicin; DHAP, cytarabine, cisplatin, and dexamethasone; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; IVAC, ifosfamide, etoposide, cytarabin, and methotrexate (intrathecal); Vanderbilt, cyclophosphamide, etoposide, vincristine, bleomycin, methotrexate, and prednisolone; VPDL, vincristine, prednisolone, daunorubicin, and L-asparaginase.

4. Chemotherapy

From January 1996 to March 2002, patients diagnosed with T-LBL in Asan Medical Center were treated with one of several chemotherapy regimens for aggressive histology lymphoma (Table 1). Those who showed no response to initial induction chemotherapy were allowed to receive second-line aggressive chemotherapy. All of those who attained CR or partial remission (PR) underwent ASCT. Patients diagnosed with T-LBL between April 2002 and October 2005 were treated with VPDL chemotherapy after modification from the original regimen without

Table 2. Drugs used in the VPDL protocol

Drugs	Dosage	Route	Day	Comments
Induction				
Daunorubicin	45mg/m^2	IVP	D1-3	
Vincristine	2mg	IVP	D1,8,15,22	
Prednisolone	60mg/m^2	PO	D1-28	
L-asparaginase	4,000units/m^2	IM	D17-28	
Consolidation A (cycles 1, 3, 5 and 7)				
Daunorubicin	50mg/m^2	IVP	D1,2	
Vincristine	2mg	IVP	D1,8	
Prednisolone	60mg/m^2	PO	D1-14	
L-asparaginase	12,000units/m^2	IM	D2,4,7,9,11,14	
Consolidation B (cycles 2, 4, 6 and 8)				
VP16	75mg/m^2	IV	D1,4,8,11	
Ara-C	300mg/m^2	CIV	D1,4,8,11	
Consolidation C (cycle 9)				
MTX	690mg/m^2	CIV	D1	Infusion for 48 hr
Leucovorin	15mg/m^2	IVP	D3-5	Q6 hrs for 12 dose After MTX induction

Abbreviations: IVP, intravenous push; PO, per os; IM, intramuscular injection; CIV, continuous intravenous injection.

ASCT. Dose of daunorubicin was reduced from 50mg/m^2 to 45mg/m^2, dose of L-asparaginase was reduced from 6,000units/m^2 to 4,000units/m^2 and VP-16 was substituted for teniposide (Table 2).[11]

5. ASCT protocols

Two patients were mobilized with cyclophosphamide (4g/m^2) plus granulocyte-colony stimulation factor (G-CSF; 10 μ/kg/day; Lenograstim, Choongwae Pharma Corp., Seoul, Korea) for stem cell collection and nine were mobilized with on-going chemotherapy plus G-CSF. The minimum collection target was 2×10^6 CD 34^+ cells/kg. All patients received carmustine, etoposide, doxorubicin, and cyclophosphamide (BEAC) as a conditioning regimen. Patients received supportive care according to current protocols at our institution.

6. Response criteria

Responses to chemotherapy and ASCT were evaluated according to International Workshop to Standardize Response criteria.[14] Routine follow-up imaging analysis was performed every 3 months for the first 2 years after initial treatment, every 6 months for the next 3 years, and then yearly or whenever clinically indicated.

7. Statistical analysis

Overall survival (OS) was calculated from the date of first chemotherapy until death from any cause or until last follow-up for surviving patients. Event-free survival (EFS) was calculated from the date of first chemotherapy until relapse, disease progression, death from any cause or until last follow-up. Duration of CR was defined from the earliest date of complete response to the date of death from any cause, disease progression or relapse, or censored at the date of last contact. Estimated OS, EFS rates and duration of CR were calculated using the product-limit method of Kaplan-Meier and compared using the log-rank test. Two-tailed P values of <0.05 were regarded as significant. All calculations were performed using Statistical Package for the Social Sciences (SPSS) version 12.0 (SPSS, Chicago, IL, USA).

Table 3. Characteristics of all patients at presentation

		VPDL (n=13)	ASCT (n=11)	*P*-value
Age	≤30 years	7	7	0.697
	>30 years	6	4	
Sex	Male	12	9	0.576
	Female	1	2	
Stage	I, II	4	2	0.649
	III, IV	9	9	
B symptom	No	7	9	0.211
	Yes	6	2	
ECOG	0~1	11	10	1.0
	2~4	2	1	
LDH	Normal	6	4	0.697
	Above norma	7	7	
Extranodal involvement	0~1	10	8	0.537
	>1	3	3	
Mediastinal involvement	No	3	3	1.0
	Yes	10	8	
Bone marrow involvement	No	7	6	0.973
	Yes	6	5	
Age-adjusted IPI	L/LI	6	3	0.423
	HI/H	7	8	

Abbreviations: L, low; LI, low intermediate; HI, high intermediate; H, high.

