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Original article

HOW WE HAVE TREATED HAIRY CELL LEUKEMIA - A SINGLE CENTRE EXPERIENCE

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Abstract

Hairy cell leukemia (HCL) is a rare chronic B-cell malignancy, a slow-growing leukemia that involves the bone marrow, spleen and peripheral blood with hairy cells. The complete blood count may reveal pancytopenia including neutropenia. Splenomegaly is a predominant feature while lymphadenopathy and hepatomegaly are rarely seen. Signs and symptoms of HCL include frequent infections, weakness or feeling tired. The treatment and prognosis of HCL depend on many risk factors such as gender, age, and it is very important to achieve CR which is a critical factor in the success and should be the treatment goal at each stage. Starting from 1984 until 2022 we have observed a total number of 76 patients (61 male, 15 female) with age ranging from 29-83 years, all with HCL. From the total number of patients, 71 (93.4%) were treated with chemotherapy with purine analogs ±, with splenectomy ±, INFα ±, different types of chemotherapy ±, monoclonal antibodies ±. The remaining 5 (6.57%) patients with HCL were only supportive and symptomatically treated. Out of the 71 patients, 50 patients (71.4%) were treated with purine analogs, the second group of 12 patients (16.9%) were treated with different approach without purine analogs, and the third group of 9 (12.7%) were treated with purine analogs and/or splenectomy, INFα, different types of chemotherapy and monoclonal antibodies. The most effective therapy for HCL has proven to be the usage of purine analogs for classical HCL, while for variants of the disease a combination of purine analogs and monoclonal antibodies.

Keywords: hairy cell leukemia, purine analogs, splenectomy, INF-α, monoclonal antibodies

Introduction

Hairy cell leukemia (HCL) is a rare chronic B-cell malignancy, accounting for 2% of all leukemias with approximate incidence of less than 1 per 100,000 persons per year[1]. HCL is a slow-growing leukemia that involves the bone marrow, spleen and peripheral blood with hairy cells. The complete blood count may reveal pancytopenia including neutropenia[2,3].

There is a male predominance with a male-to-female ratio of 6:1, where median age at diagnosis is approximately 58, and HCL can rarely occur in adolescence[4].

While splenomegaly is a predominant feature, massive, symptomatic splenomegaly is less frequent, and rarely lymphadenopathy and hepatomegaly. Signs and symptoms of HCL include frequent infections, weakness or feeling tired, and pain or a feeling of fullness below the ribs[3]. The diagnosis is reached by analyzing the peripheral blood, including flow cytometry and review of peripheral smear, along with bone marrow biopsy. The flow cytometry markers positive in hairy cell leukemia include CD11c, CD25, CD 103, and CD123, along with typical B-cell markers such as CD19, CD20 or CD22[2].

HCL must be differentiated from other HCL-like disorders, including hairy cell leukemia variant (HCL-V) and splenic diffuse red pulp lymphoma (SDRPL). HCL-V is negative for CD25 and CD123. Response to typical or classic HCL in this disease is poor[2,5,6]. Using whole-exome sequencing in 2011, BRAF V600E somatic mutation was found in up to 70% to 100% of HCL patients, although it is not present in HCL-V. The absence of mutation of the BRAF gene is reported in up 10% to 20% of patients with HCL and could constitute a subgroup of HCL patients with poor prognosis[7-10]. A mutated IGHV profile is detected in 90% of HCL patients[11].

Given its incurable nature, HCL treatment is reserved for symptomatic patients, while asymptomatic patients should be monitored closely for disease progression with history, physical exam and complete blood count (CBC) with differential approximately every 3 to 6 months. Treatment of HCL often results in a long-lasting remission (a period during which some or all of the signs and symptoms of the leukemia are gone and mutations have also disappeared), but sometimes HCL does not respond to the initial first-line treatment and we call that disease refractory HCL[12].

