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Case Report

Therapy related AML in a case of chronic lymphocytic leukemia

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Abstract: In comparison to the general population, patients with chronic lymphocytic leukemia (CLL) are at a higher risk of developing secondary malignancies. Several factors may contribute to pathogenesis, including direct effects of chemotherapy and radiation as well as the reduction of immune surveillance. Factors influencing the increased risk include the increasing age of CLL patients, chronic antigenic stimulation, and immune impairment related to CLL or chemotherapy. Compared to patients with acute myeloid leukemia (AML) that developed from de novo, therapy-related AML (t-AML) has had a poorer outcome. The range of cytogenetic abnormalities in therapy-related AML is comparable to that in de novo AML, although these patients have a significantly higher frequency of unfavourable cytogenetics, such as a complex karyotype or a deletion or loss of chromosomes 5 and/or 7. Herein, we describe a case of therapy-related AML with monocytic differentiation and t(8;16) with a residual CLL population. The aim of the present case is to highlight rare occurrence of therapy related AML with t(8;16) in CLL after fludarabine based chemotherapy (FCR: fludarabine, cyclophosphamide, and rituximab). This case also highlights flowcytometric immunophenotyping as an ideal tool to characterize secondary AML along with the identification of minimal residual disease of CLL clone, which could have ignored at t-AML diagnosis. The pathogenesis of myeloid and lymphoid malignancies as well as their co-existence can be studied by focusing on such patients. Factors predisposing to the development of t-AML should be studied further, which would help in monitoring these patients more carefully.

Keywords: Therapy-related AML, CLL, flow cytometric immunophenotyping, FISH, t(8;16), real time PCR

Introduction

Therapy-related acute myeloid leukemia (t-AML) is a type of secondary AML which is defined as AML that occurs as a late complication of cytotoxic chemotherapy and/or radiation therapy given to treat a prior neoplastic or non-neoplastic disease. In comparison to the others, patients with chronic lymphocytic leukemia (CLL) are at higher risk of secondary malignancy. Patients of CLL can get any type of second malignancy; in the majority of cases, this is transformed to an aggressive non-Hodgkin lymphoma (diffuse large B-cell lymphoma), prolymphocytic lymphoma, or Hodgkin's lymphoma [1]. Factors influencing the increased risk include advanced age of presentation in CLL patients, chronic antigenic stimulation, immunodeficiency, and pro-tumorigenic microenvironment in CLL patients, or immunosuppression caused by chemotherapy [2-4]. Clonal hematopoiesis of undetermined potential (CHIP) is common in older persons and is associated with an increased risk of therapy related myeloid neoplasms due to the higher age of presentation in CLL patients [2]. Therapy-related AML patients have a worse outcome compared with de novo AML patients. The cytogenetic abnormalities in therapy-related AML are similar to de novo AML, but more often have unfavorable cytogenetic features, such as a complex karyotype, monosomy 7, deletion of the long arm of chromosome 5 [del(5q)] and monosomy 5 etc. [5]. Herein, we describe a case of t-AML with monocytic differentiation and t(8;16) with a residual CLL population. The aim of the present case is to highlight the rare occurrence of therapy-related AML with t(8;16) in CLL after fludarabine based chemotherapy (FCR: fludarabine, cyclophosphamide, and ritux-

