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Research Article

Berlin-Frankfurt-Munster (BFM) versus Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone (Hyper-CVAD) chemotherapy regimens in Adult T-Cell ALL and Adolescent and Young Adult (AYA) Patients: A Retrospective , Comperative Evaluation and Review

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Abstract

Objectives: Recently, in adult ALL patients, to improve prognosis, pediatric ALL protocols have been used in adolescent and young adults and positive results have been reported.

Methods: In this study, we aimed to evaluate retrospectively the demographic features, treatment responses, cytogenetic data and survival analyses of adult T-All cases followed up by the Department of Adult Hematology at Dokuz Eylul University Hospital.

Results: The mean survival time for patients receiving H-CVAD was 46.9 months (±12.9), and median survival time of patients receiving BFM treatment was 71.5 months (±11.4).The median OS of patients receiving BFM was statistically significantly longer than that of Hyper-CVAD (p=0.044).

Conclusion: The use of pediatric intensive chemotherapy regimens in adolescent and young adult (AYA) patients with low incidence and poor prognosis of ALL-type T-ALL, the inclusion of nelarabine in the first line treatment and the selection of new targeted therapies based on new genomic discoveries can increase effectiveness. The use of pediatric intensive chemotherapy regimens is promising for increased survival in adults.

Keywords: T-cell ALL, prognosis, BFM, Hyper-CVAD, AYA, survival

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Pediatric ALL patients had a 5-year event-free survival (EFS) of 80%, which remained 40% in the adult population.[1] Recently, in order to improve prognosis in adult ALL cases, pediatric ALL protocols have been used in adolescents and young adults with positive results.[2-5] The most important prognostic factor is age. The likelihood of overall survival (OS) decreases as age increases. In patients between the ages of 15-65 years old, Hoelzer et al. found

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a shorter event-free survival (EFS) rate and longer time to reach complete remission in patients older than 35 years old, which was reported as a bad prognostic marker.[6] In another study conducted by Gaynor et al., the deaths were reported to be significantly higher over 50 years old during induction therapy and post-treatment relapse to be significantly higher over 60 years of age.[7] The most important remission induction regimens in T-ALL treatment include the Berlin-Frankfurt-Munster (BFM) and hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (Hyper-CVAD) chemotherapy regimens.[8,14] In a study by Alacacioglu et al., 50 adult ALL patients were treated with BFM and Hyper-CVAD protocols. The 5-year survival rate was higher in the BFM group than the Hyper-CVAD group (34% versus 59%).[8]

Methods

The study included patients with T-ALL who were followed up in Dokuz Eylul University Hospital Adult Hematology Department between 20.04.2006 and 31.01.2019. The relationship between cytogenetic/FISH data and other demographic data and the effects of all these factors on standard treatment, follow-up time and survival were evaluated.

Results

The median age of 29 patients followed up with T-cell ALL was 32 (18-82); 19 (65.5%) were men and 10 (34.5%) were women. At the end of the median 18-month (±39-month) follow-up period, 12 (41.4%) of patients were alive, while 17 (58.6%) were dead. Table 1 summarizes, for all patients, the BM(bone marrow) blast percentages at the time of diagnosis, laboratory data including the white blood cell count (WBC), lymphocyte count, hemoglobin (Hb), platelet (PLT), lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase (AST) values and ECOG performance scores. The organ involvements (central nervous system, lymphadenopathy, hepatosplenomegaly, mediastinal mass, skin) of patients were examined at the time of diagnosis. There was SSS involvement in three patients (10.3%), LAP in 23 (79.3%), hepatosplenomegaly in 9 (31%), mediastinal mass in 10 (34.5%), and skin involvement in 4 (13.8%).There were lesions in 17 cases (58.6%) as indicated by the radiological evaluation. Two cases (6.9%) presented SSS lesion and 4 (13.8%) had mediastinal mass.The average life expectancy of high-risk patients was 34 months (±10), which was 40 months (±13.2) for standard risk patients. Although standard risk cases appear to live longer, there was no statistical significance (p=0.66). Patients were grouped by <35 years or >35 years of age and WBC counts (>100.000/µL and below). Seventeen patients were under 35 years old and 9 of them (52.9%) were found to be alive without relapse. Three (25%) patients over thirty-five years of age had no relapse and found alive at the end of the median follow-up period. Although cases under the age of 35 were seen to live longer, there was no statistical significance. It was associated with the low number of patients.