Sometimes, very soon after the initial first-line treatment, HCL comes back or relapses. There is no international prognostic system for risk stratification of HCL. Some prognostic factors are associated with lower risk that HCL will return after the treatment, called favorable risk factor. The gender and age may affect the risk of HCL with poor prognostic features. Also, other risk factors which define HCL with poor prognosis are low level of hemoglobin and platelets, the presence of lymphadenopathy and massive splenomegaly, and initially high level of leukocyte - leukocytosis. In the past, splenectomy and biological therapy Interferon-alfa (INF-α) were the best initial treatment option for HCL; the progression free survival (PFS) was 40%; it was shorter and so was the overall survival (OS)[13-17].

Nowadays, splenectomy may be considered in patients with symptomatic massive splenomegaly, also in severe pancytopenia due to splenic sequestrations and as a temporizing measure in symptomatic pregnant women. Earlier common treatment of HCL was INF-α, which is still a choice of treatment during pregnancy when treatment is warranted, also in severe pancytopenia and/or active infection to improve blood counts and allow for subsequent therapy with the most often used therapy with purine analogs. However, patients with HCL who express the CD5 antigen appear to respond poorly to INF-α[13].

There are two purine analogs approved by the Food and Drug Administration (FDA) for the first line treatment for HCL: cladribine (2-CldA) and pentostatin, both drugs are equally effective in inducing and maintaining complete remission (CR) in approximately 90% of patients, and PFS in 70-90% of patients. The 2-CldA is regarded as first-line chemotherapy for HCL due to its favorable toxicity profile and patient convenience because 2-CldA is administered subcutaneously and is suitable for outpatient treatment. One course treatment with 2-CldA (5 to 7 days) induces CR that can last for several years without additional treatments[17-20]. A CR means: normalization of blood counts (Hgb greater than 12, platelet greater than 100, ANC greater than 1500) with disappearance of hairy cells from the blood

and bone marrow, resolution of splenomegaly and at the same time absence of other disease symptoms[21]. Relapsed disease can be treated with either another course of purine analog (if relapse occurs in a period more than 1 year from the initial treatment) or a combination of 2-CldA with rituximab which is most used, or monotherapy with rituximab (if the patient is unable to receive a purine analog). Patients who relapse after a long remission of over five years may be re-treated with the same initial purine analog therapy[22-25,27-29].

There are also many other options such as the combination of fludarabine with rituximab, bendamustine, and INF-α[26,27]. Other new options for refractory disease include a CD22-directed cytotoxin given intravenously (i.v.) or a clinical trial with BRAF inhibitors and B-cell receptor inhibitors. Supportive care measures such as antibacterial, antiviral, antimycotic prophylaxis, transfused blood products and growth factors are very important part of the HCL treatment. Long term follow-up of HCL patients is essential, to treat the relapses of the disease and predict the secondary solid and hematological malignancies which develop in 10% of patients[26-30].

The objectives of this study were to evaluate the outcome of treatment with or without purine analogs; to evaluate the outcome of treatment given to patients with recurrent disease of HCL and where we are now with HCL treatment options. Is it possible to predict the relapse free survival; progression free survival and to determine overall survival of the patients.

