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ORIGINAL ARTICLE

Retrospective Analysis of Hairy Cell Leukemia Patients Treated with Different Modalities as First Line: Real-Life Experience Over 20 years

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Abstract We aimed to analyze the characteristics and response rates of different treatment modalities in hairy cell leukemia patients over 20 diagnosed as hairy cell leukemia (HCL). Clinical data, response rates and survival outcome of the patients who were diagnosed with HCL were retrospectively analyzed. Fifty-two patients with a median age of 50 (28–87) years were enrolled in the study. 38 patients (73%) were male and male to female ratio was 2.7. First line therapy was cladrabine in 36 patients (69.2%). The overall response rate was 97%. CR and PR rates were 86.1% and 11.1%, respectively. Interferon was used in 10(19.2%) patients who were diagnosed before 2000s years. CR and PR rates were 70% and 30%, respectively. Although the CR rates were lower in IFN group, this difference could not be reached statistically significance ($p = 0.24$). The median follow up was 48 months (12–252). The median OS was not reached and median PFS was 150 months (95% CI, 116–214). The OS at 36 and 48 months were 95.9% and 92.3%, respectively and the PFS at 36 and 48 months were 90.2% and 83.4%, respectively. After the introduction of purine analogues, the fate of the HCL patients have been changed. Cladrabin achieved very high response rates in both young and older patients, in our study. Although relapse still constitutes a problem, another single dose of cladrabine results in good response rates.

Keywords Hairy cell leukemia · Cladrabin · Treatment · Survival rates · Response rates

Introduction

Hairy cell leukemia (HCL), chronic B cell lymphoproliferative neoplasm, is a rare disease comprising 2% of all leukemias [1, 2]. It is more frequent in men than in women and the median age is 55 years old [3]. It is characterized by atypical lymphocytes with 'hairy' projections, bone marrow fibrosis, pancytopenia, and splenomegaly [4, 5].

The diagnosis is made by atypical lymphoid cell infiltration in bone marrow with typical flow cytometric results (CD19, CD20, CD25, CD103, CD123, and CD200) and positive Annexin and tartrate resistant acid phosphatase (TRAP) [6–8].

Since the course of the disease is indolent, asymptomatic patients require no further treatment. In the absence of effective medical therapy, splenectomy was the treatment of choice with 5-year survival rate of 68% [9]. Interferon (IFN) was the first medical option with higher survival rates [10]. After introduction of purine analogues, namely, cladribine and pentostatin, very high response rates were documented [11, 12]. Cladribine achieved more than a 95% overall response rate and a 96% survival rate at 48 months after a single dose [11].

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In this retrospective study, we aimed to analyze the clinical features, treatment modalities, and response and survival rates in HCL patients in Turkey over 20 years.

Material and Method

Patients and Data Collection

Fifty-two patients diagnosed with HCL between 1998 and 2018 were enrolled. The diagnosis was established according to WHO criteria [13] based on histopathology and flow cytometric analysis. The demographic data, clinical features, laboratory parameters, flow cytometric analysis; treatment results were recorded from the archives. Subgroup analysis was also performed according to the age of the patients at the time of diagnosis (patients $\geq$ 50 years old [groupA] and patients $<$ 50 [group B] years old). The patients diagnosed with hairy cell variant were not included in the study.

Treatment Protocol

The criteria for treatment were: (1) symptomatic splenomegaly, (2) hemoglobin(hb) $<$ 10 gr/dl, (3) neutrophil count $< 1.0 \times 10^9$/L, (4) platelets $< 100 \times 10^9$/L, (5) recurring infections [14]. Splenectomy, IFN, cladribine or rituximab were the treatment options. IFN was preferred as a first line therapy when cladribine was not available in Turkey. It was started at a dose of 3 MU three times a week and dose modifications were performed according to toxicity and response rates. Cladribine was given at a dose of 0.1 mg/kg/day as intravenous infusion (day1–7). Rituximab was administered at a dose of 375 mg/m^2 weekly for four consecutive weeks.

