Results of intensified therapy in acute lymphoblastic leukemia in adults

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The treatment results of one of the intensified chemotherapy regimens in 14 adult patients with ALL were evaluated. All patients achieved complete remission (CR), except one who died of disease progression at the beginning of the therapy. The relapse rate was 38% during the median follow-up period of 25+ months. Projected disease free survival and overall survival at 3 years were 58% and 61%, respectively. No treatment related death was seen. [Turk J Med Res 1994; 12(2): 57-61]

Key Words: Adult acute lymphoblastic leukemia, Chemotherapy

Acute lymphoblastic leukemia (ALL) has a prominent peak in early childhood. The incidence of the disease shows a trend towards dropping off to its lowest point between the second and third decade and then rises again somewhat. The biologic behaviour of ALL is a little different between childhood and adult disease. The standart regimens which includes relatively non-toxic remission-induction and maintenance therapy achieves about 90% complete remission in the children, and 50% to 60% of these remissions will be durable. The success of the same treatment in the adult patients Is inferior than that in the children. Recently, the effects of intensified induction and consolidation therapy were evaluated in adult ALL. The results of this type of the treatments have been very encouraging (1-5).

Our treatment results in adult ALL by using one of the intensified therapy were reported in this study.

MATERIALS AND METHODS

Patients: Fourteen consecutive adult patients with ALL who 'vere treated at Ankara University, School of Medicine, Section of Medical Oncology between 1988-1992 were evaluated in this study. The morphological diagnosis of ALL was based on giemsa and cytochemical staining of bone marrow and blood smears, including periodic acid-schiff (PAS) and peroxidase.

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Treatment: A chemotherapy regimen which was similar to that of Hoelzer et al (1) was applied to all patients. Table 1 shows the details of the treatment. In some case, treatment was delayed during induction and consolidation treatment because of severe bone marrow depletion+/-infection. Cases with bulky mediastinal mass had additional involved field radiotherapy. Only one patient received reinduction treatment with cyclophosphamide, doxorubicin, vincristin and prednison in addition to the peroral maintenance therapy. All patients had appropriate supportive care. Antibiotics were given only therapeutically not prophilactically.

Criteria Ofresponse: Patients were considered to be in complete remission (CR) when the neutrophil count was greater than 1500/mm^3, platelet count was greater than 100000/mm^3, the percentage of blasts in bone marrow was lower than 5 %, and all extramedullar disease resolved. To assess the response to treatment, bone marrow aspiration and/or biopsy were done after phase I and II of induction therapy.

Statistical Analysis: Disease free survival (DFS) was measured from the date of the achievement of CR until either disease relapse or death due to any reason other than ALL. Overall survival (OS) was calculated from the date of the begining of the therapy to the date of last examination or death. Estimated disease-free survival and overall survival curves were performed using the Kaplan-Meier method.

RESULTS

The 14 patients with acute lymphoblastic leukemia were treated. Two of them had transformed from lymphoblastic lymphoma and they were initially treated by CHOP or modified CHOP combinations. The others

Table 1. Treatment Schedule

Drug	Dose	Days
Induction		
Phase 1		
Prednisone (PO)	60 mg/m	1-28
Vincristine (IV)	1,5 mg/m² (max 2 mg)	1,8,15,22
Daunorubicin (IV)	25 mg/m²	1,8,15,22
L-asparaginase (IV)	5000 U/m²	1-14
Phase 2		
Cyclophoshamide (IV)	650 mg/m''	29,43,57
Cytosine arabinoside (IV)	75 mg/m	31-34, 38-41,45-48. 52-55
6-mercaptopurine (PO)	60 mg/m²	29-57
Methotrexate (IT)	10 mg/m² (max 15 mg)	31,38,45,52
Cranial irradiation	2400 cGy	
Consolidation		
Phase 1		
Dexamethasone (PO)	10 mg/m	1-28
Vincristine (IV)	1,5 mg/m²	1,8,15,22
Adriamycin (IV)	25 mg/m²	1,8,15,22
Phase 2		
Cyclophosphamide (IV)	650 mg/m²	29
Cytosine arabinoside (IV)	75 mg/m²	31-34, 38-41
Thioguanine (PO)	60 mg/m²	29-42
Maintenance		
6-mercaptopurine (PO)	60 mg/m²/d	weeks 10-18
Methotrexate (PO/IV)	20 mg/m²/wk	and 29-130

didn't receive any previous chemotherapy. The characteristics of patients are shown in Table 2.

Overall Results: One patient died of disease progression during the first week of the treatment, and she was not included in the evaluation of the results of treatment. Complete remission (CR) was achieved in all évaluable patients mostly (in 10 out of 13) after phase I of the induction treatment. Up to the date of January 1994, 5 patients had relapsed, one patient died of fulminant viral hepatitis while she was in CR, seven patients (54%) were in continuous CR and the duration of remission ranged between 23 and 63 months. Three relapsed patients achieved a second CR with the same treatment regimen. One patients died of interstitial pneumonitis during the first month of the second CR. Second CR lasted 5 and 20 months in the other two patients. One of them is still alive on treatment. Five out of 13 patients died during the median follow-up period of 25+ months. Three of these deaths were due to the progressive disease. The outcome of all patients are shown in Table 3.