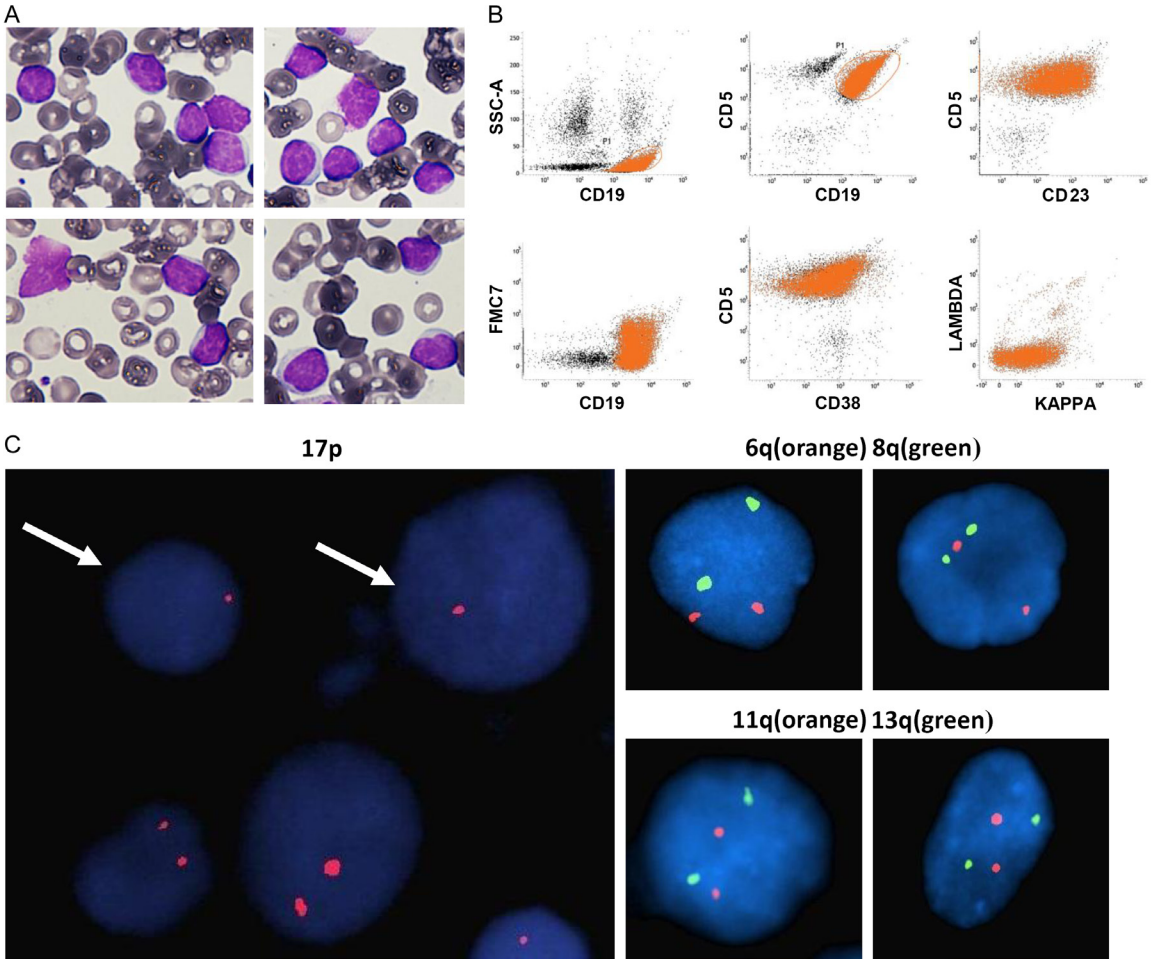

Figure 1. At initial diagnosis of CLL. A. Peripheral blood smear showing absolute lymphocytosis and presence of smudge cells (Leishman & Giemsa, 400×). B. FCMI showed CD19 positive abnormal lymphoid cells which were positive for CD5, CD23, CD38, kappa and negative for FCM 7 and lambda. C. FISH analysis showed positive for 17p deletion and negative for 6q, 8q, 11q and 13q deletion.

imab). This case also highlights flow cytometric immunophenotyping as an ideal tool to characterize secondary AML along with the identification of minimal residual disease of CLL clone that could have been ignored in the t-AML diagnosis.

