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Is there a risk of early relapse in patients with acute lymphoblastic leukemia presenting with bone-associated symptoms?

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Ethics Committee Approval
This study was approved by Bursa Uludag University Local Ethics Committee on 21.01.2021 with the number 2021-2/4.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Patients usually present with fatigue, pallor, weight loss, and joint and/or bone findings. However, the effects of bone-associated symptoms on prognosis remains controversial. We aimed to demonstrate whether bone-associated symptoms affect prognosis in children with ALL.
Methods: This retrospective cohort study included the data from 268 patients with ALL who were diagnosed and treated between January 2011 and December 2020. The patients were divided into two groups as those with and without bone-associated symptoms. We compared the groups in terms of age, gender, immunophenotyping, day 8 prednisolone response, and risk groups, in addition to minimal residual disease (MRD), relapse, and survival rates.
Results: Eighty-five out of 268 (32%) children had bone-associated symptoms at the time of diagnosis, whereas others (n=183) had none of these symptoms. The relapse rate in children with bone-associated symptoms was found to be higher than the others (17.6% versus 12%), but the difference was not significant (P=0.24). However, children with bone findings developed earlier relapse when compared with the others (18.6 versus 28.6 months; P<0.001).
Conclusion: Therefore, we suggest that bone-associated symptoms at the time of diagnosis could be considered a warning sign for earlier relapse, and these children should be carefully followed.

Keywords: leukemia, childhood, bone involvement

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Introduction

Acute leukemia is the most common malignancy in childhood [1]. Although the most common complaints at presentation are fatigue, pallor, and weight loss, more than one-third of children may present with complaints of refusal to walk, bone pain, and arthralgia. These complaints are due to leukemic cell infiltration of the periosteum, bone, and joints [2]. Such findings may be confused with growing pains or sometimes with rheumatological diseases thus prolonging the time for initiation of the correct diagnostic process [3]. The effects of bone and joint findings on prognosis remain controversial [4,5]. In this study, we investigated the demographic characteristics, prognosis, and survival of patients (children) who presented with bone-associated symptoms and acute lymphoblastic leukemia (ALL).

Materials and methods

Data from 268 children diagnosed with ALL between January 2011 and December 2020 were retrospectively analyzed. The patients' ages at diagnosis, gender, symptoms at presentation, time from symptom onset to diagnosis, radiographic findings, laboratory findings, immunophenotypes, risk groups, and survival analyses were evaluated. The information was obtained from patients' files. The time from symptom onset to diagnosis was determined from the patient's anamnesis. At the time of diagnosis, chest, vertebral, and limb/wrist x-rays were routinely performed in all patients. In cases with localized bone complaints, magnetic resonance images (MRI) were obtained. The patients were divided into two groups, namely those with and without bone complaints. The treatment risk groups of 118 out of 268 patients were evaluated according to the polymerase chain reaction (PCR)-based minimal residual disease (MRD), and in the others (n=150), the ALLIC BFM 2009 risk group stratification was used. Patients were treated according to the ALLIC BFM 2009 protocol. We divided the relapsed patients into groups A and B. Group A consisted of relapsed patients with bone-associated symptoms (bone pain, arthralgia, arthritis, limping, and traumatic fracture), whereas in group B, relapsed patients did not have any of these complaints.

Statistical analysis

The data analysis was performed using the SPSS v. 22.0. The Kolmogorov–Smirnov test was conducted to check the normality of data distribution in groups. The chi-squared and t-tests were used to compare categorical and laboratory data, respectively. The survival analyses were done using the Kaplan–Meier test. The differences between the groups were analyzed with the log-rank test. $P<0.05$ was considered significant.

Results

Of the 268 patients diagnosed with ALL, 102 (38.1%) were female, and 166 (61.9%) were male. Their mean age (standard deviation) was 6.35 (4.5) years (range, 3 months–17.8 years). According to immunophenotyping at diagnosis, 236 children (87.7 %) had an immunophenotype compatible with B-cell, and 33 (12.3%) had a T-lineage compatible with ALL. Of all patients, 31.7% (n=85) had bone-associated symptoms at the time of the first presentation. These complaints were bone pain (arm, leg, waist, and back pain), arthralgia, arthritis, limping, and traumatic fracture (Table 1).