TOXICITY: No toxic death was seen during the first induction therapy. Only one patient died because of non-neutropenic infection. This patient was in second CR and the cause of death was interstitial pneumonia probably secondary to Pneumocystis carinii. One patient died of fulminant hepatitis at the

Table 2. Characteristics of patients

	No of patients
Age (years)	
16-24	7
25-34	
>35	1
Sex	
Male	9
Female	5
WBC (/mm3)	
<4000	4
4000-49.000	5
>50.000	5
Platelet (/mm3)	
<100.000	5
>100.000	nirtfftfill
LDH (mg/dl)	
Normal	4
High	10
FAB Classification	
L1	3
L2	11
L3	—

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Table 3. Patients' outcome

Patient Initials	Age	Sex	Presenting Symptoms	WBC	Platelet	PS (ECOG)	Time to CR (Month)	DFS (Month)	Overall Surv. (Month)	Recent Disease Status
ET	21	F	V.C.S.S.	58.700	192.000	2	1	62 (+)	63 (+)	Continuous CR
SD	21	F	Weakness	3.500	157.000	2	1	8 (+)	9	Exitus in CD (viral hepatitis)
NS	27	F	Bleeding, fever	1.700	41.000	3	2	5	22	Exitus
ZB	26	F	Mediastinal mass	8.000	192.000	1	1	51 (+)	52 (+)	Continuous CR
CA	36	M	Bleeding	120.000	30.000	2	1	43 (+)	44 (+)	Continuons CR
IÖ	17	M	Fever	1.500	60.000	3	2	13	17	Exitus
CD	24	M	Leukemic relapse from lymphoblastic lymphoma	50.000	100.000	2	1	*9	*11	Exitus
EB	28	M	Mediastinal mass	60.000	377.000	2	2	11	40 (+)	Alive in third CR
KÖ	32	F	Pleural and pericardial effusion	24.000	40.000	2	1	28	32	Exitus in second CR (Interstitial Pneumonitis)
EÇ	16	F	Abdominal mass	12.800	109.000	4	—	—	1	Exitus
MY	16	M	Fever, multiple LAP	2.000	220.000	1	1	24 (+)	25 (+)	Continuons CR
CY	28	M	Med. mass, bleeding	4.000	50.000	2	1	23 (+)	25 (+)	Continuons CR
FK	31	M	Mediastinal mass	5.000	250.000	1	1	22 (+)	23 (+)	Continuons CR
MÇ	22	M	Leukemic relapse from lymphoblastic lymphoma	60.000	300.000	1	1	*15 (+)	*16 (+)	Continuons CR

DFS: (Disease free survival) and overall survival were calculated from the diagnosis of leukemia (not lymphoma)
VCSS: Vena Cava Superior Syndrome, CR: Complete remission, PS: Performance status

