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Case Report

CD56-Positive Acute Myeloid Leukemia Following Treatment of Hairy Cell Leukemia with Cladribine – Report of 2 Cases and Review of the Literature

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Abstract

Treatment of hairy cell leukemia (HCL) with alfa-interferon and purine analogs significantly prolongs survival in these patients. However, with life prolongation, an increased risk of secondary malignancies has been reported. Acute myeloid leukemia (AML), as a second malignancy after HCL treatment is extremely rare and has been reported in only 12 cases so far. We here report additional 2 cases of CD56+ AML developed after sustained clinical remission of HCL achieved with cladribine (2 and 6 years after, respectively). The first patient refused chemotherapy and shortly thereafter died. The second patient responded to chemotherapy and was successfully allo-transplanted. Three years later, the patient is in stable clinical remission, which is a unique case in the literature. In conclusion, it is not clear whether development of AML in HCL patients is caused by mutagenic potential of the applied chemotherapy or by immune suppression/ perturbations as a characteristic of the underlying disease.

Keywords: CD56 antigen, Cladribine, Hairy cell leukemia, HSC transplantation, Secondary acute myeloid leukemia

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Introduction

Treatment with purine analogs, such as pentostatin (2'-deoxycoformycin) and cladribine, produces high rate of complete remissions and prolonged survival in patients with hairy cell leukemia (HCL). However, several studies and case reports described an increased risk of secondary malignancies in HCL patients.[1-3] The relative risk of secondary malignancies in HCL reported in various series range from 0.95 to 4.33.[1-5] In a large study of 3,104 patients with HCL, the authors have found a statistically significant 1.24-fold increase in cancer risk relative to incidence in the general population.[3] The main finding of this study was an increased incidence of Hodgkin and non-Hodgkin lymphoma, as well as thyroid cancer, but not acute leukemias.[3] In the Italian Cooperative Group for the Study of HCL, 54 out of 1022 patients developed secondary malignancies.[6] Among them, only one case of acute leukemia, treated with interferon alfa (IFN-α), was reported.[6] These studies could not conclude whether purine analogs are responsible for the increased risk of secondary cancers in HCL patients because only a small number of patients were treated with these medications.[6] Additionally, inconsistent reporting policies, incomplete follow-up and different treatments do not allow for clear quantification of the risk.[2] Lastly, an alternative explanation could be the fact that these patients live longer, such that the expected risk of malignancies is similar to that in the rest of the population of the same age.[6]

Herein, we report 2 patients with HCL who developed secondary acute myeloid leukemia (AML) after achieving sustained complete remission with cladribine.

Case Reports

The first patient was a 60-year-old male who presented in January 2008 with malaise, splenomegaly and weight loss (10 kg for several months). Physical examination revealed painless, maculopapular brick-red skin infiltrates 1–2 cm in diameter and splenomegaly measuring 28 × 12 × 20 cm on abdominal ultrasonography (US). Complete blood counts (CBC) showed hemoglobin (Hb) 90 g/L, platelets 73 × 10^9/L, white blood cells (WBC) 101 × 10^9/L (differential count: neutrophils 6%, lymphocytes 4% and tricholymphocytes 90%). Bone marrow aspirate was normocellular with 70% TRAP positive "hairy" lymphocytes. Peripheral blood immunophenotyping revealed presence of atypical B-cell population with specific immunophenotype: CD19+, CD20+, CD22+, CD103+, CD11c+, FMC+, CD45+bright, CD25-, mkappaIg-,

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mlambdaIg-. Surgical biopsy of dermis and hypodermis showed patchy perivascular infiltrates composed of small to medium-sized DBA44+ lymphoid cells, with abundant, pale-blue cytoplasm (described in detail in separate publication: Colovic et al, Med Oncol 2010;27(2):559-61). The patient was treated with 2 cycles of cladribine (0.14 mg/kg for days 1–5) and splenectomy. Complete remission was achieved. However, in June 2011 his CBC showed Hb 81 g/L, platelets 26 × 10^9/L and WBC 21 × 10^9/L with 6% of blasts and 32% tricholymphocytes in differential count. The immunophenotype of bone marrow mononuclear cells (MNC) showed presence of residual hairy cells (13% MNC) and population of atypical blast cells (58% MNC) with immunophenotypic characteristics of acute monocytic leukemia (HLA-DR+, CD34+, CD36+, CD64+, CD14+) with aberrant CD56 expression. The karyotype was normal. The patient was advised to receive intensive chemotherapy, which he refused. He left the hospital and died one month later.