On the other hand, 25 patients (86.2%) had a white blood cell count less than 100,000/µL and 10 of them (40%) were alive without relapse. In four (13.8%) patients, the white blood cell count was above 100,000/µL and 2 (50%) were found to be alive without relapse. While the patients in the WBC<100,000/µL group were observed to live longer than the other, no statistical significance was detected (60 months ± 13.7 x 43 months ± 20.5, p=0.928). It was asso-

Table 1. T-ALL patient demographic data at the time of diagnosis

	N=29	%	Mean	Median	Standard deviation	Minimum	Maximum
F/M	10/19	35/65					
AGE			37.5	32	2.99	18	82
BM BLAST%			73	80	21.7	35	100
WBC(10^3/µL)			51,710	15,000	89733.1	2,700	428,000
Lymphocyte(10^3/µL)			23,296	6,300	40465.5	0	193,000
PLT (10^3/µL)			120,317	116,000	80693.0	0	270,000
Hemoglobin (g/dl)			10.7	10.4	2.6	4.7	15.9
AST(mg/dl)			28.1	21	29.9	10	160
LDH			741	226	1489.9	152	7402
Creatinine(mg/dl)			0.89	0.74	0.4	0.42	2.52
ECOG							
0	3	10.3					
1	17	58.6					
2	6	20.7					
3	3	10.3					

ciated with the low number of patients. The survival data according to age and WBC are given in Table 2.The survival function analysis according to ECOG performance status-survival analysis, leukocyte count-survival analysis ,age-survival analysis and early relaps-survival analysis are given in Figure 1.

Nine (31%) of 29 patients were found to have relapse at the end of the median 18-month (±39 months) follow up. Six patients (20.7%) had early relapse (<12 months) and 3 (10.3%) had late relapse (after 12 months). Relapse times had a significant effect on the OS (early relapse x late relapse: median OS; 10 months [±2.6] x 18 months [±13.8], p=0.016).

Table 2. T-ALL patients' survival status according to risk groups

	Mean (±SD)	Median months	p
Age <35	73 months ±18.4	34 months	0.210
Age >35	41 months ±15.9	12 months	
WBC < 100,000/µL	60 months ±13.7	22 months	0.928
WBC > 100,000/µL	43 months ±20.5	4 months	

When they were evaluated by the first line treatments administered, the majority of adults was composed of the HCVAD (High cyclophosphamide, vincristine, anthracycline, dexamethasone) group with 20 patients (69%). Seven patients (%24.1) received BFM (Berlin-Frankfurt-Munster) and 1 patient received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) protocol. In one patient, the treatment was not performed due to advanced age and comorbidities. With the first line of treatment, TR was achieved in 78.6 patients (22%), while 6 (21.4%) were refractory to the treatment. All patients were treated with intrathecal 12.5 mg mtx for the SSS prophylaxis.

20 (74.1%) of 27 patients received HCVAD and 7 (25.9%)