Response Evaluation

The response was evaluated made by complete blood count (CBC), peripheral blood smear, biochemical parameters and bone marrow biopsy at 3 months after the therapy. Complete response (CR) was defined as (1) the disappearance of hairy cells in the peripheral blood smear and bone marrow (2) absolute neutrophil count $> 1500 \times 10^6$/L, platelet $> 100 \times 10^9$/L and hb $>$ 12 gr/dl and (3) normalization of hepatosplenomegaly. Partial response (PR) was defined as (1) $>$ 50% decrease in hepatosplenomegaly and infiltration in bone marrow. Relapse was defined as (1) reappearance of hairy cells in peripheral blood or bone marrow and recurrence of cytopenias or organomegalies or (2) $>$ 50% increase in residual disease after PR. Presence of PR or CR was accepted as overall response(OR). Any response rather than PR or CR was regarded as no response [15].

Survival

Overall survival (OS) was defined as the time from the first treatment until the time of death, or last follow up and progression free survival (PFS) was calculated from the onset of first line treatment until progression.

Statistical Analysis

Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) 16.0. The results were provided as median (min–max) for abnormally distributed parameters. P values less than 0.05 were accepted as statistically significant.

OS and PFS were estimated by Kaplan–Meier methods. Log-rank test was used to evaluate the variables affecting OS and PFS (univariate analysis). Cox proportional hazards regression was used for multivariate analysis to analyze the independent variables affecting PFS and OS.

Results

Patients' Characteristics and Laboratory Tests at Diagnosis

Fifty-two patients with a median age of 50 (28–87) years old were included in this study. Seven (13.4%) patients were younger than 40 years of age. Thirty eight patients(73%) were male and male to female ratio was 2:7. The most common presenting symptom was fatigue observed in 33 (63.4%) patients. Nine patients (17%) were asymptomatic at the time of diagnosis. The median duration of symptoms was 7 months [2–16]. Splenomegaly was reported in 46(88.4%) patients and the median size of the spleen was 180 mm (135–230). Massive splenomegaly (spleen size $\geq$ 180 mm) was recorded in 25(54%) patients. The baseline characteristics of the patients were summarized in Table 1.

Regarding laboratory tests (Table 1); the median white blood cell count (WBC), Hb and platelet count were 2680×10^9/l (range, 910–9510), 8.7 gr/dl (range, 5.8–15.4) and 78×10^9/l (range, 16,400–298,000), respectively. Bone marrow biopsy results revealed TRAP positivity in 95% of the patients. The immunophenotypic profile was available in 83% of our cohort. CD 11c, CD 103, CD123, CD 25 and anexin A1 was positive in 82.6%, 81%, 71.4%, 90%, 95% of the patients. Dry tap was recorded in 61.5% of the patients.

Table 1 The baseline characteristics of the patients and laboratory tests' results of the patients

Number of patients	52
Female	14 (27%)
Male	38 (73%)
Age (median, range) (years old)	50 (28–87)
Leukocyte (median, range) ($\times 10^9$/l)	2680 (910–9510)
Hb (median, range) (gr/dl)	8.7 (5.8–15.4)
Platelet (median, range) ($\times 10^9$/l)	78 (16,400–298,000)
Number of cytopenia (median, range)	2 (1–3)
Patients with no cytopenia	1 (2%)
Patients with 1 cytopenia	3 (5.7%)
Patients with 2 cytopenia	22 (42.3%)
Patients with 3 cytopenia	26 (50%)
Lactate dehydrogenase(IU/L)	300 (200–540)
Hairy cells in the peripheral blood smear*	
Present	31 (64.5%)
% (Median, range)	52% (4–90)
Absent	17 (35.5%)
Reticular fibrosis**	
Grade 1	9 (20.4%)
Grade 2	26 (59.2%)
Grade 3	9 (20.4%)

*Results were available in 48 patients

**Results were available in 44 patients

Treatment Outcomes

First line therapy was initiated in 49(94.2%)patients. Three patients were not treated due to asymptomatic disease and progression was not reported during a median 32 months of follow up. IFN (10 patients), cladribine (36 patients), splenectomy (1 patient) and rituximab (2 patients) were used as first line therapy.

The CR and PR rates were 82.6% and 13.4% in all treated patients. The only parameters effecting CR rates were the age at the diagnosis and the duration of the symptoms. The age at the diagnosis and the duration of the symptoms was statistically lower in patients who achieved CR.