Case presentation

A 51-year old man presented with shortness of breath on exertion for 1 month. Examination revealed cervical and axillary lymphadenopathy but no hepato-splenomegaly. His hemoglobin (Hb) was 139 g/L, total leucocyte count (TLC) was 80.93×10^9/L and his platelet count was 217×10^9/L. Peripheral blood smear (PS) (**Figure 1A**) showed leucocytosis with absolute lymphocytosis and the presence of smudge cells, compatible with chronic lymphoproliferative disease. Peripheral blood flow cytometric immunophenotyping (**Figure 1B**) showed these abnormal lymphoid cells were positive for CD19, CD5, CD23, CD200, CD38, CD20dim, CD22dim, kappa restriction, and negative for CD4, CD8, and FMC7; consistent with a diagnosis of CLL. Karyotyping revealed normal karyotype, 46,XY [20]. However, fluorescence in situ hybridization (FISH) (**Figure 1C**) for CLL panel revealed 17p deletion (17%) and was negative for 6q, 8q, 11q and 13q deletion. He was started on fludarabine, cyclophosphamide and rituximab (FCR) chemotherapy and completed 6 cycles. After chemotherapy, blood counts were normal and biochemical parameters were within normal range. After 1 year of completion of chemotherapy, the patient presented with pain in the upper and lower limbs. A positron emission tomography scan showed multiple medias-

