Original Article

Characteristics and Outcome of Patients with Chronic Myelomonocytic Leukemia: Experience of a Single Center

Kronik Miyelomonositik Lösemi Hastalarının Özellikleri ve Tedavi Yanıtları: Tek Merkez Deneyimi

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ABSTRACT

Introduction: Chronic myelomonocytic leukemia (CMML) is a condition that overlaps with myelodysplastic syndrome and myeloproliferative neoplasms. The prognosis is generally poor, with a median survival of 20 to 40 months and approximately 15-30% of patients progressing to acute myeloid leukemia (AML). We aimed to evaluate the characteristics and outcomes of CMML patients who were treated at our institution.

Material and methods: A retrospective cohort study examined data from 14 CMML patients between January 2013 and January 2022.

Results: The median age of fourteen patients at diagnosis was 66 years (min 43-max 84 years). Only one patient (7.1%) had the JAK 2 V617F mutation. Most of the patients had CMML stage-0 disease (64.3%) and 13 patients had the proliferative type of disease. Nine patients were treated with hydroxyurea, which resulted in two responders. Eight patients were treated with azacitidine, which resulted in three responders. During follow-up, AML transformation was observed in five patients (35.7%) and the median duration between diagnosis and AML transformation was 12 months (10-33 months). In the AML-transformed group, at the time of diagnosis, the percentage of neutrophils was lower (52.5% vs 72.3%), and the percentage of monocytes was higher (27% vs 15.6%). In AML-transformed group the total disease duration was longer (21 (11-44) vs 5 (2-48) months) than non-transformed group.

Discussion and Conclusion: In patients receiving hypomethylating agents and hydroxyurea treatments for CMML, adequate response cannot be obtained. The rate of AML transformation increases with disease duration.

Keywords: Hydroxyurea, Azacitidine, Myelodysplastic Syndromes, Splenomegaly, Monocytes

ÖZET

Giriş ve Amaç: Kronik miyelomonositik lösemi (KMML), miyelodisplastik sendrom ve miyeloproliferatif neoplazmların ortak özelliklerine gösteren, kötü prognozlu, medyan sağkalımı 20-40 ay arasında değişen ve takip sürecinde %15-30 oranında akut miyeloid lösemi (AML) gelişen bir hastalıktır. Bu çalışmanın amacı, merkezimizde takip edilen KMML hastalarının özelliklerini, tedaviye yanıtlarını ve AML dönüşüm oranlarını değerlendirmektir.

Yöntem ve Gereçler: Ocak 2013- Ocak 2022 tarihleri arasında KMML tanısı ile takipli 14 hastanın verilerileri retrospektif olarak değerlendirilmiştir.

Bulgular: On dört hastanın ortalama yaşı 66 (en küçük 43-en büyük 84) olup sadece bir hastada (%7.1) JAK2 V617F mutasyonu saptandı. Hastaların çoğunda Evre-0 KMML (%64.3) olup ve 13 hastada proliferatif tip hastalık olduğu gözlendi. Dokuz hasta (%64.3) hidroksiüre ile tedavi edildi ve iki hastada

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yanıt alındı. Sekiz hasta azasitidin ile tedavi edildi ve üç hastada yanıt elde edildi. Takip sırasında beş hastada (%35.7) AML dönüşümü saptandı. KMML tanısı sonrası AML dönüşümünün medyan 12 ayda (10-33 ay) olduğu gözlendi. AML dönüşümü gözlenen grupta, tanı anında nötrofil yüzdesinin daha düşük (%52,5 ve %72,3) ve monosit yüzdesinin daha yüksek (%27 ve %15.6) olduğu gözlendi. AML dönüşümü gözlenen grupta toplam hastalık süresinin daha uzun (21 ve 5 ay) olduğu saptandı.
Tartışma ve Sonuç: KMML tedavisinde kullanılan hipometile edici ajanlar ve hidroksiüre tedavileri ile hastalarda yeterli yanıt elde edilememektedir. AML dönüşüm oranı hastalık süresi arttıkça artmaktadır.