Cladribine Therapy

First line therapy was cladribine in 36 patients (69.2%). The overall response rate was 97%. CR and PR rates were 86.1% and 11.1%, respectively. During the follow up period of median 36 (12–204) months, six (16.6%) patients relapsed after a median of 24 months (12–44). Four patients received another cycle of cladribine and CR was achieved in all patients. We did not treat one patient with relapse due to lack of indication for treatment and in one patient rituximab was administered.

Interferon Therapy

Interferon was administered in 10(19.2%) patients who had been diagnosed before 2000s. CR and PR rates were 70% and 30%, respectively. Although CR rates were lower in IFN group, this difference did not reach statistical significance ($p = 0.24$). Six (60%) patients relapsed after a median 20 months (10–48). Time to relapse was similar in both cladribine and IFN groups ($p > 0.05$). Four of the relapsed patients were treated with single cycle of cladribine and CR was achieved in all patients. Two patients were followed up with stable disease. The relapse rate was higher in IFN group when compared to cladribine group.

Other Therapy Modalities

Splenectomy was performed in only one (1.9%) patient and two (3.8%) patients were treated with rituximab. CR was achieved in all patients and no relapse was documented.

Survival Analysis

The median follow up was 48 months (12–252). The median OS was not reached and median PFS was 150 months (95% CI, 116–214). The OS at 36 and 48 months were 95.9% and 92.3%, respectively and the PFS at 36 and 48 months were 90.2% and 83.4%, respectively (Figs. 1 and 2). When we analyzed the patients according to age (group A and group B), OS was not reached in both groups and OS at 48 months was 100% and 84.1% in group B and group A respectively ($p > 0.05$). Regarding to PFS, in group A, the median PFS was 132 months (95% CI, 55–209) and PFS at 48 months was 70%. In group B, the median PFS was 174 months (95% CI, 110–238) and PFS at 48 months was 95%($p = 0.06$).

When we compared the survival rates according to the first line treatment, the OS at 48 months, was higher in patients treated with cladribine without statistical significance(100% in cladribine group vs 88.4%, in IFN group, $p = 0.29$). No statistical significance was documented in terms of PFS or OS related to symptom duration, laboratory parameters, or splenomegaly. But PFS was 62.8% and 98.7% in patients with splenomegaly greater than 180 mm and lesser than 180 mm, respectively. This difference was statistically different with a p value of 0.03. OS was also lower in patients with a spleen size greater than 180 mm (84.3% vs 100%) without significance ($p = 0.08$). We also documented a lower OS in patients with grade 3 reticular fibrosis (100% in grade 1 and grade 2 fibrosis vs 76.2% in grade 3 fibrosis) without a statistical significance($p = 0.059$).