Materials and methods

This retrospective-prospective study was realized at the University Clinic for Hematology in Skopje, in the period from October 1984 until October 2022 with 76 patients with HCL included. The diagnosis of HCL was established in accordance with the WHO criteria by morphological evidence of hairy cells, on flow cytometry expression on the CD11c, CD103, CD123, CD25 markers, the trepine biopsy which makes it possible to specify the degree of tumoral medullary infiltration and immunohistochemical analysis of peripheral blood, bone marrow and sonography. Purine analog 2-CldA is indicated in symptomatic first-line treatment in HCL patients, and was administered either as a 2-h i.v. infusion at a dose of 0.12-0.14 mg/kg for 5-7 days or subcutaneous (s.c.) 2-CldA at a dose of 0.1 mg/kg/day for 5-7 days or 0.14 mg/kg/day for 5 days as a single course. S.c. administration does not usually require hospitalization, and seems to be an easier way of giving the drug rather than i.v. administration, plus there is a better efficacy of s.c. application. A repeated cycle of 2-CldA was given, without interim relapse, in cases where CR was not attained after the first cycle. Earlier, the choice of therapy was based on era-specific guidelines, ranging splenectomy +/- long term administration of INF-α $1,5x10^6$/U weekly. We had patients who were treated with chemotherapy alone, but after revision of diagnosis we continued with 2-CldA. Most of our patients who did not respond to initial therapy or had a relapse of the disease, received a second-line therapy. The combination of the monoclonal antibody rituximab with 2-CldA or splenectomy or INF-α was given; also, in some patients we repeated the mono therapy with 2-CldA. Rituximab was administered i.v. at 375 mg/m 2 weekly with 2-CldA in refractory or relapse patients. Responses are defined according to the Consensus Resolution criteria for CR, with morphological absence of hairy cells in the blood and bone marrow, normalization of cytopenia and any organomegaly, for partial response (PR) required normalization of peripheral counts, together with at least 50% reduction in organomegaly and hairy cells in bone marrow. Clusters of three or more positive cells indicated residual HCL and were recorded as PR, and more positive cells and organomegaly were recorded as a refractory disease (RD)[21]. Relapse was defined as any deterioration in blood counts, confirmed by a bone marrow biopsy and flow cytometry. We had a small group of patients with active HCL disease (AD) who were initially treated only

supportive without any other therapeutic approach. Progression-free-survival (PFS) was defined for patients achieving a CR or PR and was measured from the date of treatment initiation until the first relapse or death from any cause. Observation of PFS was censored at date of last contact for patients with no report of relapse who were last known to be alive. Overall survival (OS) described the time from the date of diagnosis to the event of death. PFS and OS were determined by Kaplan-Mayer survival curves (cumulative proportion surviving).

A written informed consent was obtained from all patients before starting the treatment. All medical history data were taken from patients' record database at the University Clinic for Hematology.

Results

A total number of 76 patients were involved in the study, realized between October 1984 and October 2022. There were 61 male (80.3%) and 15 female (19.7%) patients, at the age ranging from 29 to 83 years (mean range 56). In our Center we had the same disproportion, males have been more affected compared to females, with a ratio 4:1. The initial risk factors influencing the survival of patients with HCL and the duration of the period without progression of the underlying disease are gender and age.

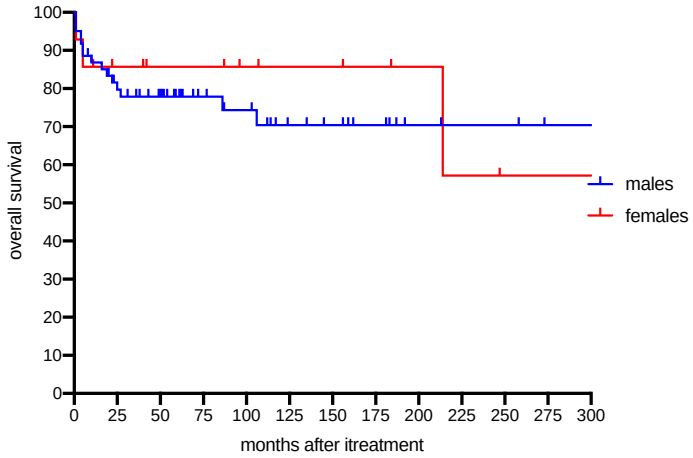

Fig. 1. Overall survival according to sex distribution of patients

In our group, there was no statistical significance (p=0.6220) in terms of survival between male and female HCL patients (males 85.7% at 5 years and females 75.8%) (Fig.1).

Our patients were divided into two groups: under the age of 65 (55 patients, 72.4 %) and above the age of 65 (21 patients, 27.6%).

