Introduction

Hairy cell Leukaemia (HCL) is a chronic B-cell lymphoproliferative disorder with an indolent but progressive course (Saven et al., 1998). It was first described as a distinct entity in 1958 by Bouroncle. The prevalence of this disease is about 0.6-2.9 per million and is 4 to 5 times more frequent in men than in women with the average age of 50-55 (Flandrin et al., 1984). The etiology is unknown but exposure to radiation, chemical agents and also viral infections such as EBV have been suggested as probable reasons (Robak, 2006). Presence of irregular cytoplasmic projections in cells (hairy cells) is the reason of nomination.

Although many diagnostic methods have been suggested, differential diagnosis should be considered between HCL, prolymphocytic Leukaemia, chronic lymphocytic Leukaemia and etc.

Patients with HCL typically present with nonspecific complaints of fatigue or
weakness. Splenomegaly without a change in lymph nodes sizes and pallor have been reported as common signs (Matutes et al., 1993). Weakness and fatigue are also of the reported complaints of HCL patients. In addition, abdominal fullness due to splenomegaly, hemorrhage and early ecchymosis as a result of thrombocytopenia or opportunistic infections related to neutropenia have been observed (Golomb and Vardiman, 1978). Infiltration of bone marrow with hairy cells, splenomegaly and inhibition of hemopoieses by means of cytokines released from hairy cells, like TNFα, are suggested causes of cytopenia (Swords and Giles, 2007).

About 90% of HCL patients should be treated after diagnosis (Robak, 2006). Purine analog complexes such as 2-chlorodeoxyadenosine can cause long term cure in HCL patients. Splenectomy and interferon-a were formerly used as treatment of HCL (Robak et al., 1999). Recently, CLADREBIN has been known as the best choice in treatment of these patients and it is being used in our hematology and oncology center, too.

Although some statistics about clinical presentations and laboratory findings of this disease have been reported, no accurate statistics on epidemiological characteristics of HCL are available in Iran as no population-based studies of HCL have been conducted. The use of epidemiological findings provides health officials with baseline data for monitoring trends, early detection and management of disease. Since prevalence of clinical presentations such as splenomegaly, lymphadenopathy, hepatomegaly, vasculitis and osteitis are different in distinct places, identifying the risk factors will be more accurate if age and sex distribution, signs and symptoms of disease are thoroughly understand.

This study is going to describe clinical findings, age and sex related incidence of HCL and long term survival in patients of Ghazi Tabatabaee Hematology-Oncology Hospital. Furthermore, the rate of response to standard treatment of disorder, CLADREBIN, has been assessed.

**Patients and Methods**

Data were acquired from Ghazi Tabatabaee Hematology-Oncology Hospital, Tabriz University of medical sciences, Tabriz, Iran, as a referral oncology center for North West of Iran. In this retrospective cross-sectional study we have studied archive of the center to check medical recordings of all patients, admitted to this center with hairy cell Leukaemia and diagnosed from 1 October 2002 to 1 October 2012. Inclusion criteria were confirmed diagnosis of hairy cell Leukaemia based on bone marrow morphology, TRAP staining and flow cytometry.

Demographic information including age and sex, patient's chief complain, clinical presentations, laboratory findings and response to CLADREBIN treatment were collected from medical recordings. Complete response to CLADREBIN has been defined as Hemoglobin=12, platelet more than 100000, neutrophil more than 1500 per micro liter and absence of hairy cell in peripheral blood smear. Good partial response has been defined as hemoglobin=12, platelet more than 100000, neutrophil more than 1500 per micro liter and hairy cells number less than 5% of bone marrow cells. Partial response has also been defined as hemoglobin=12, platelet more than 100000, neutrophil more than 1500 per micro liter and reduction in number of hairy cells to less than 50% of initial value in bone marrow. Overall response rate has been defined as CR+GPR+PR and was considered as increase in hemoglobin more
than 2 mg per deciliter, more than 25% increase of neutrophil numbers and increase of platelet numbers to less than 50000 per micro liter.

In this study also the follow up time was defined as the date of diagnosis up to 1st October 2013, the time of the associated death to disease (as the exact failure time) or survival (as the censoring time). Deaths were confirmed through the telephonic contact to relatives of patients.