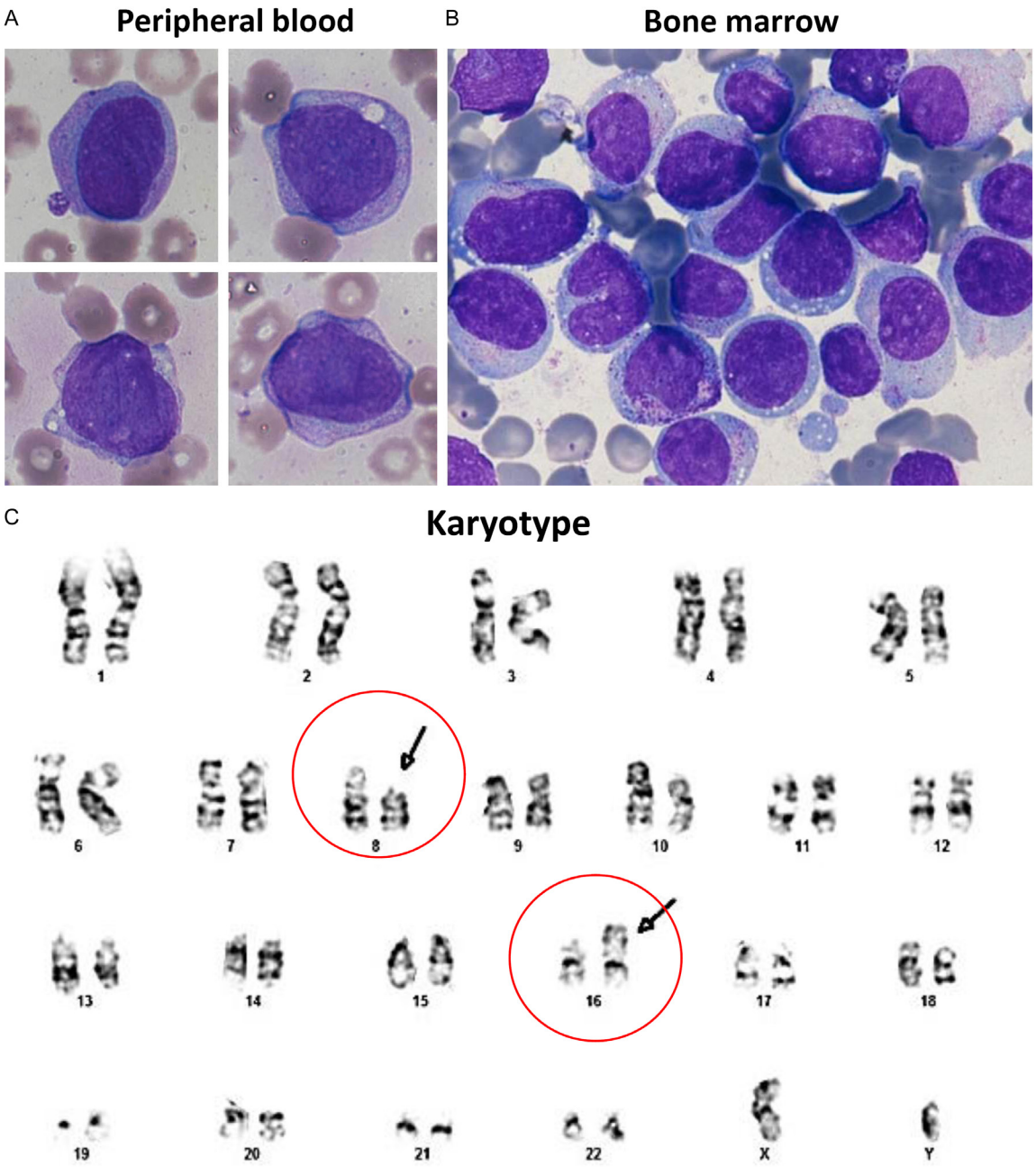

Figure 2. At diagnosis of therapy related AML. A. Peripheral blood smear (Leishman & Giemsa, 1000×). B. Bone marrow aspirate showing blasts and promonocytes (Leishman & Giemsa, 1000×). C. Karyotyping showed 46,XY, t(8;16)(p11.2;p13.3).

tinal, axillary and abdominal lymph nodes with mild diffuse bone marrow hypermetabolism and hepato-splenomegaly. CBC was Hb 66 gm/L, TLC: 3.6×10^9/L, Platelets: 20×10^9/L. PS and bone marrow aspirate (**Figure 2A**, **2B**) revealed the presence of 28% and 52% of blasts and promonocytes, respectively. Blasts are large with high nucleo-cytoplasmic ratio, lacy chromatin, a few with nuclear folding, 1-2 inconspicuous nucleoli, and abundant cytoplasm. On flow cytometric immunophenotyping (FCMI) (**Figure 3A**), these blasts were positive for CD33, CD64, HLA-DR, CD123, CD4, CD13 (partial), CD7 (dim), CD11b (partial), CD11c (heterogenous), CD14 (partial), CD117 (dim), CD56 and negative for cCD3, CD34, CD19, CD10, CD20, CD22, CD8,CD5, CD16, CD41a. There was a cell population constituting 1% of