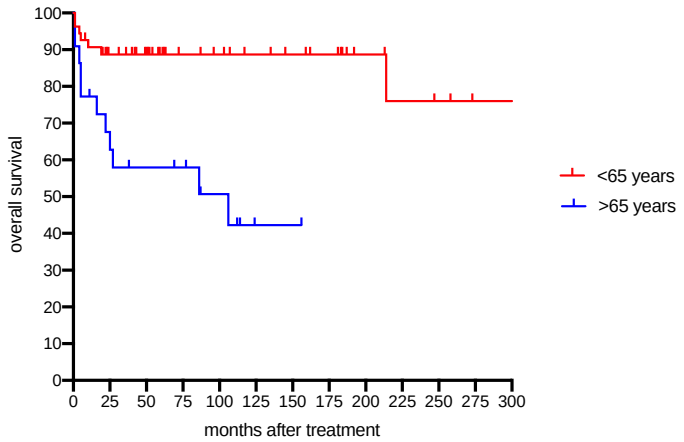

Fig. 2. Overall survival according to age distribution

Patients with < 65 years of age had statistically better survival (88.5%) at 5 years after treatment than patients with > 65 years of age (57.9%) (p=0.0022, HR = 0.2296, 95%CI= 0.04741 to 0.4134) (Fig.2).

From our group of HCL patients, 71 patients (93.4%) received different initial first-line therapy. Out of these 71 treated patients, 50 patients (71.4%) of which 49 patients were treated with purine analogs 2-CldA and 1 patient was treated with pentostatin. Patients' outcome was: 45 patients (90%) achieved CR, 3 patients (6%) achieved PR, and refractory disease was shown in 2 patients (4%). In 13 (27.1%) patients of this group relapse occurred.

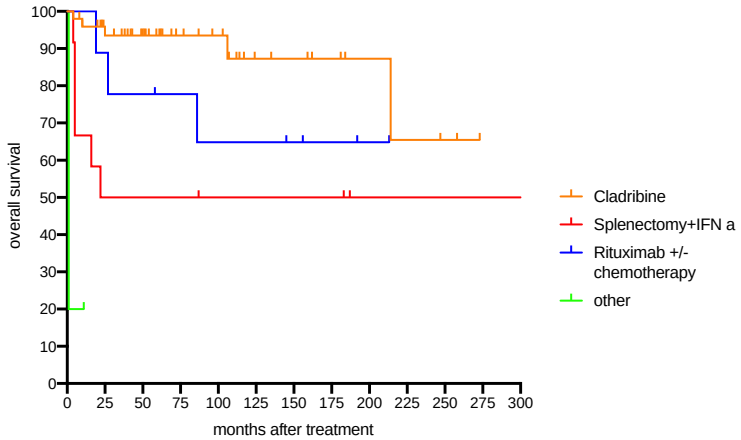

Fig. 3. Overall survival according to treatment modality

Patients treated with Cladribine had 93.5% OS at 5 years after treatment, which was statistically significant compared to other treatment options (77.7% for splenectomy + IFN-α and 50% for Rituximab ± chemotherapy) (p<0.0001) (Fig.3).

From this group of patients who experienced relapse, 6 patients (46.2%) were treated with the purine analog 2-CldA and the monoclonal antibody Rituximab, of which in 2 patients (15.4%) monotherapy with 2-CldA was repeated, 2 patients (15.4%) were treated with splenectomy and 2 patients (15.4%) were treated with INF-α. Only one patient with a relapse of the underlying disease was not treated at all. Equally important to note, however, is the substantial proportion of 37 patients (72.9%) not requiring any further retreatment after first-line 2-CldA.

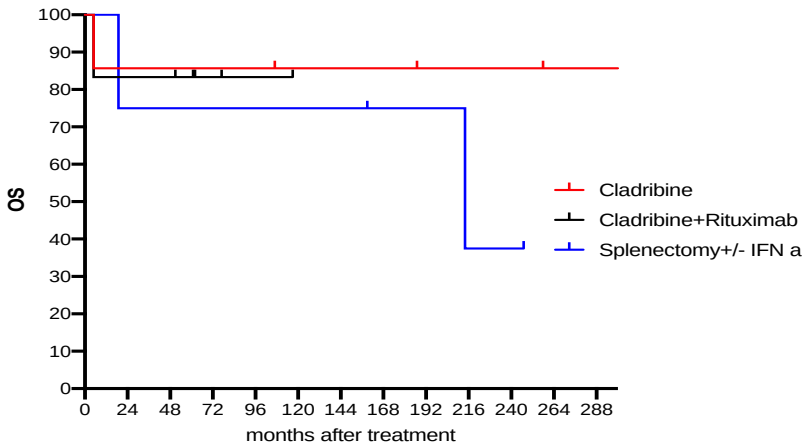

Fig. 4. Overall survival after second-line treatment in HCL patients with relapse