Table 1: Bone-associated symptoms at the time of diagnosis

	n (%)
Complaints at presentation	n=85/268 (31.7%)
Bone pain	36 (42.3)
Arthralgia	20 (23.5)
Limping	15 (17.6)
Arthritis	12(14.1)
Spontaneous fracture	2 (2.4)

It was observed that 24 (9%) of the 268 patients had radiological findings consistent with ALL. Of these cases, 22 were in the group presenting with bone-associated symptoms (25.8%; n=22/85) while two were asymptomatic. Of these 24 patients, a total of 32 ALL-related radiological findings were defined, mostly observed in upper extremities and vertebrae (n=15/32, 68%). The most frequent radiographic findings were focal, osteolytic, and osteosclerotic lesions, and related details are given in (Table 2). All patients with radiographic findings had B-cell ALL.

Table 2: Radiographic findings

Radiographic findings	n=32 (%)
Focal, osteolytic, and osteosclerotic lesions	8 (25)
Vertebral height loss (not compression fracture)	6(18)
Periosteal reaction	6(18)
Osteopenia, density loss, osteoporosis	3 (9)
Increased signal intensity (T2 MR)	3 (9)
Increased lucency	2 (6)
Metaphyseal radiolucent band	2 (6)
Fracture	2 (6)

The patients with and without bone-associated symptoms were compared in terms of age, gender, immunophenotyping, whole blood count, day 8 prednisolone response, risk group, and MRD results. The demographic characteristics of the patients based on study group are given in Table 3.

Table 3: Demographic characteristics of the patients

	Group A n=85	Group B n=183	*P*-value	Total n=268
Gender				
Girl	35(41.2%)	67 (36.6%)	0.28	102(38.1%)
Boy	50(58.8%)	116 (63.4%)		166(61.9%)
Age, mean (SD) (years)	6.09 (3.9)	6.47 (4.8)	0.53	6.35 (4.5)
Immunophenotype				
B-cell	79 (92.9%)	156 (85.2%)	0.05	236 (87.7%)
T-cell	6 (7.1%)	27 (8%)		33 (12.3%)
Laboratory findings				
Leukocyte	29.983	45.937	0.02	40.768
Hemoglobin	8.74	8.3	0.21	8.45
Platelet	112.923	75142	0.002	87.110
Day 8th prednisolone response				
Good	68 (80%)	142 (77.6%)	0.1	210 (78.4%)
Poor	13 (15.3%)	39 (21.3%)		52 (19.4%)
Mature B-cell ALL	4 (4.7%)	2 (1.1%)		6 (2.2%)
Risk group				
SRG	8 (9.4%)	15(8.2%)	0.3	23 (8.6%)
MRG	43 (50.6%)	95(51.9%)		138(51.5%)
HRG	34 (40%)	73(39.9%)		107(39.9%)
Relapse	15 (17.8%)	22(12%)	0.24	37 (13.8%)
Resistant disease		3(1.6%)		3 (1.1%)
Time to diagnosis (days) mean (SD)	31.18 (4)	15.9 (1.6)	<0.001	20.8 /1.8

Group A: patients with bone-associated symptoms, Group B: patients without bone-associated symptoms, SRG: Standard risk group, MRG: Moderate risk group, HRG: High-risk group

Risk stratification was done according to PCR-based MRD in 118 (44%) children. In the remaining 150 (56%) cases, classification was defined according to the ALLIC BFM 2009. When the patients with and without bone-associated symptoms were compared, no significant differences in terms of age and gender ($P=0.28$ and $P=0.53$, respectively) were found. The leukocyte count was significantly lower, and the platelet count was significantly higher in the group presenting with bone-associated symptoms ($P=0.02$ and $P=0.002$, respectively).

Although the relapse rate was higher (17.6%) in children with bone-associated symptoms, the difference was not significant (*P*=0.24). The time from the onset of complaints to diagnosis was significantly longer in the symptomatic group (*P*<0.001).

Relapse was seen in 15 (17.6%) of the 85 patients who presented with bone-associated symptoms and 22 (12%) of the 183 patients without these complaints (*P*=0.24). Of the 37 relapsed patients, 17 had genetic abnormalities (9p21 deletion, t (12;21), t (9;22)). Table 4 shows the demographic data of the relapsed cases in the two groups.