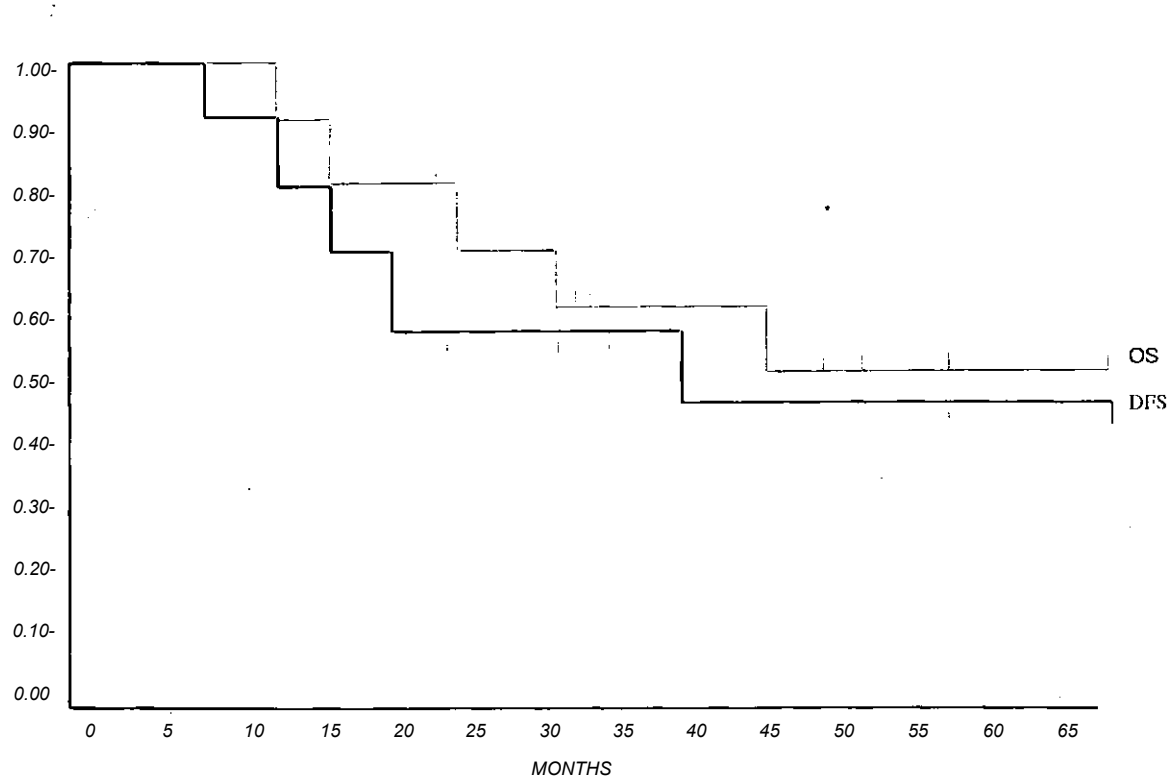

Figure 1. Probability of DFS (Disease Free Survival) and OS (Overal Survival) estimated by the Kaplan-Meier method for all évaluable patients.

eighth month of remission while she was receiving maintanence therapy. Almost all patients experienced febril episodes during the induction and/or consolidation treatment which were treated with appropriate antibiotics successfuly. Interstitial pneumonitis were observed in three patients. Two of them responded to the treatment with trimethoprim+sulfamethoxasole. Thrombocytopenia developed in 80% of the patients and platelet transfusions were done as necessary. No life threatening bleeding was observed during the treatment.

DISCUSSION

In this study, the results of one of the intensified therapies were presented in adult patients with acute lymphoblastic leukemia. In spite of the small number of patients, the results of this treatment are very promising. The rate of CR was 100% and median disease free survival (DFS) was not yet reached during 25 months of follow-up (relapse rate 38%); Three out of 13 patients had long durable CR (44, 52, 63 months). When compared to the results of the study of Hoelzer et al (1), our results seemed better. The rate of CR in that study was 73.9% and median DFS was 24.3 months. This difference could be related to the small number of our patients. On the other hand, the relatively younger mean age of our cases (24,6 years old) should be taken into account too, since the age of younger than 35 years was reported a good prognostic factor in the same study (1). Linker et al reported that 88% of the adult patients with ALL achieved CR with another intensive chemotherapy and 42% of patients achieving CR were projected to remain disease-free at 5 years (5). The rates of the estimated DFS and overall survival of our cases at 3 years were 58% and 61%, respectively, as showns on Figure 1. These results were comparable with those of a similar treatment in the high risk childhood ALL in Turkey (6) and the 3-year results of the study of Linker et al (5).

The toxicity of this treatment was acceptable and it can be applied in the institutions which had good supportive care conditions. The relative disadvantage of the therapy could be the long hospitalization period since the median time of hospitalization in our cases was 20 weeks. However, this long time was mainly due to social problems. One of the cases stayed in the hospital for only 4 weeks and the remaining of the treatment was mostly given in the outpatient clinic.

In conclusion, this regimen could be considered as a convenient and successfull therapy for adult patients with ALL in Turkey.

Erişkinlerin akut lenfoblastik lösemisinde yoğun kemoterapi sonuçları

Ondört erişkin ALL'li hastada, yoğun bir kemoterapi rejiminin tedavi sonuçları değerlendirildi. Tedavinin başında progresif hastalık sonucu ölen bir hastanın dışında, tüm hastalarda tam remisyon (TR) sağlandı. Median takip süresi olan 25+ ay boyunca, nüks oranı %38 bulundu. Hastalıksız sağkalım ve 3 yıllık sağkalım oranları sırasıyla %58 ve %61'di. Tedaviye bağlı ölüm görülmedi. [Turk J MedRes 1994, 12 (2): 57-61]

REFERENCES

1. Hoelzer D, Thiel E, Löffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood, 1988; 71:123-31.
2. Radford JE, Burns CP, Jones MP, et al. Adult acute lymphoblastic leukemia: Results of the Iowa HOP-L protocol. J Clin Oncol 1989; 7: 58-66.
3. GIMEMA Cooperative Group. GIMEMA ALL 0183: a multicentric study on adult acute lymphoblastic leukemia in Italy. Br J Haematol 1989; 71: 377-86.
4. Kantarjian HM, Walters RS, Keating MJ, et al. Results of the vincristine, doxorubicin, and dexamethasone regimen in adults with standart and high-risk acute lymphocytic leukemia. J Clin Oncol 1990; 8: 994-i 004.
5. Linker CA, Levitt LJ, O'Donnell M, et al. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: A follow-up report. Blood 1991; 78: 1814-1 822.
6. Babacan E, Yavuz G, Gözdaşoglu S, et al. Yüksek risk ALL-'li olgularda yoğun kombine kemoterapiden (CCG-106 B) alınan sonuçlar (Results of intensive combination chemotherapy in high-risk All patients). XXIII. Ulusal Hematoloji Kongresi Özet Kitabı, İstanbul, 1993 (abs. No.219).
7. Üskent N, Başak M, Yaylacı M, et al. Erişkin ALL olgularında CVPD protokolü ile aldığımız sonuçlar (Results of CVPD regimen in adult ALL patients). X. Ulusal Kanser Kongresi Özet Kitabı, p. 33, istanbul-1993.