Data management and analysis was performed using SPSS 17 with descriptive statistics (percentage, median, and mean± standard deviation). Survival time was calculated in months and was represented as mean ±Standard Deviation survival time using Kaplan-Meier test. Also 1, 3 and 5 year survival was calculated and represented as percentage. Ethical considerations were fully respected and the study has been approved by the ethic committee of Tabriz University of Medical Sciences.

**Results and Discussion**

After studying all the attainable documents, 66 cases were detected. Of the 66 patients 53(80.3%) were men and 13(19.7%) were women. The average age of the patients was 54.75±6.01 (ranging 45-65).

Of all the patients, chief complaint of 32(48.5%) cases was fatigue. Other complaints included pain in left flank (n=10, 15.2%), feeling of tumor in left flank (n=9, 13.6%), repeated infections (n=9, 13.6%) and other complaints (n=6, 9.1%).

In clinical findings 60(90.9%) patients had splenomegaly, 4(6.5%) patients had lymphadenopathy and 2(2.6%) patients didn’t show any clinical symptoms. In Laboratory findings: 6(9.1%) patients had leukopenia, 7(10.6%) had anemia, 35(53%) had leukopenia accompanied with anemia, 5(19.7%) had thrombocytopenia and 13(19.7%) had pancytopenia.

In terms of responsiveness to CLADREBIN, 43 patients (65.2%) achieved complete response, 16 patients (24.2%) achieved relative response to the treatment and 7 patients (10.6%) didn’t show any response to the treatment.

Owing to some changes in patients’ phone number or address, unfortunately only 33 patients were accessible. Followings distinguished that 5 patients were dead because of other causes including sudden cardiac death, traffic accident and pulmonary embolism. 20 (71.43%) patients were still alive but 8 (28.57%) were dead. Mean survival time of patients was 69.66±7.51 months but Median survival was incomputable. 1 year survival was 89%, 3 year survival was 78% and 5 year survival was calculated 65%. Hairy cell Leukaemia specific survival curve based on adjusted analysis showed that, adjusted survival of HCL patients fell down at about 0.6 in 40 months and continued up to the end of study time with a straight line (Figure 1).

**Fig.1** Hairy cell Leukaemia specific survival curve based on adjusted analysis
The most common age of diagnosis for HCL in our study was 5th decade which is confirmed by other investigators (Pettitt, 2003; Genini et al., 2000; Goodman et al., 2003). In the study of Foratyazdi which was conducted on HCL patients in Tehran and Yazd, Iran, patients ages were reported between 55- 67(11). Also in the study of Jalaeekhoo et al that was conducted in Tehran, Iran, the mean age of HCL patients were 50 which replicate our findings (Jalaee et al., 2009). In another report, most patients were white males over the age of 50 (Wintrobe, 2003). However, the disease has been diagnosed in at least one teenager (Yetgin et al., 2001). Cannon et al reported that hairy cell Leukaemia occurs mostly in middle-aged men, with a median age of 52 years (Cannon et al., 2008). In a French study, 30 cases of HCL were diagnosed over a 25-year period; the median age was 67.8 years (Malfuson et al., 2003). This is more than our findings. And Teodorescu et al reported the mean age of patients in Denmark 63.5 for female and 62.7 for male (Teodorescu et al., 2003). In the study that was conducted in India the median age of patients was 47 years, which is relatively lower than our findings (Chatterjee et al., 2008). And similarly in the study of Stewart et al in USA median age of the patients was 46 with 6 patients under the age of 40 (Stewart and Bodey, 1981). Considering that the average age of HCL patients varies in different geographical regions, it can be inferred that there is a relationship between disease incidence and location that could be explored in future researches.

Many studies suggest that the incidence of disease is more common in men than in women, which is in accordance with our findings which demonstrate that of 66 patients 53 (80.3%) were men and 13 (19.7%) were women. Also in Foratyazdi study it has been reported that 80% of the patients were men and only 20% were women (Forat yazdi, 2007). Jalaeekhoo et al mentioned that the ratio of incidence among men and women is 3 to 1 which is relatively in accordance with our study that suggests the approximate proportion of 4 to 1 (Jalaee et al., 2009). Other findings variously suggest incidence of hairy cell Leukaemia mostly in males, with a male-to-female ratio of 4:1 to 5:1 (Malfuson et al., 2003). However, in the study of Teodorescu et al in Denmark the female to male ratio for patients was 1 to 2.7 which is less than previous reports (Teodorescu et al., 2010). Given that most studies have shown that HCL is more common in males than in females, it is estimated that there is a relationship between gender and disease incidence.

