Therapy-related acute myeloid leukemia in patients with lymphoma: A report of four cases and review of the literature

DAN YANG[1*], XIAORUI FU[1*], XUDONG ZHANG[1], WENCAI LI[2] and MINGZHI ZHANG[1]

[1]Lymphoma Diagnosis and Treatment Center, Department of Oncology; [2]Department of Pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China

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Abstract. Due to advances in the treatment of lymphoma, the remission and overall survival rates for this disease have improved in recent years. However, the incidence of therapy-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) has increased. In order to further the understanding of the mechanisms of t-MDS/AML and reduce its incidence, the present study reports 4 cases of t-AML following treatment for lymphoma. The 4 patients presented aggressive forms of lymphoma in stage III/IV, and 3 were diagnosed with non-Hodgkin's lymphoma. All patients had previously undergone chemotherapy containing alkylating agents and/or topoisomerase II inhibitors. The latency period between the time of primary diagnosis and occurrence of t-AML ranged from 15 to 42 months. At the time of diagnosis of t-AML, 3 of the 4 patients presented pancytopenia, whilst the remaining patient exhibited leukocytosis. The majority of the patients succumbed to their disease within 1 year of t-AML diagnosis, with the exception of the patient in case 3, who survived following allogeneic hematopoietic stem cell transplantation (allo-HSCT). The present cases indicate that an advanced stage of disease at the time of primary diagnosis, prior exposure to radiotherapy, and administration of ≥4 regimens and ≥8 cycles of chemotherapy may be risk factors for the development of t-AML. Based on the present findings and a review of the literature, we propose that allo-HSCT should be recommended for patients at high risk of developing t-AML. In addition, chimeric antigen receptor T-cell immunotherapy may constitute a novel type of immunotherapy for the treatment of cancer, particularly for cases of relapsed and refractory lymphoma or leukemia.

Correspondence to: Professor Mingzhi Zhang, Lymphoma Diagnosis and Treatment Center, Department of Oncology, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road, Zhengzhou, Henan 450052, P.R. China
E-mail: mingzhi_zhang1@163.com

*Contributed equally

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Introduction

It is well known that chemotherapeutic agents and ionizing radiation are carcinogens, and may cause DNA damage through double-strand breaks and loss of elements of the DNA mismatch repair system, resulting in genomic instability (1,2). The development of hematopoietic neoplasms in patients who had received chemotherapy/radiation was first identified by Crosby *et al* in 1969 (3). In the 2008 World Health Organization (WHO) Classification of Hematopoietic Neoplasms (4), the International Agency for Research on Cancer recognized the unique characteristics associated with these myeloid neoplasms, and placed them under a separate category designated therapy-related myeloid neoplasm (t-MN). t-MNs are often referred to as therapy-related myelodysplastic syndromes (t-MDS) or therapy-related acute myeloid leukemia (t-AML). t-MDS/AML is a serious complication that may occur following chemotherapy/radiation treatment for malignancies or, more rarely, for non-malignant diseases. This may result from damage to normal hematopoietic stem cells and immune cells by anticancer regimens, leading to genetic mutations (5). According to the WHO 2008 classification system, diagnosis of t-MDS/AML is based on a clinical history of previous treatment for a primary malignancy and on hematological findings (6). Patients are diagnosed with t-MDS or t-AML if the percentage of blasts in the marrow is <20 or ≥20%, respectively (7). Treatment of t-MDS/AML with conventional therapy is associated with poor prognosis, with a median survival rate of 6-12 months (8). Therefore, reducing the risk of developing t-MDS/AML is of increasing importance.

The current study presents 4 cases of t-AML following lymphoma, in addition to a review of the literature, in order to analyze the pathogenesis, risk factors, clinicobiological features, treatment strategies and prognosis of t-AML, which may aid in understanding this type of cancer. Novel risk-adapted strategies aiming to decrease the incidence of t-MDS/AML in patients with lymphoma merit further investigation. In this regard, chimeric antigen receptor (CAR) T-cell immunotherapy constitutes a promising treatment for these patients.