The second group of 12 patients (16.9%) were treated with a different approach, some of them with splenectomy +/-, INF-α +/-, chemotherapy but without 2-CldA. CR was achieved by 6 patients (50%) from this group, RD was shown by 6 patients (50%). Relapse was recorded in 5 patients and all of them were treated with 2–CldA.

The third group of 9 patients (12.7%) with HCL were patients who were treated with 2-CldA + rituximab. CR was achieved by 8 patients (88.9%), only one patient showed refractoriness to this therapeutic approach. No relapse of the primary disease was recorded in this group.

There was no statistical difference (p=0.35) in the treatment groups for second-line therapy in HCL patients (Fig.4).

PFS was observed in groups which achieved CR and PR remission after first-line treatment, but have also shown relapse of the underlying disease.

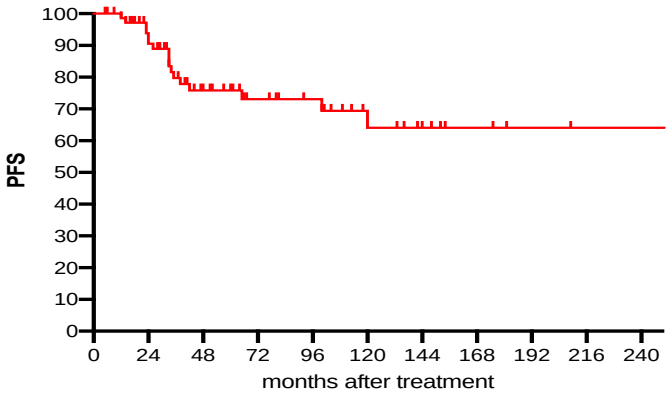

Fig. 5. Progression free survival (PFS) in HCL patients

PFS at 24 months (2 years) post-treatment was 97.1%; at 60 months (5 years) it was 75.8% and at 120 months post-treatment (10 years) 69.3% (Fig.5).

A second relapse of HCL was recorded in 2 patients (2.8%) out of 71 patients who were treated. Refractoriness of the primary disease to the therapy was shown by 9 patients (12.7%), of which 2 patients (22.2%) were treated only with 2-CldA and died of HCL (sepsis and hemorrhage). The group treated with splenectomy, INF-α and chemotherapy had the highest refractoriness, 6 patients (66.7%) died from the underlying disease (sepsis and hemorrhage). In the third group, refractoriness was shown by one patient (11.1%) who died from a cerebrovascular stroke, not related to the underlying HCL disease.

Of the total number of 19 deceased patients in our study, 5 (26.3%) were treated with 2-CldA, of which 2 patients died of the underlying disease (1 of sepsis and 1 of bleeding), while the other 3 patients died of complications unrelated to the underlying disease, they had cardiorespiratory failure.

In the second group of 7 (36.8%) deceased patients who were initially treated with splenectomy +/- INF-α +/-chemotherapy without purine analogs 2-CldA, the main cause of mortality in 5 patients was the main disease (sepsis and bleeding), while the remaining 1 patient died of cirrhosis and 1 from pulmonary embolism.

Of the third group of 3 (15.8%) deceased patients who were treated with purine analogs 2–CldA and all other therapeutic modalities such as splenectomy, INF-α, chemotherapy and/or rituximab, 2 died due to cardiorespiratory failure and 1 patient died from bleeding unrelated to the underlying disease.