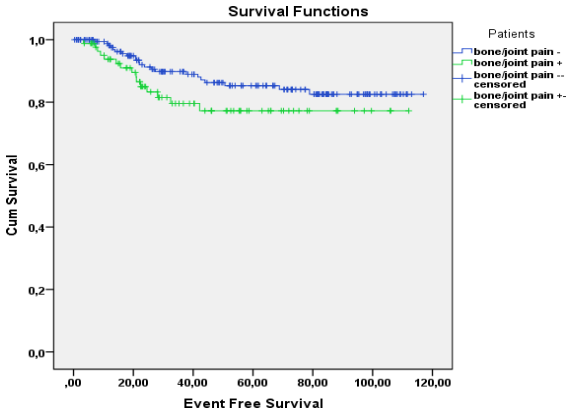
Table 4: Characteristics of relapsed patients

	Group A n=15/85 (17.6%)	**Group B n=22/183 (12%)**
Age, mean (SD) (years)	6.55 (4.1)	7.69 (5.2)
Gender		
Girl	8 (53.3%)	8 (36.4%)
Boy	7 (46.7%)	14 (63.4%)
Relapse region	Bone marrow, n=12 Combined relapse, n=3	Bone marrow, n=13 Combined relapse, n=6 Extramedullary (CNS), n=2 Extramedullary (testis), n=1
Immunophenotype		
B-cell ALL	13 (86.6%)	18 (81.8%)
T-cell ALL	2 (13.4%)	4 (18.2%)
Time to relapse (months) mean (SD)	18.6 (10.5)	28.6 (19.06)

Group A: relapsed patients with bone-associated symptoms Group B: relapsed patients without bone-associated symptoms, ALL: acute lymphoblastic leukemia *P<0.05 CNS: central nervous system

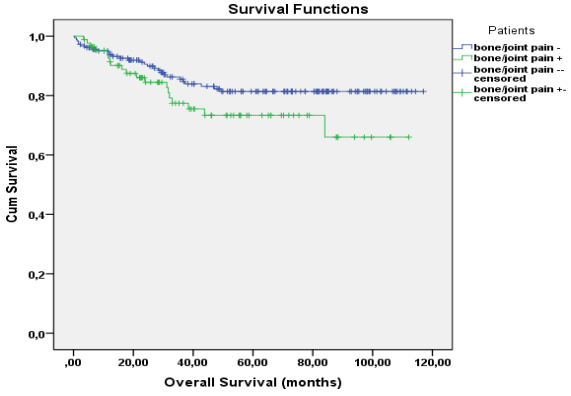
The patients presenting with bone-associated symptoms relapsed significantly earlier than the other group (*P*=0.04). The mortality rate in the whole group was 17.5% (47/268). The causes for mortality were relapse 59.5% (n=28), infection 34% (n=16), and resistant disease 6.5% (n=3). The death rates in group A and B were similar (22%: n=19/85 versus 15%: n=28/183; *P*=0.19). The overall survival rates of the patients with and without bone-associated symptoms were found to be 77.6% and 84.8%, respectively (*P*=0.109) while the event-free survival rate was 82.4% and 88%, respectively (Figures 1 and 2).

Figure 1: Event-free survival of patients with and without joint and/or bone pain complaints



Bone/joint pain -: patients without bone/joint pain, bone/joint pain +: patients with bone/joint pain

Figure 2: Overall survival of patients with and without joint and/or bone pain complaints



Bone/joint pain -: patients without bone/joint pain, bone/joint pain +: patients with bone/joint pain.

