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Therapy-Related Acute Myeloid Leukemia After Single-Agent Treatment With Fludarabine for Chronic Lymphocytic Leukemia

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A 70-year-old man with B-cell chronic lymphocytic leukemia (CLL) received single-agent treatment with the purine analogue fludarabine, which led to complete remission. After 8 years, he presented with pancytopenia. Marrow examination showed acute myeloid leukemia (AML) with trilineage myelodysplasia (MDS). Cytogenetic analysis showed an unbalanced der(1;7)(p10;q10) that resulted effectively in deletion 7q; confirming the diagnosis of therapy-related AML (t-AML). No residual CLL was present. Together with previous reports of secondary cancers after fludarabine treatment and the association of monosomy 7/7q- with another purine analogue azathioprine, results suggest that t-AML might develop after fludarabine therapy. Am. J. Hematol. 79:288–290, 2005. © 2005 Wiley-Liss, Inc.

Key words: pancytopenia; MDS; t-AML; fludarabine

INTRODUCTION

Secondary malignancies are increased in patients who have received chemotherapy or radiotherapy for the treatment of an initial malignancy. Therapy-related acute myeloid leukemia and myelodysplastic syndrome (t-AML/MDS) is particularly common after prior treatment with alkylating agents and topoisomerase II inhibitors [1]. It has been proposed that t-AML/MDS related to alkylating agents are associated with monosomies or deletions of the long arm of chromosomes 5 and 7, whereas those related to topoisomerase II inhibitors are associated with aberrations of 11q23 and the *MLL* gene [1].

The purine analogue fludarabine has been used for over a decade in the treatment of indolent B-cell lymphoid malignancies, including chronic lymphocytic leukemia (CLL) and other low-grade lymphomas [2]. Fludarabine is highly effective and results in durable remissions in many patients, so that its long-term safety has become an important issue. Although earlier studies indicated that fludarabine treatment did not result in a significantly increased risk of secondary malignancies [3], recent reports have suggested that there might be an association with t-AML/MDS [4,5].

In this report, we describe a patient who developed t-AML 7 years after single-agent treatment with fludarabine for CLL.

CASE REPORT

A 70-year-old man was found incidentally to have B-cell CLL (Rai stage 0) in 1996. Examination of the marrow showed infiltration by small lymphoid cells that expressed CD5, CD19, CD23, and weak surface immunoglobulin G with κ light chain restriction. The residual hematopoiesis was otherwise normal in morphology. After explanation of the indications,

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risks and benefits of treatment, he opted for single-agent therapy with fludarabine. Six monthly courses of fludarabine (25 mg/m^2/day × 5 days) were given, which resulted in complete remission with normalization of the blood count and bone marrow. He remained in complete remission until 8 years later, when he presented with fever and symptoms of anemia. Physical examination did not show any lymphadenopathy or organomegaly. A full blood count showed hemoglobin 8.0 g/dL, white cell count 1.8×10^9/L, and platelet count 32×10^9/L. Bone marrow examination showed trilineage myelodysplasia with 37% blasts, confirming the diagnosis of AML with multilineage dysplasia. There was no morphologic evidence of residual CLL. Cytogenetic analysis showed 46,XY,+1, der(1;7)(q10;p10) [3]/46,XY [6]. Owing to advanced age, the patient and his family accepted symptomatic treatment only.

DISCUSSION

The pathogenetic mechanisms of therapy-related secondary malignancies include direct oncogenic effects of chemotherapy and irradiation as well as immunosuppression leading to decreased immunosurveillance. The purine analogue fludarabine causes intense and prolonged immunosuppression, thus raising the concern that secondary malignancies might be increased. In an early study, fludarabine treatment of CLL patients was associated with a 1.65-fold increase in the risk of second malignancies (Table I) [3]. However, all of these patients had received prior chemotherapy including alkylating agents. Moreover, CLL per se might also increase the risk of second cancers [6]. Therefore, fludarabine therapy had not initially been regarded to be associated with secondary malignancies.

On the other hand, later studies have shown that fludarabine might predispose to t-AML/MDS (Table I). The risk was significantly increased when prior or concomitant chlorambucil had been administered [4]. Again, all of these patients had also received alkylating agents, so that the role of fludarabine in leukemogenesis was not clear.

Our patient had only received single-agent treatment with fludarabine, without the use of other chemotherapeutic drugs. The leukemia was characteristic of t-AML in showing trilineage myelodysplastic features. Furthermore, the unbalanced translocation der(1;7)(q10;p10), resulting effectively in monosomy 7q (7q−), was also typically found in t-AML/MDS [7]. Therefore, according to the current World Health Organization classification scheme, the leukemia was classified as t-AML.

The finding of 7q− in our patient is intriguing. In fact, monosomy 7/7q− is much more frequently related to prior treatment with alkylating agents. The mutagenic mechanisms of alkylating agents include DNA alkylation, cross-linking, and damage. In contrast, purine analogues act by incorporating themselves into the DNA molecule, as well as inhibiting DNA polymerases. Interestingly, although the putative mutagenic mechanisms of purine analogues are different from those of alkylating agents, the purine analogue azathioprine has been reported to cause t-AML/MDS with monosomy 7/7q− [8–10]. Our observations, together with one previously reported case of fludarabine-related t-AML with monosomy 7

TABLE I. Secondary Malignancies and Therapy-Related Myelodysplasia/Acute Myeloid Leukemia After Fludarabine Treatment*

Malignancies	Number	Latency (m)	Other chemotherapy	Cytogenetic analysis	Reference
Carcinoma of bladder	2	NA	Alkylating agents	—	Cheson et al. [3]
Hodgkin lymphoma	5	NA	Alkylating agents	—	
Carcinoma of colon	4	NA	Alkylating agents	—	
Carcinoma of liver	1	NA	Alkylating agents	—	
Carcinoma of lung	6	NA	Alkylating agents	—	
Leukemia	1	NA	Alkylating agents	—	
Head and neck cancer	2	NA	Alkylating agents	—	
Sarcoma	1	NA	Alkylating agents	—	
t-AML	2	30, 35	Chlorambucil	Complex karyotype in one case, including monosomies 5 and 7	Morrison et al. [4]
t-MDS	4	27,34,51,53	Chlorambucil	Complex karyotypes in two cases, including 5q and 7q aberrations in one case	
t-AML	2	NA	Chlorambucil	—	Astrow [5]
t-AML	1	12	—	Monosomy 7	
t-AML	1	88	—	Der(1;7)(q10,;10)	This report

*Abbreviations: latency, time from fludarabine to secondary malignancies, in months (m); NA, not available; t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome.

[5], suggest that purine analogues might also predispose to monosomy 7/7q− (Table I), possibly via a direct mutagenic effect.

In conjunction with the possible increased risks of solid tumors, our findings suggest that fludarabine might predispose to secondary malignancies either through immunosuppression, or a direct mutagenic effect. This proposition needs further evaluation by long-term studies.

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