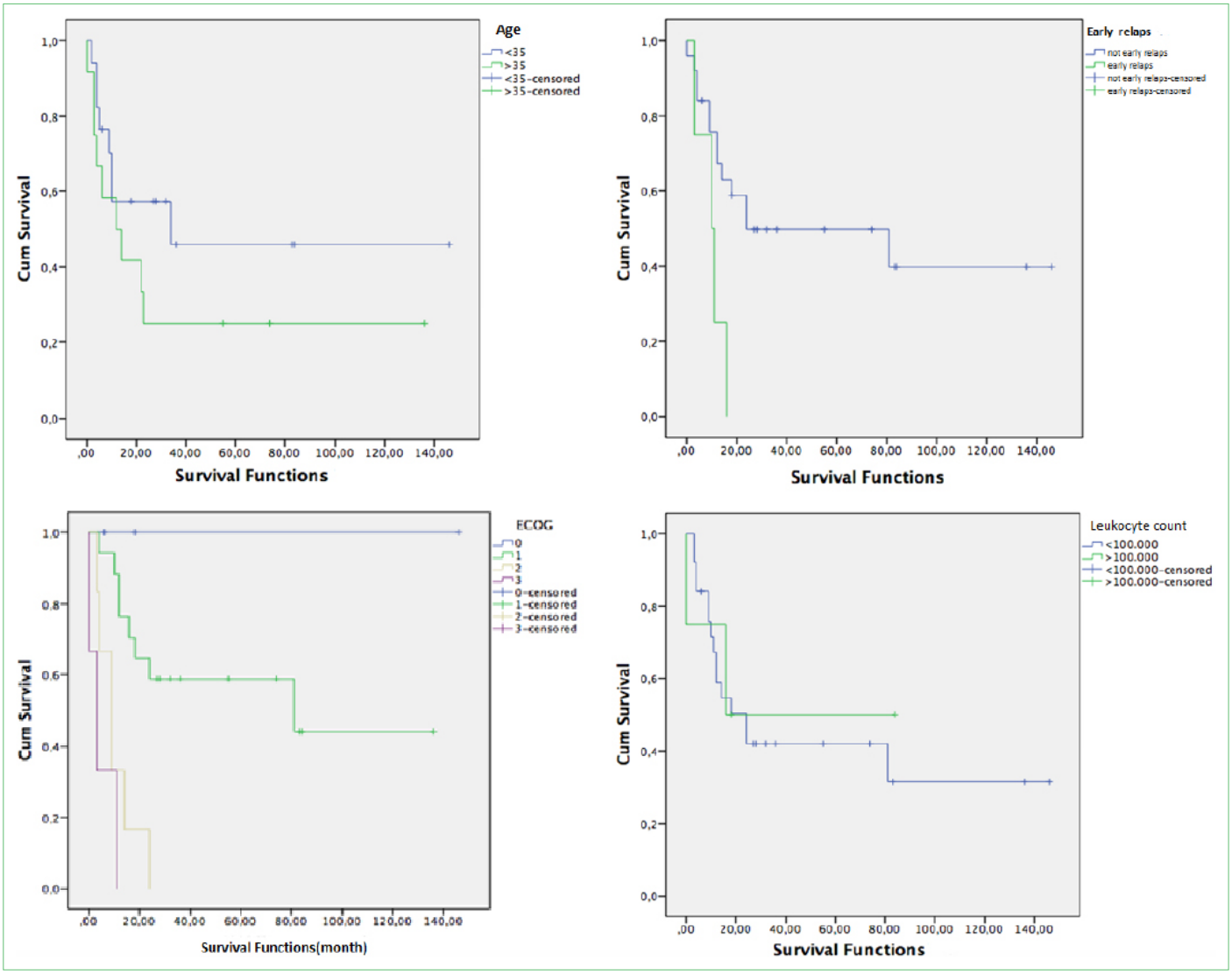

Figure 1. The survival function analysis according to Age, Early relaps,ECOG perfomans and leukocyte count.

had BFM regimens. The mean diagnostic age of the BFM fields was 23.8 (±1.3) and the median diagnostic age was 25 (18-28 years). The mean diagnostic age for H-CVAD-treated patients was 38.7 (±2.92) with a median diagnostic age of 36.5 (20 to 59 years). The mean survival time of patients who received H-CVAD treatment was 46.9 months (±12.9) and the median survival was 14 months (0 to 146 months). The average life expectancy of patients receiving BFM treatment was 71.5 months (±11.4), with a median survival of 28 months (6 to 84 months). The median OS and RFS of patients receiving BFM were significantly longer than the Hyper-CVAD treatment arm (p=0.044, p=0.03). Survival and RSF times according to the first line of treatment are given in Table 3. The survival data according to the first line of treatment survival analys is given in Figure 2.

Eight of the patients (29,6%) were treated with rescue therapy. The median OS of the patients subject to rescue therapy was 12 months (9 to 14months). Nine (31%) patients underwent autologous stem cell transplantation(ASCT). The median OS of the patients subject to ASCT was 14 months (±2.9). Two patients were administered ASCT as the first line of treatment because of high risk, two refractory patients underwent it after rescue therapy, and one high-risk patient underwent it during relapse. The other 4 patients had standard risk and underwent ASCT during relapse. One of these patients (BFM receiving, standard risk) was alive in month 81.

The results were also examined in terms of FISH/cytogenetic analysis. There was no cytogenetic analysis in 5 (17.2%) of twenty-nine patients, insufficient metaphase reported in 8 (27.6%), normal karyotype in 14 (48.3%), and marker chromosome reported in 2 (6.9%). In addition, FISH anomalies were detected in 4 of the 10 patients who underwent FISH.

The mean OS of the patients was 63 months (±12.5), the median OS was 24 months (11.6–35.9) .Five-year survival rate was 41%. It was 83% and 30% for those who received BFM and H-CVAD, respectively.

