Original Study

Patients With Therapy-Related CMML Have Shorter Median Overall Survival Than Those With De Novo CMML: Mayo Clinic Long-Term Follow-Up Experience

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Abstract

Treatment-related (t-) chronic myelomonocytic leukemia (CMML) carry a worse clinical outcome than de novo (dn-) CMML (dn-CMML). Most t-CMML patients had received previous chemotherapy exposure. Patients with t-CMML had a shorter median overall survival than those with dn-CMML but similar time to leukemic transformation. Patients with t-CMML have a poor prognosis and should be considered for investigational treatment.

Background: Chronic myelomonocytic leukemia (CMML) is a malignant hematologic neoplasm characterized by peripheral blood monocytosis and bone marrow dysplasia. The World Health Organization classified therapy-related (t-) myeloid neoplasm (MN) as another category. It is known that t-MNs tend to have a worse prognosis than de novo (dn-) MN (dn-MN). **Patients and Methods:** Previous exposure to chemotherapy (CT), radiotherapy (RT), or both were defined as t-CMML and lack of both as dn-CMML. **Results:** Of 265 CMML patients, 30 (11%) had t-CMML. Seventeen (57%) patients had previous exposure to CT, 6 (20%) to RT, and 7 (23%) to CT and RT. Leukemic transformation (LT) was seen in 5 (17%). In comparison, only lower platelet count was found to be statistically significant compared with dn-CMML. Median overall survival (OS) was 20 months in the dn-CMML group versus 11 months in the t-CMML group ($P = .02$). Median OS was 9 months in the CT group versus 4.4 months in the RT group versus 13 months in the CT and RT group ($P = .7$). **Conclusion:** t-CMML comprises a small portion of all CMML cases (11%). Median OS in the dn-CMML group was longer than in the t-CMML group but LT seemed to be similar in terms of incidence and time to occurrence. Additional studies are needed to confirm our results.

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Introduction

Chronic myelomonocytic leukemia (CMML) is a heterogenous hematologic disease with myelodysplastic and myeloproliferative features. It is characterized by peripheral blood (PB) monocytosis and bone marrow (BM) dysplasia. Clinic and laboratory features include pancytopenia, hyperleukocytosis, transformation to acute myeloid leukemia (AML), constitutional symptoms (fever, weight loss), splenomegaly, and other organ involvement.

The World Health Organization (WHO) redefined its classification in 2008.[1] They defined therapy-related (t-) myeloid neoplasms as 2 groups. These first group was 'topoisomerase II inhibitor-related AML' and the second was 'alkylating agent—related or radiation-related AML and myelodysplastic syndromes (MDS).' It is important to mention WHO does not distinguish between t-MDS and t-AML and combines them as t-myeloid neoplasia.

Therapy-related myeloid neoplasms including AML, MDS, and CMML are rare conditions. Generally, t-neoplasms account for approximately 10% to 20% of all myeloid neoplasms.[2-4] Overall survival (OS) for patients with these diseases is shorter than for those with de novo (dn-) forms. Allogeneic stem cell transplantation is

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usually recommended for fit patients because of poor prognosis and encouraging results of transplantation.[5] Because CMML is a rare disease, a description of t-CMML patients is difficult.[6-8] We therefore studied the clinical outcome of t-CMML versus dn-CMML.

Patients and Methods

A retrospective chart review was used to evaluate CMML patients diagnosed at Mayo Clinic between 1994 and 2014. Data on previous treatment exposure was captured. Patients were designated as t-CMML if there was previous exposure to any chemotherapy (CT) or/and radiotherapy (RT). The diagnosis of CMML was defined according to WHO 2008 criteria as CMML-1 and CMML-2.[1] CMML cytogenetic risk classification was performed using the Such et al criteria in CMML.[9,10] Patient cytogenetics at the time of t-CMML diagnosis were placed into 3 categories: low-risk (normal and isolated−Y); high-risk (trisomy 8, complex karyotype as ≥ 3 abnormalities, and abnormalities of chromosome 7); intermediate-risk (other abnormalities). Leukemic transformation (LT) was defined if blasts were recorded ≥ 20% in the PB or/and in BM biopsy samples. Data were collected from a review of electronic records, pathology reports, and laboratory records. Appropriate institutional review board approval was obtained in accordance with the Declaration of Helsinki. OS was defined for all patients as the time from CMML diagnosis to date of death. A comparison between group medians was done using the Wilcoxon test and survival estimates were calculated using Kaplan−Meier curves using JMP (SAS, Cary, NC) version 10.