Anahtar Kelimeler: Hidroksiüre, Azasitidin, Miyelodisplastik Sendromlar, Splenomegali, Monositoz

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematological cancer with proliferative and dysplastic features. It is classified as one of the overlapping conditions of Myelodysplastic syndrome (MDS) and Myeloproliferative neoplasms (MPN) in the 2016 World Health Organization (WHO) classification [1]. Chronic myelomonocytic leukemia is a rare hematological cancer that affects only 4 people out of every million. It primarily affects older people and is more prevalent in men. The disease is classified as proliferative or dysplastic based on peripheral white blood cell (WBC) counts. Blast percentages in bone marrow and peripheral blood determine the stage of disease. The risk group primarily drives treatment selection. Patients with low risk and no symptoms are followed without treatment or with cytoreductive therapy (hydroxyurea), whereas patients with medium or high risk are treated with hypomethylating agents (HMA) or hydroxyurea. The prognosis is generally poor, with a median survival of 20 to 40 months and approximately 15% to 30% of patients progressing to acute myeloid leukemia (AML) [2, 3].

Since the disease is uncommon and the number of randomized controlled studies is limited, the therapy is based primarily on physician discretion, rendering real-world data essential in this context. Here we are presenting the characteristics and outcomes of CMML patients treated at our center.

Methods

This retrospective cohort study examined data from patients with CMML who were treated at our center between January 2013 and January 2022. Patients were diagnosed with CMML according to the WHO classification [1].

Manual file records and electronic medical record systems were used to obtain clinical information from patients. The demographics, comorbidities, CMML diagnosis date, CMML type, disease stage at diagnosis, therapy and response, last control date, and survival status of all patients were documented. The 2016 WHO classification was used for staging [1].

The local human research ethics committee approved this study. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Permission granted /Decision number: 2022-03/1709).

The SPSS software (Version 25.0; Armonk, NY: IBM Corp) was used for statistical analysis. The numerical variables were presented as median (min-max), while the categorical variables were presented as ratios. Disease duration was calculated as the time defined as the period between the date of CMML diagnosis and the date of last follow-up or death from any cause.

Results

The characteristics of the patients

Between January 2013 and January 2022, 14 CMML patients were diagnosed and included

in the study. The median age at diagnosis was 66 years (a range of 43-84 years). At the time of presentation, half of these patients had splenomegaly and hepatomegaly. All patients had been evaluated for the presence of JAK2 V617F and cytogenetic abnormalities. Only one patient (7.1%) had the JAK2 V617F mutation, and no cytogenetic abnormality was found in any of the patients. Most of the patients had CMML stage-0 (64.3%) and 13 patients had proliferative type of disease according to WHO staging. According to Mayo risk stratification, seven patients (50%) were in the high-risk group, six patients (42,9%) were in the intermediate-2 risk group, one patient (7,1%) was in the intermediate-1 risk group, and none of them were in the low-risk group. In the bone marrow examination, six patients had grade 1-2 fibrosis, none of them had grade 3 fibrosis. All patients' characteristics are shown in Table 1.

Table 1. Characteristics of the patients

Parameters	N =14, (%)
Age (years) (median, min-max)	66 (43-84)
Gender (M/F)	10 (71.4) / 4 (28.6)
CMML Stage	
CMML-0	9 (64.3)
CMML-1	4 (28.6)
CMML-2	1 (7.1)
CMML type (Dysplastic/ Proliferative)	1 (7.1) / 13 (92.9)
CMML risk group, n (%)	
Low risk	0
Intermediate-1	1 (7.1)
Intermediate-2	6 (42.9)
High risk	7 (50)
Peripheral blood Parameters, median (min-max)	
WBC count (x10^9/L)	49.2 (9.8-94)
Monocyte percentage	20.1 (2.1-78.3)
Absolute Monocyte counts (×10^9 /L)	5.496 (413-44.574)
Hemoglobin concentration (g/L)	9.47 (4.2-13.4)
Platelet count (×10^9 /L)	83 (15-338)
Lymphocyte percentage	11.6 (3.3-20.1)
Neutrophil percentage	70.2 (5.8-85.4)
Bone marrow blast percentage, median (min-max)	2 (0-15)
JAK 2 V617F mutation	1 (7.1)
Splenomegaly	7 (50)
Hepatomegaly	6 (42.8)
Disease duration, median (min-max), months	8.4 (2-48)

CMML; chronic myelomonocytic leukemia, M; male, F; female, WBC; white blood count, AML; acute myeloid leukemia