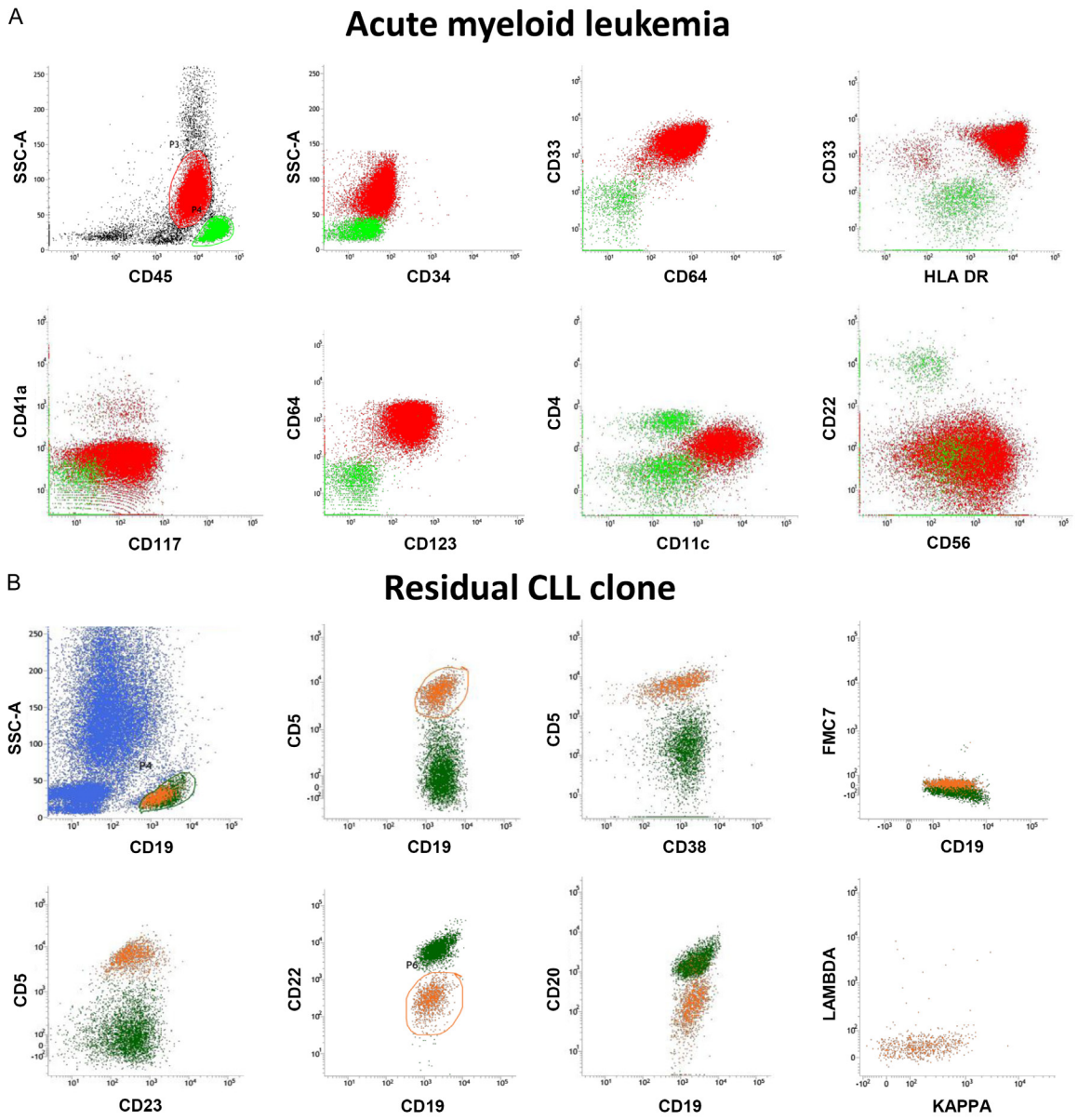

Figure 3. At diagnosis of therapy related AML. On FCMI (A), these blasts were positive for CD33, CD64, HLA-DR, CD123, CD4, CD11c (heterogenous), CD117 (dim), CD56 and negative for CD34, CD22, CD41a. (B) There is a residual abnormal lymphoid cell population constituting 1% of all nucleated cells which are CD19+CD5+CD23+ with FMC7 negative, CD22 (dim) and kappa restriction, corresponding to the diagnostic CLL clone.

all nucleated cells (**Figure 3B**), which were positive for CD19, CD5, CD23, IgM (weak), CD22 (dim), and kappa restricted, and FMC7 negative, corresponding to the diagnostic CLL clone. A diagnosis of therapy related AML with monocytic differentiation with residual CLL population was made. Karyotyping (**Figure 2C**) revealed 46,XY, t(8;16)(p11.2;p13.3) [20]. Real time polymerase chain reaction (qualitative) for BCR-ABL, *PML-RARA, AML ETO, INV 16* (p13q22)/t(16;16)(p13;q22) gene rearrangements, *NPM1* and *FLT3 (ITD/TKD)* mutations were negative.

Discussion

Secondary acute myeloid leukemia defined as AML arising from antecedent hematopoietic malignancies, such as myelodysplastic syndrome (MDS) or chronic myeloproliferative neoplasms, or myelodysplastic/myeloproliferative overlap syndromes or as a late complication in