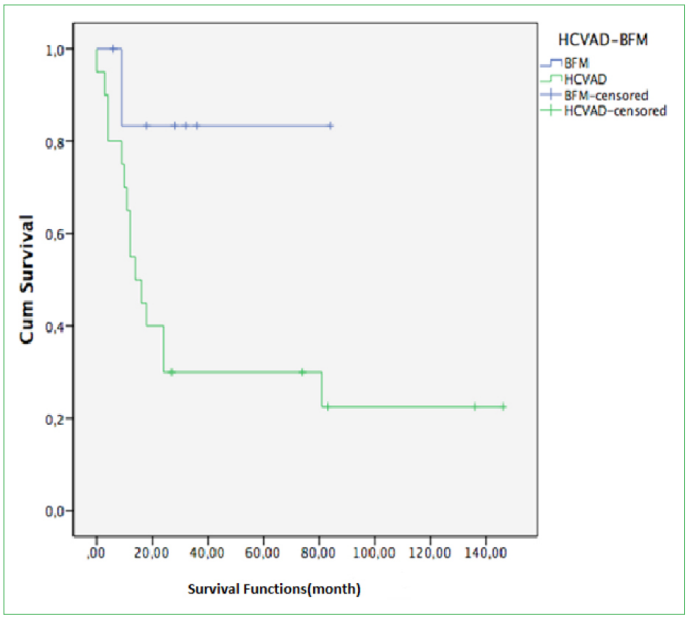

Figure 2. The survival data according to the first line of treatment.

Discussion

T-ALL is rarerand comprises about 20% of all ALL cases. While adult cases are more common than children, the incidence of the disease decreases with older age.[9,10] Dores GM et al. noted that in these studies, survival was associated with age at diagnosis particularly for acute leukemia, and especially for all subtypes, 60 years of age and above were associated with negative survival times.[11] Hoelzer D. et al. also reported that advanced age was closely associated with poor prognosis.[6,15] In a 21-year study, Thomas X. et al. emphasize that age is the most important factor that determines total survival and describe it as a marker of poor prognosis.[12] In a multi-centered study by Le QH et al., who investigated early (first 100 days) and late prognostic factors that affect survival in adult ALL patients in a population of 922 ALL cases, age was found to be the primary factor that determined survival in the early phase (p<0.01).[13] A study by Alacacioglu et al. reported the median age of 50 adult ALL patients who were treated with BFM (n=20) and Hyper-CVAD (n=30) protocols were 25 and 30, respectively. The 5-year survival rate was higher in the BFM group than the Hyper-CVAD group (34% versus 59%).[8] In our study, the median age of 29 patients followed up with T-cell ALL was 32 (18 to 82 years), which is consistent with these published data. Seventeen were under the age of 35, and the

Table 3. Induction treatments for T-ALL patients and effects on OS and RFS

Treatment Protocol	N (%)	Mean age (±SD)	Median age (min-max)	Mean RFS (months)	Mean OS
HYPER-CVAD	20 (69)	38.7 (±2.92)	36.5 (20-59)	43 (±13.3)	46.9 (±12.9)
BFM	7 (24.1)	23.8(±1.3)	25 (18-28)	65 (±11.4)	71.5 (±11.4)
CHOP	1 (3.4)	63		55 (survivor)	55 (survivor)
Without treatment	1 (3.4)	82		3 (ex)	3 (ex)
Total	29 (100)	37.4(±2.9)	32(18-82)	61.5 (±12.9)	61.5 (±12.9)

survival of patients under thirty-five were found to be longer, albeit not significant. The lack of statistical significance is associated with the low number of patients.

The studies published so far have often included the dominance of male sex in acute leukemia. According to this, it has been reported that ALL is more common in men. The study by Alacacioglu et al. was also male dominated by 15:5 and 17:13 men/women ratios in the BFM and Hyper-CVAD group, respectively [8]. The male dominance (65.5%) in our study is also largely consistent with the data published.

Values above 100,000/mm3 for T-ALL are included in the poor risk group, and in our study, it was found that the patients in the group with WBC<100,000/μL lived longer than the other group (60 months±13.7 x 43 months±20.5, p=0.928). The lack of statistical significance was again associated with the low number of patients.

In prognostic data, the ECOG performance scale at the time of diagnosis is also important. In a study conducted by Serefhanoglu et al. including 65 cases, 75% of the cases were reported to present an ECOG performance status equal to or lower than 1; and with 16%, these cases had a longer total survival time than those with an ECOG performance >1 (6%). According to the multi-variable analysis in the same study, the age and ECOG performance status were reported as variables that affect total survival (p=0.018 and p=0.010, respectively).[14] Supporting these data, in their study that included 288 ALL patients, Kantarjian et al. found that ECOG performance status of 87% of patients was 0-2 and only 4.5% of patients were ECOG 3-4, describing poor performance status (ECOG 3-4) as a prognostic factor affecting remission time.[16] In our study, as part of the ECOG classification, which was conducted in line with the data in the literature at the end of the 18-month (±39-month) median follow-up period, low ECOG performance score is significantly associated with longer survival times (p=0.00).