Treatment and the response of patients

Nine patients (64.3%) were treated with hydroxyurea and only two patients responded to hydroxyurea according to their peripheral blood count. Four patients (28.6%) were treated with azacitidine and two of them responded to azacitidine. Three of the patients refractory to hydroxyurea were treated with azacitidine and one patient was treated with azacitidine plus ruxolitinib, only one patient responded to azacitidine. One of the hydroxyurea-refractory patients was treated with ruxolitinib, but no response was observed. One patient was treated with the best support due to poor performance status and comorbidities. During follow-up, AML transformation was observed in five patients (35.7%) and the median duration between diagnosis and AML transformation was 12 months (10-33 months). Allogeneic hemato-poietic cell transplantation was performed on a male patient who had AML transformation (allo-SCT). After allo-SCT, he achieved a complete response, and he is still alive and has been in remission for 40 months. During the follow-up period, three patients died (one patient without AML transformation due to

Table 2. AML-transformed and non-transformed group characteristics

Parameters	AML-transformed group, (N=5)	Non-transformed group, (N=9)
Age,years, median (range, min-max)	66 (63-82)	66 (43-84)
WBC count, median (range, min-max) ($X10^9$/L)	56.800 (9.840-60.000)	55.000 (19.710-94.060)
Monocyte percentage, median (min-max), %	27.9 (24.9-78.3)	15.6 (2.1-24.5)
Absolute Monocyte count, median (min-max), ($\times10^9$ /L)	10.2 (2519-44.474)	4.7(413-18.906)
Hemoglobin concentration, median (range, min-max) (g/L)	9.5 (8.0-13.4)	9.2 (4.2-12.9)
Platelet count, median (range, min-max) ($\times10^9$ /L)	84 (41-338.000)	83 (15-121))
Lymphocyte percentage, median (min-max), %	13 (11.6-15.8)	10.9 (3.3-20.1)
Neutrophil percentage, median (min-max), %	52.6 (5.8-54.3)	72.3 (53.4-85.4)
Disease duration, median (min-max), months	21 (11-44)	5 (2-48)
Bone marrow fibrosis (Grade 1-2/3), %	2 (40)	4 (44)

WBC; white blood count, AML; acute myeloid leukemia,

septicemia and two patients due to AML transformation).

There was no difference in patients' gender, age, CMML stage, risk status, first treatment option and responses, WBC, PLT, and lymphocyte percentage at the time of diagnosis between the AML-transformed and non-transformed groups. In the AML-transformed group, at the time of diagnosis, the percentage of neutrophils was lower (52.5% vs 72.3%), and the percentage of monocytes was higher (27% vs 15.6%). The total disease duration was longer (21 (11-44) vs 5 (2-48) months). AML-transformed and non-transformed group characteristics are shown in Table 2.

Bone marrow fibrosis

At the time of diagnosis, six patients were diagnosed with grade 1-2 bone marrow fibrosis; none had grade 3 fibrosis. During follow-up, two patients with bone marrow fibrosis developed AML.

Discussion

In our study, 14 patients were examined. Patients were 66 years old on average, with half having hepatosplenomegaly and the majority having CMML stage 0, proliferative phase, and high-risk disease. Nine patients received hydroxyurea treatment, and eight patients received azacitidine treatment. During the follow-up period, AML-

transformation was observed in five patients; two of these patients died due to disease progression, and one was treated with allo-SCT. The AML-transformed group had a higher percentage of monocytes, a lower percentage of neutrophils, and the disease lasted longer than the non-transformer group.

CMML is a rare hematological disease with heterogeneous disease characteristics, so it is critical for centers to share their experiences. It is extremely beneficial to learn about the factors that influence the outcome and risk of AML transformation. Furthermore, optimal treatment choice according to the type and risk of the disease is another matter of debate.