Table 4. Patient outcomes after VPDL or ASCT

	VPDL (n=13)	ASCT (n=11)	*P*-value
Response			0.695
CR	9 (69.2%)	6 (54.5%)	
PR	2 (15.4%)	2 (18.2%)	
PD	2 (15.4%)	2 (18.2%)	
NA	-	1 (9.1%)*	
Status			0.006
Alive	10 (76.9%)	3 (27.3%)	
Dead	2 (15.4%)	8 (72.7%)	
Lost to follow up	1 (7.7%)	-	
Cause of death			0.625
Disease progression	1 (7.7%)	3 (37.5%)	
Infection	1 (7.7%)	3 (37.5%)	
Other	-	2 (25.0%)†	

*Patient died before response assessment. †One patient expired from GVHD after salvage allo-SCT and the other from VOD.
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; NA, not available.

RESULTS

1. Patient characteristics

Patient characteristics at presentation are listed in Table 3. The ASCT and VPDL groups did not differ significantly in age, sex distribution, stage, B symptom status, performance (ECOG), level of LDH, extranodal involvement, mediastinal involvement, bone marrow involvement and age-adjusted IPI.

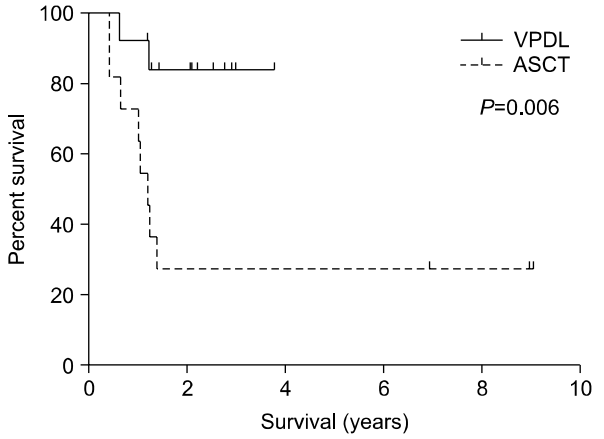

Fig. 1. Probability of overall survival in 13 patients treated with VPDL chemotherapy (solid line) and 11 patients with ASCT (dashed line).

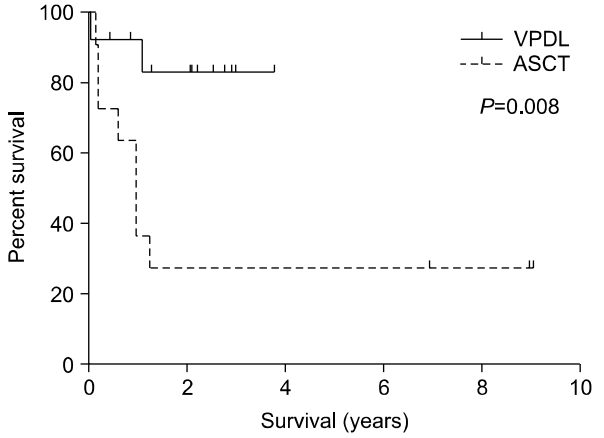

Fig. 2. Probability of event free survival in 13 patients treated with VPDL chemotherapy (solid line) and 11 patients with ASCT (dashed line).

2. Response and survival after treatment

Of the 13 patients in the VPDL group, 9 attained CR and 2 attained PR, whereas the other 2 patients showed progressive disease (PD) (P=0.695). Of the 11 patients in the ASCT group, one who achieved CR after initial chemotherapy sustained CR after ASCT, and additional 5 patients attained CR following ASCT. Of the remaining five patients in this group, two attained PR, two showed PD and one died before assessment (Table 4). At a median follow-up of 17 months (range, 5～109 months), the 2-year OS rate was 83.9% in the VPDL group and 27.3% in the ASCT group, with an overall rate of 61.3% for all of the 24 patients (Fig. 1, P=0.006). The 2-year EFS rate was 83.1% in the VPDL group and 27.3% in the ASCT group (Fig. 2, P=0.008). Median OS and EFS for the ASCT group were 14.4 and 11.7 months, respectively, whereas the median OS and EFS for the VPDL group were not reached. Two-year CR duration was 87.5% in the VPDL group and 50.0% in the ASCT group (P=0.096). Median CR duration was not reached in the VPDL group and 9.8 months in ASCT group.

3. Toxicity and causes of death

All the patients in both groups experienced grade 4 neutropenia and grade 3 or 4 thrombocytopenia.

Systemic antibiotics were required in 10 out of 11 courses (90.9%) of ASCT and 69.2% in VPDL courses for infection (P=0.085). All the patients in ASCT group experienced grade 3 or 4 stomatitis but 2 patients (7.7%) in VPDL group experienced grade 2 stomatitis. Nausea and vomiting were minimal in VPDL group. No patient in VPDL group experienced acute pancreatitis related to L-asparaginase. Of the 11 patients in the ASCT group, 8 died, 3 of infection (2 pneumonia and 1 varicella-zoster virus related sepsis), 3 of disease progression, 1 of graft versus host disease (GVHD) after salvage allo-SCT and 1 of veno-occlusive disease (VOD). Two deaths in the ASCT group were attributed to treatment; one patient died of pneumonia 14 days after ASCT and the other of VOD 1 month after ASCT. Of the 13 patients in the VPDL group, two died, one of sepsis and the other of disease progression.