Of the total group of HCL patients, for a long-term follow up, at the end of the study period, the overall survival showed that 57 patients (75%) were alive and 19 patients (25%) had death outcome (Fig. 6). Regarding the treatment for HCL, out of 76 patients, only 4 patients (5.26%) passed away before starting the management plan, and they received only supportive treatment; the death outcome was due to complications of the disease like infections and bleeding. One patient is alive, but only supportively treated.

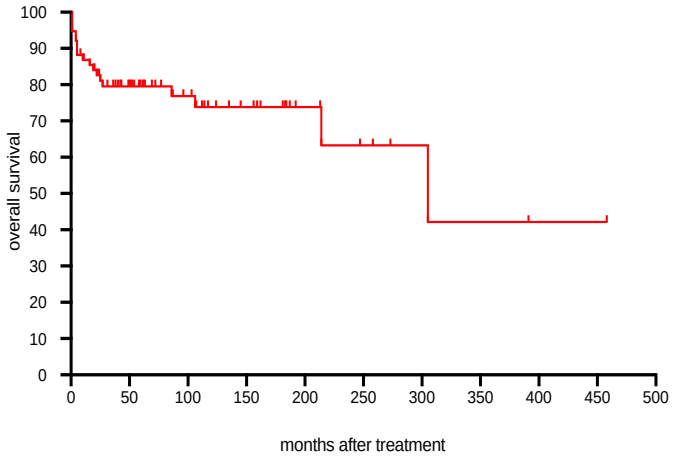

Fig. 6. Overall survival (OS) of patients after treatment

The five-year-overall survival of patients was 79.51% and compared to the world literature data our results were similar.

Discussion

Our results suggest that HCL patients could have a normal life expectancy if treated with the purine analog 2-CldA regardless of the treatment history prior to 2-CldA application, such as age at diagnosis or whether they were previously treated with another type of therapy. The percentage of response to therapy with purine analogs shows us that the treatment of this recurrent and indolent disease has improved, and also the time without progression of the primary disease has been extended and overall survival is increased. A poorer response is noted in HCL variants that are more aggressive and prone to relapse and refractoriness. Also, the conclusion for all those patients who were not treated with adequate anti-HCl therapy, and who were treated only supportively and symptomatically, all of whom died, is that it is necessary to approach more aggressively in this small number of selected patients, of course with timely application of therapy for the underlying disease, but also with more aggressive supportive and symptomatic treatment.[31]

The inclusion of new BRAF inhibitors and monoclonal antibodies is the future in the treatment of refractory and relapsed subtypes of HCL, so it is especially important to identify these patients. HCL remains incurable disease but highly responsive if optimal treatment with purine analogs 2-CldA is implemented. Our analysis has also shown that 2-CldA, as an initial treatment, is the best option for patients with classical type of HCL disease for achieving durable remission. These patients treated initially with 2-CldA develop the lowest refractoriness to the treatment and less mortality in comparison with the patients initially treated with splenectomy or INF-α and/or chemotherapy without 2-CldA. Further, the results correlate with the literature data - that the second treatment in cases of relapse is more successful if 2-CldA has been used in combination with rituximab rather than monotherapy, together with the period of remission which also shows great relevance[32]. The achievement of CR is a critical factor in this success and should be the goal of treatment at each stage. Of those patients who were still in their first CR at five years, only one quarter relapsed by more than twenty years[33-36].

Conclusion

The 2-CldA has proven to be a potent treatment and very effective in establishing longer and better relapse-free survival and overall survival. With these excellent long-term outcomes, the analysis of patients with HCL has shown that the application of the purine analog 2-CldA as a first-line treatment is very needed. It is also necessary to further differentiate the subtype of HCL in order to avoid possible refractoriness to purine analogs, but also to the other type of therapy implemented. Further differentiation of HCL subtype is also necessary in order to predict any possible relapse and consequently the shortened survival, as well as to initially stratify the risk of each patient individually because it is still a rare disease, as evidenced by the small number of patients in our study in a long follow-up period. At this very moment, most of the HCL patients can look forward to a normal life expectancy.

Conflict of interest statement. None declared.

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