Hypomethylating agents are the first-line therapy for CMML, particularly in high-risk patients. In CMML patients, HMAs have a response rate of 25–75% [5–9]. Coston et al. reported, HMAs have a response rate of 39% and a median time to response of five months (range 2–5) [9]. Responses of HMAs treatments were similar in dysplastic and proliferative CMML patients in the azacitidine-treated arm, but better responses were seen in dysplastic CMML patients in the decitabine-treated arm [9]. HMA responses were linked to lower serum LDH levels as well as the absence of KRAS, NRAS, and c-KIT [9]. Only one patient in our study had dysplastic CMML. Eight patients (four as first-line treatment and four as second-line treatment) received azacitidine (75 mg/m^2 for 7 days in 28-day cycles), but only three (37.5%) responded. The criteria affecting treatment responses were not evaluated in our study due to the small number of patients.

Hydroxyurea is the most commonly used cytoreductive therapy for the treatment of leukocytosis and organomegaly associated with CMML. In our study, nine patients were treated with hydroxyurea, but only two of them (22.2%) responded.

The median overall survival is 20 to 40 months and approximately 15–30% of patients progress to AML [2, 3, 9]. In our study, during the follow-up period, five patients (35.5%) developed AML. In the AML-transformed group, at the time of diagnosis, the median percentage of peripheral blood monocytes was higher (27.9% vs. 15.6%), while the median percentage of neutrophils was lower (52.5% vs. 72.3%). The disease duration was longer in AML-transformed groups than in non-transformed groups (21 vs 5 months). CMML disease duration was longer in AML-transformed patients (21.9 vs 17.1 months, p =0.0002) than in non-transformed patients [10].

Gur et al. reported that 20% of CMML patients had grade 2-3 fibrosis. In the fibrosis group, WBC and monocyte counts were higher, and splenomegaly was more common. Furthermore, the survival time in this patient group was shorter [4]. In our study, there was no patient with grade 3 fibrosis. Six of our patients had bone marrow fibrosis of grades 1-2. There was no difference in many parameters examined between patients with fibrosis and those without fibrosis.

While the only curative treatment is allo-SCT, the majority of patients are not candidates due to their advanced age and comorbidities [11]. Allo-SCT was performed on one patient in our study, and he has been in remission for 40 months.

Conclusion

In conclusion, CMML is a rare disease with a poor prognosis that shares features with MDS and MPN. The only curative treatment is allo-SCT but many patients are unable to receive it due to their advanced age and comorbidities. The current CMML treatment options and outcomes are far from satisfactory. Therefore, whenever possible, patients should be encouraged to participate in clinical trials.

REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391-405.
2. Bacher U, Haferlach T, Schnittger S, et al. Recent advances in diagnosis, molecular pathology and therapy of chronic myelomonocytic leukaemia. Br J Haematol. 2011; 153: 149–167.
3. Germing U, Kundgen A, Gattermann N. Risk assessment in chronic myelomonocytic leukemia (CMML). Leuk Lymphoma. 2004; 45: 1311–1318.
4. Gur HD, Loghavi S, Garcia-Manero et al. Chronic Myelomonocytic Leukemia with Fibrosis Is a Distinct Disease Subset with Myeloproliferative Features and Frequent JAK2 p.V617F Mutations. Am J Surg Pathol. 2018; 42(6): 799-806.
5. Braun T, Itzykson R, Renneville A, et al. Molecular predictors of response to decitabine in advanced chronic myelomonocytic leukemia: a phase 2 trial. Blood 2011; 118: 3824-31.
6. Drummond MW, Pocock C, Boissinot M, et al. A multi-centre phase 2 study of azacitidine in chronic myelomonocytic leukaemia. Leukemia 2014; 28: 1570-2.
7. Tantravahi SK, Szankasi P, Khorashad JS, et al. A phase II study of the efficacy, safety, and determinants of response to 5- azacitidine (Vidaza®) in patients with chronic myelomonocytic leukemia. Leuk Lymphoma 2016; 57: 2441-4.
8. Santini V, Alli one B, Zini G, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. Leukemia 2018; 32: 413-8.
9. Coston T, Pophali P, Vallapureddy R, Lasho TL, Finke CM, Patnaik MM. Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. Am J Hematol. 2019; 94(7): 767-779.
10. Patnaik MM, Wassie EA, Lasho TL, Hanson CA, Ketterling R, Tefferi A. Blast transformation in chronic myelomonocytic leukemia: Risk factors, genetic features, survival, and treatment outcome. Am J Hematol. 2015; 90(5): 411-6.
11. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2018 update on diagnosis, risk stratification and management. Am J Hematol. 2018; 93(6): 824-840.

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