Results

Of 265 CMML patients, 30 (11%) had t-CMML. The median age was 72 (range, 27-86) years, with 19 (63%) patients being male. Laboratory findings at the time of diagnosis included median white blood cell (WBC) count of 16.8 (range, 2.9-102) × 10^9/L, hemoglobin (Hg) 10.5 (range, 8.9-14.6) g/dL, platelet (PLT) count 65 (range, 8-312) × 10^9/L, monocytes (Mon) 3.8 (range, 0.56-29) × 10^9/L, BM blasts 4% (range, 0%-18%), PB blasts 0% (range, 0%-7%), and lactate dehydrogenase (LDH) 241 (range, 102-922) U/L (Table 1).

Chronic myelomonocytic leukemia-1 was reported in 28 of 30 patients (93%) and CMML-2 in 2 (7%). Splenomegaly was present in 7 (23%) patients and absent in 21 (70%); 2 patients underwent splenectomy (7%). Cytogenetic risk categories were low in 21 patients (72%), intermediate in 2 patients (7%), and high in 6 patients (21%). LT was seen in 5 patients (17%). In an evaluation of previous therapy, 17 patients (57%) were treated with CT, 6 patients (20%) were treated with RT, and 7 patients (23%) received CT and RT (Table 2). Previously treated cancer types included 12 different cancers, most commonly prostate and colon cancer (24% and 20%, respectively; Table 1).

Of 265 patients, 235 (89%) had dn-CMML. The median age was 71 (range, 20-95) years, with 158 (67%) male. Laboratory findings at diagnosis were median WBC count of 12 (range, 1-302) × 10^9/L, Hg 10.4 (range, 6-15.7) g/dL, PLT count of 95 (range, 1-1110) × 10^9/L ($P = .046$), Mon 2.1 (range, 0-35.5) × 10^9/L, BM blasts 4% (range, 0%-19%), PB blasts 0% (range, 0%-19%), and LDH level 222 (range, 84-2283) U/L. CMML-1

Table 1 Characteristics of t-CMML and dn-CMML

Variable	t-CMML (n = 30)	dn-CMML (n = 235)	P
Median Hgb (Range), g/dL	10.5 (8.9-14.6)	10.4 (6-15.7)	.25
Median PLT (Range), × 10^9/L	65 (8-312)	95 (1-1110)	**.046**[a]
Median WBC (Range), × 10^9/L	16.8 (2.9-102.3)	12 (1-302.2)	.86
Median Monocytes (Range), × 10^9/L	3.75 (0.56-29)	2.1 (0-35.5)	.29
Median Bone Marrow Blasts (Range), %	4 (0-18)	4 (0-19)	.77
Median Peripheral Blasts (Range), %	0 (0-7)	0 (0-19)	.46
Median LDH (Range), U/L	241 (102-922)	222 (84-2283)	.99
Previous Therapy, n (%)			
CT	17 (57)	NA	
RT	6 (20)	NA	
CT and RT	7 (23)	NA	
Cytogenetic Risk Category, n (%)			.54
Low	21 (72)	163 (71)	
Intermediate	2 (7)	31 (13)	
High	6 (21)	37 (16)	
Primary Cancer Types			
Ewing sarcoma	1 (3)	NA	
Prostate	7 (24)	NA	
Colon	6 (20)	NA	
Breast/ovarian	2 (7)	NA	
Sweat gland adenocarcinoma	1 (3)	NA	
Malignant melanoma	1 (3)	NA	
Myeloproliferative disorder	2 (7)	NA	
Multiple myeloma	1 (3)	NA	
Non-Hodgkin lymphoma	3 (10)	NA	
AML	2 (7)	NA	
B-CLL	1 (3)	NA	
Rheumatologic	3 (10)	NA	

Abbreviations: AML = acute myeloid leukemia; B-CLL = B-chronic lymphocytic leukemia; CT = chemotherapy; dn-CMML = de novo chronic myelomonocytic leukemia; Hgb = hemoglobin; LDH = lactate dehydrogenase; PLT = platelets; RT = radiotherapy; t-CMML = treatment-related chronic myelomonocytic leukemia; WBC = white blood cells.
[a]Statistically significant.

Table 2 Type of Previous Chemotherapy Exposure

Type of Chemotherapy	Patient n (Total n = 24)	%
Alkylating Agents	12	50
Topoisomerase Inhibitors	6	25
Antimetabolite	14	58
Antimicrotubule Agent	7	29
Cytotoxic Antibiotic	4	17
Other	4	17

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