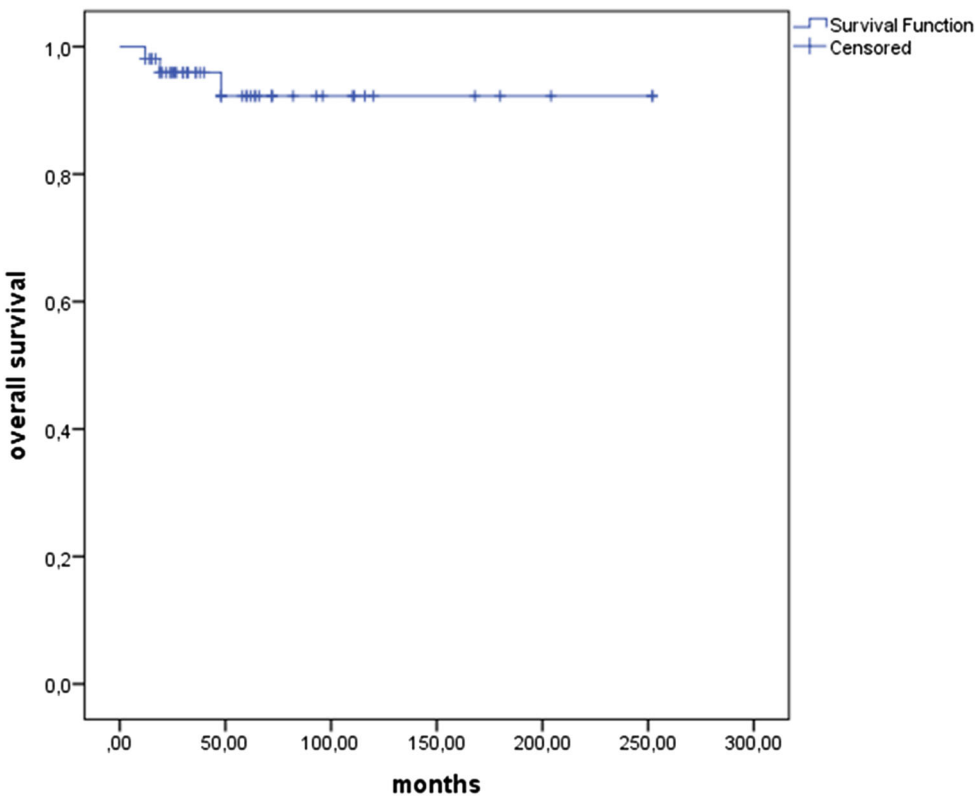

Fig. 1 The Kaplan–Meier curves of overall survival (OS) in all patients

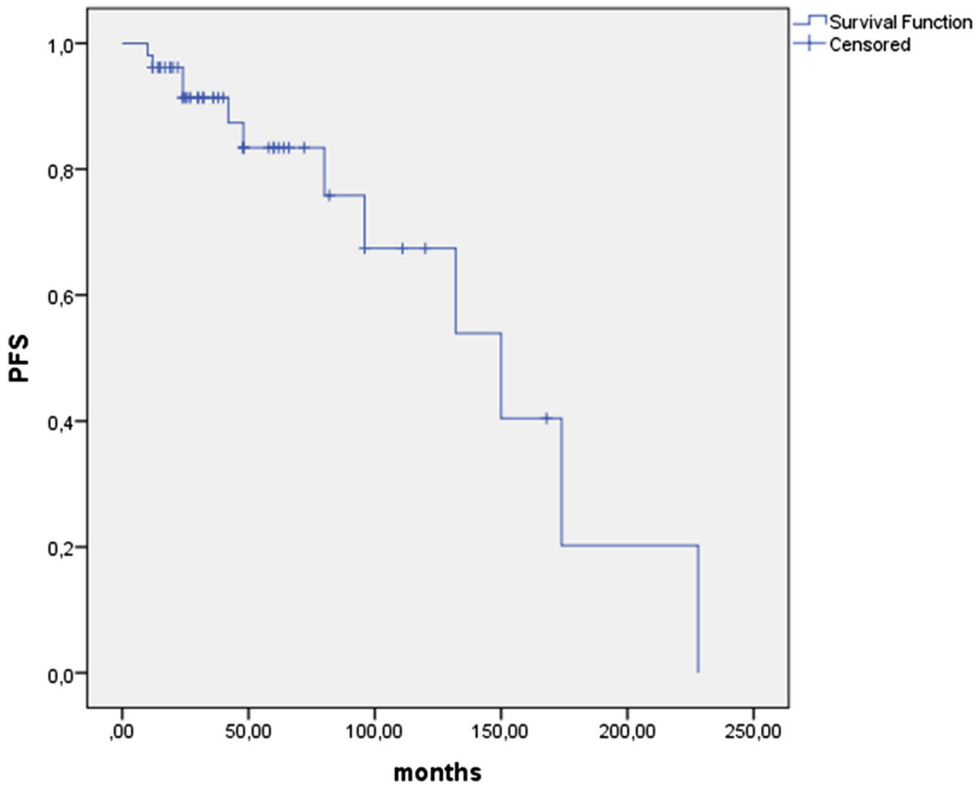

Fig. 2 Kaplan–Meier curves of PFS in all patients. PFS: progression free survival

During the follow up period, three patients died. Secondary malignancy, glioblastoma, was reported in one patient who died due to progressive glioblastoma. Three patients died due to infection: pneumonia in two patients, and sepsis in one patient.

Discussion

In this study, we retrospectively evaluated the demographic features and treatment outcomes of 52 HCL patients, a relatively a large cohort when considered the rarity of the disease.

We reported a male predominance (male/female ratio: 2:7) with a median 50 years of age similar with the literature [16, 17]. The youngest patient was 28 years of age and 13.4% of the patients were younger than 40 years. Getta et al. [17] reported as young as 19 years old patient in their cohort and 19% of the patients younger than 40 years of age.