In a study including 1500 patients, Rowe JM et al. remarked that 91% full remission was achieved with an induction regimen of Daunorubicin, Vincristine, L-Asparaginase and Prednisone, and it was emphasized that the induction regimen in ALL should consist of these four agents.[17] In a study conducted with BFM-90 and BFM-95 protocols, Laks et al. reported remission rates at 92.5% and 95.7%, respectively. [18] Alacacioglu I. et al, in another study using the BFM and Hyper-CVAD protocols, reported that the 5-year survival rate was higher in the BFM group than the Hyper-CVAD group (34% vs. 59%).[8] The adolescent and young adult (AYA) population, generally considered to include the patients between 15 and 39 years old, currently attracts great attention especially in treatment selection.

The current trend is to treat patients of the AYA group based on pediatric protocols.[20] Our patients also often received the Hyper-CVAD treatment (69%), and more rarely, BFM (Berlin-Frankfurt-Munster (24,1%) and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (1 patient) protocol. With the first line of treatment, CR was achieved in 22 patients (78.6%), while 6 (21.4%) were refractory to the treatment. Those treated with BFM were mostly of the young age group (AYA) (mean age at diagnosis: 23,8 (±1.3). The median OS of our BFM receiving patients was significantly longer than the Hyper-CVAD arm (28 months x 14 months; p=0.044). Our findings supported the literature. Some studies have used the BFM regimen on patients aged 50 to 60 years old and reported tolerable toxicity and advanced results compared to previous regimens, as achieved in AYA patients with ALL. Based on these studies, it is recommended that AYA patients with T-ALL be treated with a pediatric intensive regimen in diagnosing and potentially treating them.[19,20]

In our study, the average of the total remission times was calculated as 38.7 months (±9.8). Similar to the studies published in the literature, 78.6% CR was obtained with the first line treatment in our patients, while 21.4% were refractory to treatment. 29.6% of relapsed/refractory cases were treated with rescue chemotherapy. The median OS for patients who were administered a rescue treatment was 12 months (9 to 14 months). Fifty percent of 12 relapsed/refractory cases underwent ASCT. The median survival time of ASCT-administered patients appeared to be longer than the other arm but was not statistically significant. This was associated with a low number of patients (12 months x 9 months, p=0.195). In total, 9 (31%) of the patients underwent ASCT. The median OS of all patients who underwent ASCT was 14 months (±2.9). Two patients had ASCT in the first line because of high risk and one patient after rescue treatment due to being refractory. ASCT is the only curative treatment in T-ALL, as is the case with B-ALL.

In relapsed/refractory cases, treatment responses are very low and new agents are being studied. These include nelarabine, a purine nucleoside analogue, which is the only new drug licensed for relapsed/refractory T-ALL. With single agent nelarabine, 55% and 41-46% response rates have been reported for children and adults, respectively.[19] Two of our cases were treated with nelarabine due to multiple relapses. Both cases were treated for 2 months, and patients were lost. It may be appropriate to use nelarabine in the first or second line to evaluate the treatment activity.

In the last decade, we have made great progress in our understanding of T-ALL's pathogenesis and management. New molecular genetic findings, including NOTCH1 and FBXW7 mutations and further identification of T-ALL sub-

types such as ETP and nearly ETP, have increased our ability to be prognostic in these patients. After induction and early consolidation, the minimal residual disease (MRD) assessment has emerged as a strong predictive indicator for relapse, and individualized risk classification and treatment strategies have been provided. However, it is still not practiced routinely in many centers. Due to the unavailability of MRD measurement in our center, only WBC, cytogenetic data, and CR achievement after the first cycle can be used as a prognostic marker. In T-ALL, which is a rare subtype of ALL with poor prognosis, the use of pediatric intensive chemotherapy regimens in AYA patients, including nelarabine in the first line treatment, and selection of new targeted treatments based on new genomic discoveries can increase treatment efficiency and survival times in adults.

Conclusion

The use of pediatric intensive chemotherapy regimens in adolescent and young adult (AYA) patients with low incidence and poor prognosis of ALL-type T-ALL, the inclusion of nelarabine in the first line treatment and the selection of new targeted therapies based on new genomic discoveries can increase effectiveness. The use of pediatric intensive chemotherapy regimens is promising for increased survival in adults.

Disclosures

Ethics Committee Approval: Dokuz Eylül University, 3847-GOA protocol 2018/07-05, Date:15.03.2018.

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Conflict of Interest: None declared.

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