The second patient was a 60-year-old male who presented with general malaise in June 2009. He suffered from diabetes mellitus and absolute arrhythmia years before admission. Physical examination revealed spleen palpable on the left costal margin and 143mm in diameter on abdominal US. His CBC was as follows: Hb 139 g/L, platelets 59 × 10^9/L, WBC 2.1 × 10^9/L (differential count: lymphocytes 54%, neutrophils 46%). Bone marrow trephine biopsy showed hypercellular marrow with intense (80%–90% b.m. cells), diffuse and uniform lymphoid cell infiltration with CD79α+, CD20+, CD10-, CD3-, CD5-, CD23-, CD43-, DBA44+, bcl-2+, Cyclin D1+/- cells. HCL was diagnosed and the patient received a single course of cladribine. After achieving complete remission, the patient was closely followed-up. He remained well for the following six years. However, in March 2015 patient developed general malaise. His CBC showed pancytopenia (Hb 86g/L, platelets 13 × 10^9/L, WBC 3.8 × 10^9/L with differential count: neutrophils 24%, lymphocytes 46%, monocytes 29% and eosinophils 1%). Bone marrow cytology and histology showed normocellular marrow with moderate dysplasia of E- and G-lineage with 9% of myeloblasts (some with Auer rods) and fibrosis grade II. Cytogenetic analysis of bone marrow cells was normal. Based on these findings a diagnosis of myelodysplastic syndrome, subtype RAEB-1 was established. However, few months later, progression of the disease was noticed in the peripheral blood with Hb of 83g/L, platelet count of 34 × 10^9/L and WBC of 33.5 × 10^9/L with 21% of myeloblasts. The bone marrow aspirate was hypercellular with presence of 48% myelomonoblasts indicating transformation of RAEB-1 to acute myelomonoblastic leukemia (AML-M4). The immunophenotype of b.m. MNC showed: HLA-DR+, cMPO+, cLizozim+, CD117+, CD13+, CD33+, CD15+, CD11b+, CD11c+, CD64+, VD36+, CD14+, CD163+, CD56 +. The karyotype was normal. Molecular analysis detected *NPM*+ and *FLT*+ mutations. The patient underwent intensive chemotherapy. He achieved complete remission after single course of chemotherapy and then successfully allo-transplanted in November 2015. On his last follow-up (May 2018) patient is in good clinical condition and with normal CBC.

Discussion

AML, as a second malignancy after HCL therapy, is extremely rare and has been reported in only 12 cases in the period from 1993 until 2018 (Table 1). Most of the reported cases (i.e. 8 out of 12) were treated with purine analogues,[4,5,7-10] suggesting the possibility of mutagenic potential of these drugs. Another explanation of possible propensity for developing AML in HCL patients treated with these antimetabolite cytotoxic drugs is prolonged immune supression or immune perturbations. However, there are several reports of secondary AML after treatment of HCL patients with a non-cytotoxic and immunomodulatory agent - IFN-α[2,6,11,12] (Table 1). Moreover, Rimner and colleagues reported a concomitant case of AML and HCL.[13]

Table 1. Secondary AML in Patients with HCL Published in the Literature

Authors (Reference)	No. of Secondary Leukemia	FAB type of AML	Treatment of HCL	Time from Diagnosis of HCL to Secondary AML (months)
Hassan et al[7]	1	AML	Cladribine	11
Cheson et al[4]	3/928	AML	Cladribine	Not specified
Federico et al[6]	1/1022	AML	IFN	20
Al fair et al[8]	1	AML-M5b	Cladribine	46
Flinn et al[5]	1/241	AML	Pentostatin	n.s.
Kampameir et al[12]	1/69	AML-M2	IFN	76
Au et al[2]	1/117	AML	IFN	64
Sashardi et al[9]	1	AML	Cladribine	44
Spilberger et al[11]	1	AML	IFN	18
Todd et al[10]	1	AML	Pentostatin	35
Colovic et al (present cases)	1	AML-M5 (CD56+)	Cladribin, splenectomy	27
	1	AML-M4 (CD56+)	Cladribin	57

Abbreviations: AML, Acute myeloid leukemia; HCL, hairy cell leukemia.

These findings indicate that additional (i.e. "secondary") malignancies may reflect inherent, genetic predisposition for both types of malignancies.[13] One possible explanation for concomitant hematologic malignancies may be that underlying progenitor cell damage is responsible for both malignancies, regardless of whether they were diagnosed at the same time or in the following months and years.[13]

Our second patient is partiqularly unique since he achieved complete hematological remission after a single course of chemotherapy and then was successfully allo-transplanted despite secondary MDS/AML, his advanced age, present comorbidities and CD56 positivity of AML cells.[14]

In conclusion, one cannot make any definitive conclusions regarding secondary versus accidental nature of AML in patients treated for HCL with purine analogs. In other words, it is still not clear whether development of AML in patients with HCL is caused by mutagenic potential of the applied chemotherapy or by immune suppression/perturbations as a characteristic of the underlying disease.

Authors' Contribution

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

Not applicable.

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