The most common presenting symptom was fatigue (63.3%) preceding by early satiety and weight loss as concordant with the literature [16, 18, 19] and the most common physical finding was splenomegaly and was observed in 88.4% of the patients. In the literature splenomegaly was observed in 60–90% of the patients [18, 20, 21]. Although splenomegaly was more prominent in younger patients in the literature [23, 24], we could not document a statistical difference in spleen size according to age.

We reported pancytopenia and bicytopenia in 50% and 42.3% of the patients, respectively. The most common abnormal laboratory test was anemia documented in 75% of all patients. The median WBC, hb and platelet levels were compatible with the literature [18, 20–22].

In our study, immunophenotypic profile for CD 11c, CD 103, CD123, CD 25 and anexin A1 and TRAP were positive in high percentage of the patients. High positive rates for the given markers were also reported in the literature and they were accepted as important clues for the diagnosis of HCL [16, 18, 21].

In the last two decades, the treatment options were changed from splenectomy and IFN to nucleoside analogues. In our cohort, IFN and cladribine was used as a first line therapy in 19.2% and 69.2% of the patients, respectively with a 86.1% CR and 11.1% PR rates. High response rates were reported in other studies in the literature [8, 11, 14, 16, 17, 24–26]. Beside high response rates, relapse still constituted a problem and wide range (16–37%) of relapse rate was reported in the literature [16, 27, 28]. This wide range was related to heterogeneity of the studies in terms of follow up periods and response rates. In our analysis, 16.6% of the patients relapsed that was within the range documented in the literature.

In the IFN group, although high CR and PR rates were achieved, (70% CR and 30% PR), remissions were not durable and we found a statistically higher relapse rate (16.6.% in cladribine group vs 60% in IFN group) ($p < 0.05$). Higher relapse rates were also reported in IFN treated group, in the literature [10, 24].

The only parameters which were related with higher CR rates were young age and short-term symptoms in our study. In the literature several factors including advanced age, CBC parameters, lymphadenopathy, presence of prior treatment, the absence of splenomegaly were studied, but the data was conflicting [16, 29–31] and should be confirmed by other studies.

Regarding the survival analysis, high OS and PFS were determined. During a median 48 months of follow up, median OS was not reached as expected for a chronic leukemia during a relatively short duration of follow up in our cohort. In the literature, high survival rates were also reported. 3, 5 and 12 year survival rates were as high as 100%(31), 95–98%(5, 16) and 79–87%(27, 28) respectively. High survival rates resulted in similar survival in HCL patients with general population approximately five years after diagnosis [20].

Since OS could not be reached in many studies similar to our results, the main aim of the treatment in HCL patients was achievement of long term DFS. DFS rates were as high as 80% at 5 year and [29, 32] and PFS at 3 years was reported to be 84%(31). We also reported high PFS rates in our cohort (PFS rates at 36 and 48 months were 90.2% and 83.4%, respectively).

Although HCL is a disease of older patients, younger patients were also diagnosed as HCL. We reported a better survival rates in younger patients but this difference did not reach statistical significance. Inbar et al. [23] analyzed the outcome of 203 HCL patients and 10- and 20-year survival rates were reported as 100% and 100% for patients $\leq$ 40 years of age and 88% and 83% for patients above the age of 40 years.

In our cohort, survival rates were higher in patients treated with cladribine without a statistical significance compatible with the results reported by Ongoren et al. [24].

Our study also had some limitations. First, it was a retrospective study: so, we could not reach all the data including adverse events and secondary malignancies properly, and losing the follow-up was another problem. In a chronic leukemia, the median follow up period of 48 months was a relatively short period for determining to OS rates benefit. Beside these limitations, this was a very rare disease and a relatively large cohort of 52 patients who were treated with different type of therapies over 20 years was analyzed.

In conclusion, after the introduction of purine analogues, the fates of the HCL patients have been changed. In our study, cladribine achieved very high response rates in both young and older patients. Although relapse still constituted a problem, another single dose of cladribine resulted in good response rates. The addition of monoclonal antibodies to the therapy will increase the response and survival rates. This should be considered especially in refractory patients.

Compliance with Ethical Standards

Conflict of interest Authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all participants included in the study.

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