In the study of Jalaeekhoo and Foratyazdi et al it was mentioned that the main chief complaint in HCL patients is fatigue (Foratyazdi, 2007; Jalaee et al., 2009). Similarly Chattarjee et al in India reported that 60% of their patients suffered from fatigue and pallor (Chatterjee, 2008). Our data are in agreement with these findings in a way that among 66 patients of this study fatigue was the most common chief complaint with 32 (48.5%) cases.

Many studies suggest that the most common sign during physical examinations is splenomegaly which corroborate our findings that show Splenomegaly has been seen in 60cases (90.9%). In a study from Hong Kong in 18 HCL cases; fever, splenomegaly and monocytopenia were the predominant manifestations (Au et al., 2000). In the study conducted by Chatterjee et al in India among 15 cases, common manifestations of the disease were splenomegaly, fever and cytopenia too (Chatterjee et al., 2008).

In our study the major laboratory finding was leukopenia accompanied with anemia
(53%) which can indicate the reason of fatigue in patients as a main chief complaint. Pancytopenia also was seen in our patients as another laboratory finding that can explain why these patients are at higher risk of infections. Many investigators have noted the importance of infection as a cause of morbidity and mortality in patients with hairy cell Leukaemia (Bouroncle et al., 1958; Burke et al., 1974; Lang et al., 1976; Manes and Blair, 1976). In the study of Stewart et al of 22 patients, 18 had potentially life-threatening infections that 9 of them finally died as a result of proven or presumed infections (Stewart nad Bodey, 1981). Unfortunately since in this study we couldn’t follow all the patients, we couldn’t assess the rate of morbidities caused by infections in HCL patients either.

Treatment of HCL is indicated in patients with significant neutropenia, anemia, thrombocytopenia, symptomatic splenomegaly, constitutional symptoms or recurrent serious infections (Goodman et al., 2003). Several studies investigate the efficacy of CLADREBIN in remission of HCL in a way that invasive treatments like splenomegaly are gradually going to be replaced by this method (Forat yazdi, 2007; Jalaee et al., 2009; Von Rohr et al., 2002). In this study 43 patients (65.2%) achieved complete response to the CLADREBIN and 16 patients (24.2%) achieved partial response and 7 patients (10.6%) didn’t show any response. However, a single dose of CLADREBIN induces a long-term complete response. In an extended follow-up of patients treated with 2-CdA conducted by Goodman et al among 207 HCL patients that had at least 7 years of follow-up the complete response rate was 95% and the partial response rate was 5%. The relapse rate was 37%, and the overall survival was 97% at 108 months (Goodman et al., 2003). Mean long term survival of our patients was 69.66±7.51 months and 5 year survival was calculated 65% which was lower than findings of Goodman (Von Rohr et al., 2002). Because of large number of censored patients in our study median was not calculable.

Cumulative survival graph shows that mortality did not increase after 40 months survival. We can understand that long term survival of disease is very good. In an Italian study over 90% of patients were alive for 13 years later and over 50% of patients appear to be clinically cured by this treatment. Survival rate in this study also was higher than ours (Zinzani et al., 2004). The overall survival was 79% in German patients 12 years after the start of CLADREBIN therapy (Jehn et al., 2004). A long-term follow-up study from USA showed an excellent progression free survival and up to 14 years overall survival after 2-CdA treatment with median 9.7 years (Chadha et al., 2005). In another study conducted by Chatterjee, most patients responded to CLADREBIN therapy (Chatterjee et al., 2008). However, previous studies from Mumbai have shown responses to alpha-interferon therapy (Au et al., 2000; Malhotra et al., 1992). Pai et al found an overall response of 88.9% and disease free survival of 83% on interferon therapy (Pai et al., 1999). As is obvious, long term survival in our study is lower than in developed countries. Several reasons can be mentioned for this issue such as, incomplete post-treatment cares, high costs of the cares that mostly are not supported by insurances and imposes large costs to the patients and limited facilities of medical centers. Furthermore, limited access to drugs, mostly as a result of sanctions, can be an important reason.

References

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