Discussion

Acute leukemia patients often present with fatigue, pallor, weight loss, and bleeding. However, other complaints, such as joint and/or bone pain, arthritis, and limping, are not uncommon. In the current study, 31.7% had bone-associated symptoms. Pain in the long bones was the most frequently reported complaint (n=36, 42.3%). Its frequency varies between 14% and 55% as reported in previous studies [6–10]. Although joint and/or bone pain is common in childhood, parents often delay doctor visits since they associate these complaints with benign growing pains or children's activities. The children presenting with joint and/or bone pain are usually treated with anti-inflammatory agents and can be misdiagnosed as rheumatological diseases [3]. Therefore, the diagnosis of leukemia is usually delayed . In the current data, three children received anti-inflammatory treatment before diagnosis, and the average time to diagnosis from the onset of first clinical symptoms was found to be significantly longer compared to the children without bone complaints. Clinicians should consider ALL rather than rheumatological diseases in the presence of hepatomegaly, splenomegaly, and lymphadenopathy in patients who present with osteoarticular findings [1]. In the literature, the duration of the diagnostic process varies between 42 and 80 days [4–8]. In our sample, one of the patients was diagnosed with rheumatoid arthritis and used methotrexate and prednisolone for one year before a correct diagnosis was obtained. Patients who used steroids before the diagnosis of ALL may have a poor prognosis [11].

Imaging technics performed on patients at the stage of diagnosis differs in previous studies. In a study by Zhou et al. [12], scanning was performed with single photon-emission computed tomography (PET/CT). In another study, only the bone radiographs of the patient were examined [6]. We examined the radiographic images of all patients, and if the patient had pathological findings, we performed MRI. In the literature, the frequency of radiographic findings varies between 18% and 55% [5,6,12,13]. We observed that 9% (n=24) of children had ALL-related radiographic findings. The most common radiographic findings in ALL are metaphyseal radiolucent bands, periosteal reaction, osteolytic lesions, and osteopenia [6,13,14]. In our data, the most frequent ALL-related findings were osteolytic, osteosclerotic, and focal lesions (25%). Metaphyseal radiolucent bands were present in only two patients.

Of our patients, 87.7% had B-cell ALL. At the time of presentation, bone complaints were higher among those with B-cell ALL, but this finding might be related to the low incidence of T-cell ALL. Similarly, in previous studies, more bone complaints were observed in patients diagnosed with B-cell ALL [7,15]. We also did not observe any radiographic findings in our patients with T-cell ALL who presented with bone complaints.

In the current study, no differences in age and gender between the two groups were found. The literature suggests that patients presenting with bone-associated symptoms have low leukocyte levels and high hemoglobin and platelet levels at the time of diagnosis. Consistent with the literature, we also found significantly low leukocyte and high platelet counts in symptomatic patients, but no difference was found in terms of the hemoglobin values [16]. Tragiannidis et al. [15] also reported

no difference in the hemoglobin values between patients with and without bone involvement.

In terms of the current data, the distribution of risk groups in two groups was found to be similar. Although the number of patients with relapse was higher in the group with bone- associated symptoms, the difference was not significant. The relapse rate was also not significantly different in terms of children's bone radiographic findings. While some studies in the literature report that the risk of relapse increases as the number of radiographic findings increases, others do not indicate such a risk [5,6,12,13].

The most important prognostic factor in childhood ALL is MRD [17]. We did not find a significant difference in the PCR MRD results of our patients with and without bone- associated symptoms. In the survival analysis, we found that the overall and event-free survival rates of the patients presenting with bone complaints were lower than the other group. However, these differences were not significant. In a study by Kang et al. [4], no significant difference in the overall survival between the patients with and without musculoskeletal complaints was found. In the literature, it was reported that the survival rate of patients with severe radiographic findings is significantly better than those without these findings [4,13].

Although the relapsed rate was found to be similar, in the children with bone complaints, relapse time occurred significantly earlier than in the other group. However, we did not find any related data in the literature that compared this finding. In our study, the distribution of risk groups and day 8 prednisolone response in both groups were similar. Since we were previously not able to do advanced genetic evaluations, such as next-generation sequencing, we cannot comment further on this finding.

Conclusion

In conclusion, we did not find any significant difference in terms of survival and relapse rates in children with bone-associated symptoms when compared with the children without bone-associated symptoms. However, relapse time in this group occurred significantly earlier than in the other group. Although we were not able to perform advanced genetic testing, the distribution of risk groups was found to be similar within the two groups. Therefore, we suggest that bone-associated symptoms at the time of diagnosis could be considered a warning sign for earlier relapse and these children should be carefully followed. Many factors, including treatment, early treatment response, and genetics, contribute to relapse, In the absence of these details, it is not possible to attribute bone and joint symptoms as an independent risk factor for early relapse. In addition, cases presenting with joint/bone pain should be carefully examined, and the diagnosis of leukemia should be included in the differential diagnosis.

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