patients receiving chemotherapy or radiation therapy for primary hematological and non-hematological solid malignancies (therapy-related AML). Therapy-related acute myeloid leukemia is generally defined as AML with prior history of cytotoxic chemotherapy, ionizing radiotherapy, and/or immunosuppressive therapy for an unrelated neoplastic or non-neoplastic disease [6]. This is a consequence of mutations in hematopoietic stem cells and/or the bone marrow microenvironment induced by these agents. In comparison to de-novo AML, it is associated with adverse cytogenetics and shorter survival. Compared with de novo AML, patients with t-AML do not have any specific clinical features except they are generally older. The diagnosis of t-AML is made by integrating overall morphological findings from peripheral blood and bone marrow, cytochemistry, FCMI, cytogenetics, and molecular findings [7]. Blasts are generally CD34 positive with the expression of myeloid antigens such as CD13, CD33 and myeloperoxidase. AML with monocytic differentiation, as in our case, expresses monocytic markers as CD64, CD14, and CD11c. Factors that predispose to poor outcome in these patients of therapy-related AML are advanced age, poor performance status, poor bone marrow reserve, an adverse karyotype, and the presence of certain mutations (as *TP53*) [8]. Therapy-related AML develops from a few months to several years following chemotherapy and/or radiation depending on several factors, including the type and dose of therapy and patient associated factors. It typically has a shorter latent period of 1-5 years in patients who received topoisomerase II inhibitors; and a longer latent period of 5-10 years in patients who received alkylating agents and/or radiotherapy [5]. In previously diagnosed cases of CLL, the occurrence of therapy-related myeloid malignancy (t-MN) (MDS/AML) is very rare, with an incidence of less than 1% [9]. The exact pathogenesis is not clear due to the rarity of the development of AML in CLL patients. Pathogenesis may involve direct cytotoxic effects of chemo and radiotherapy as well as immunosuppression. According to the literature, the occurrence of therapy-related myeloid neoplasm is associated with prolonged cytopenia caused by therapy [2]. As reported earlier, fludarabine may be associated with higher risks of therapy-related myeloid malignancies [10, 11]. Combination with other therapeutic agents causing DNA damage, such as cyclophosphamide or mitoxantrone, may further increase the risks of t-AML [12]. An enhancement of DNA damage affected progenitors in the bone marrow, which resulted in prolonged myelosuppression and impaired immune surveillance, thus increasing the risk of t-AML [13-15]. Laribi et al demonstrated the occurrence of 1.9% therapy-related myeloid neoplasms in CLL patients treated with fludarabine based chemotherapy (FCR/FC). Among them, only 0.3% of total patients (19.6% of t-MN) had therapy related AML [2]. The median time between CLL diagnosis and development of therapy related myeloid malignancy was 78.9 (12.6-305.6) months [2]. Morrison et al demonstrate 1.2% cases of therapy related myeloid neoplasm including 0.6% therapy related AML in a cohort of 521 cases of CLL after treatment with fludarabine and/chlorambucil with a median interval of 34 months from diagnosis and a median survival of 3.5 months after diagnosis of t-MN [9]. Other agents causing therapy-related AML are alkylating agents (busulfan, melphalan), nitrosureas and topoisomerase-II inhibitors [12]. The current case also highlights the uncommon possibility of AML with t(8;16) developing in a patient receiving fludarabine based chemotherapy for CLL. AML with t(8;16)(p11;q13) is a rare chromosomal abnormality, detected in 0.5% of AML and is associated with a poor prognosis. It is characterized by a high frequency of extramedullary disease, commonly leukemia cutis; frequent bone marrow hemophagocytosis, higher rate of therapy-related AML; frequent coagulopathy and morphologic features that mimic acute promyelocytic leukemia [16]. AML with t(8;16) mostly exhibits a monocytic differentiation with the presence of CD64, CD14, and CD11b and the absence of CD34 as reported in our case [16]. FCMI is an ideal tool to characterize secondary AML along with identification of minimal residual disease of CLL clone. Treatment for t-AML depends on type of AML as well as associated cytogenetic and/or molecular features and other patient factors as comorbidities and performance status [8]. In patients fit for chemotherapy, initial treatment involve conventional chemotherapy, 7+3, ideally followed by hematopoietic cell transplantation (HCT) [8, 17]. In patients with a prior history of anthracycline or with cardiotoxicity, alternative regimens are generally used as FLAG (fludarabine, cytarabine, and granulocyte colony-stimu-

lating factor), topotecan-cytarabine (TA), clofarabine-cytarabine (CLARA), and gemtuzumab ozogamicin [18]. Patients who are not candidates for intensive therapy may benefit from lower-intensity therapies. Other agents and combination regimens are currently being investigated in clinical trials. Azacitidine and the combination of venetoclax and decitabine have been proposed for the treatment of patients with t-AML who have concurrent active cancer [8, 19, 20]. Patients with t-AML are at high risk of relapse and the outcome after HCT remains poor [8]. Further studies on such patients could shed light on the pathogenesis of myeloid and lymphoid malignancies, their coexistence as well as prognosis of these cases. A deeper understanding of pathogenesis and predisposing factors in development of therapy-related acute myeloid leukemia in patients with lymphoid malignancies would help clinicians to better monitor these patients.

Disclosure of conflict of interest

None.

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