DISCUSSION

In an overview of the Non-Hodgkin's Lymphoma Classification Project, the EFS rate for T-LBL was 24% at 6 years.[1] In addition, the CR rate has been reported to be only 10%, with a median survival of 12 months.[15] A variety of therapeutic approaches have been attempted for adult LBL due to the relatively high relapse and poor response rates. Conventional NHL protocols with CHOP or CHOP-like regimens have yielded low CR rates, ranging between 53% and 79%.[3-6] Intensive multiagent chemotherapy analogous to that used in ALL (ALL-type chemotherapy) in patients with B-/T-LBL have resulted in CR rates of 77% to 100% and EFS rates of 45% to 67% suggesting that ALL-type chemotherapy may be effective for T-LBL.[5,16-18] The use of high-dose therapy (HDT) and SCT has been attempted to consolidate first remission after standard induction therapy, with 60% to 80% of patients achieving long-term EFS.[5,7-9] Although a randomized study comparing chemotherapy alone and chemotherapy consolidated with ASCT was initiated to define the role of SCT in the treatment of LBL, the trial had to be terminated early because of poor accrual.[10] This study failed to show significant survival benefit of ASCT with 2-year OS rate of 57% in ASCT group compared with 53% in patients treated with chemotherapy alone (P=0.71). Two-year relapse-free survival rates in ASCT and chemotherapy alone groups were 50% and 29%, respectively (P=0.065).

Our results showed that chemotherapy alone could produce very good outcomes in patients with T-LBL, with 2-year OS and EFS rates in the VPDL group of 83.9% and 83.1%, respectively.

Six of the 11 patients in the ASCT group attained or sustained CR after ASCT, whereas all those who failed to attain CR died of disease progression or infection. In contrast, 9 of the 13 patients (69.2%) in the VPDL group attained CR and all survived through last follow-up. The results of VPDL chemotherapy compared favorably with those of previously published studies. The regimen known as 'Stanford/NCOG' of modified CHOP chemotherapy incorporating asparaginase, central nervous system prophylaxis and maintenance therapy showed CR rates of 79% to 100% and EFS rates of 23% to 58%.[5,19,20,21] Our results was not inferior to other ALL-type chemotherapy which resulted in CR rates between 77% and 100% and EFS rates of 45% to 67% in patients with B-/T-LBL.[5,16-18]

We found that our group of ASCT patients had a poorer outcome compared with previous reports.[5,7-9] This may be due to different study populations. In most studies, ASCT was performed as consolidation therapy for patients in CR after initial chemotherapy. In contrast, 10 of our 11 ASCT had achieved PR after initial chemotherapy, suggesting that ASCT may have yielded better outcomes if performed on patients in CR only. Also proportion of patients with high or high intermediate age-adjusted IPI was higher in the ASCT group although it was not statistically significant.

Our study has several limitations, including its small sample size and short follow-up period, as well as its inhomogeneous population and diverse regimens of initial chemotherapy in the ASCT group. Nevertheless, our experience with the VPDL regimen in patients with T-LBL is very encouraging, especially considering the potential adverse effects of ASCT, including severe mucositis, infection, VOD and treatment-related mortality. We have shown that VPDL chemotherapy without ASCT effectively induced and sustained remission of T-LBL. This study suggests that VPDL chemotherapy is very effective and can be superior to upfront ASCT in the treatment of T-LBL patients in conclusion.

요 약

배경: T세포림프구성림프종에 CHOP 또는 CHOP과 유사한 항암화학요법을 적용하였을 때 장기치료효과는 저조하였다. 예후가 좋지 않은 이 질환에 대하여 고용량항암화학요법 및 선행자가조혈모세포이식이 적용되었으나 그 효과에 대해서는 아직 이견이 있다. T세포림프구성림프종은 급성백혈구성백혈병의 림프절 또는 림프절외의 표현형으로 생각되며 성인 급성백혈구성백혈병에 VPDL 항암화학요법을 적용하였을 때 좋은 결과가 보고된 바 있다. 따라서 저자들은 VPDL 항암화학요법을 다소 변형하여 T세포림프구성림프종 환자에게 적용하였고 이 결과를 선행자가조혈모세포이식을 받은 환자의 결과와 비교하였다.

방법: 1996년 1월부터 2005년 10월까지 치료받은 24명의 T세포림프구성림프종 환자 중 11명은 선행 자가조혈모세포이식을, 나머지 13명은 자가조혈모세포이식을 병행하지 않은 VPDL 항암화학요법을 시행받았으며 이 결과를 후향적으로 검토하였다.

결과: 생존환자의 중간추적기간은 17개월(범위, 5~109개월)이었다. 2년 무사건생존율은 VPDL군은 81.3%, 선행 자가조혈모세포이식군은 27.3%였으며(P=0.008) 2년 전체생존율은 각각 83.9%와 27.3%였다(P=0.006).

결론: 이 결과는 VPDL 항암화학요법이 T세포림프구성림프종 환자의 치료에 있어 매우 효과적이며 선행 자가조혈모세포이식과 비교하여 우월할 수 있음을 제시하고 있다.

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