Written informed consent for the publication of these reports was obtained from each patient or their family.

Case report

Case 1. An 87-year-old male was admitted to The First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China) on January 1st, 2014, complaining of dysphagia and a burning sensation of the tongue that had lasted for 4 months. The patient, who was also affected by heart disease, had been diagnosed with mixed cellularity classical Hodgkin's lymphoma of stage III at The Fifth People's Hospital of Zhengzhou (Zhengzhou, Henan, China) in December 2011 after complaining of cervical lymphadenopathy lasting for seven months. Consequently, 2 cycles of chemotherapy with cyclophosphamide (650 mg/m^2; days 1 and 8), vincristine (2 mg; days 1 and 8), procarbazine (100mg/m^2; days 1-14) and prednisone (40 mg/m^2; days 1-14) (28-day cycle) had been administered to the patient, followed by involved-field radiotherapy of the inguinal and cervical regions at 200 cGy x 20 and 200 cGy x 26, respectively, resulting in complete remission (CR).

At the time of the current admission, the patient presented spontaneous ecchymosis, and the complete blood cell (CBC) findings were as follows: White blood cell (WBC) count, 2.2x10^9 cells/l [normal, (4.0-10.0)x10^9 cells/l]; hemoglobin level, 119 g/l (normal, 130-175 g/l); and platelet count, 28x10^9 cells/l [normal, (100-300)x10^9 cells/l]. The levels of β2-microglobulin and lactate dehydrogenase were 3.08 mg/l (normal range, 0-3 mg/l) and 336 U/l (normal range, 75-245 U/l), respectively. A peripheral blood smear revealed numerous unclassified immature cells, which accounted for 37% of all cells (including mature red blood cells). On flow cytometry (FCM), this cell population accounted for 75.64% of all karyocytes, and exhibited positive expression of cluster of differentiation (CD)34, CD117, CD33, CD13 and human leukocyte antigen (HLA)-DR, and negative expression of CD14, CD16, CD11b and CD11c; these characteristics were consistent with non-promyelocytic AML (9). At the time of diagnosis, the patient exhibited blood-stained sputum, melena and a progressively reducing number of blood cells. The CBC findings were as follows: WBC count, 1.6x10^9 cells/l; hemoglobin level, 72 g/l; and platelet count, 3x10^9 cells/l.

The patient received palliative treatment without chemotherapy, due to his advanced age and Eastern Cooperative Oncology Group score of 4. The patient succumbed to hemorrhagic shock 2 days after diagnosis, on January 23rd, 2014.

Case 2. The patient was a 56-year-old male diagnosed with stage IV peripheral T-cell lymphoma who was first admitted to the People's Hospital of Anyang (Anyang, Henan, China) in May 2010 complaining of axillary lymphadenopathy which had lasted for 2 months.

During the subsequent 14 months, the patient received 16 cycles (each 21 days) of chemotherapy with 9 different regimens, consisting of the following: (i) 1 cycle of cyclophosphamide (750 mg/m^2; day 1) vincristine (1.4 mg/m^2, day 1; max 2 mg), adriamycin (50 mg/m^2; day 1) and prednisone (100 mg/day; days 1-5) (CHOP regimen); (ii) 1 cycle of CHOP regimen plus etoposide (100 mg/m^2; days 1-3); (iii) 2 cycles of cyclophosphamide (750 mg/m^2; day 1), vincristine (1.4 mg/m^2; day 1; max 2 mg) and prednisone (100 mg/day; days 1-5); (iv) 2 cycles of gemcitabine (1.0 g/m^2; days 1 and 8), cisplatin (25 mg/m^2; days 1-3), dexamethasone (20 mg/day; days 1-5) and thalidomide (200 mg/day; days 1-21); (v) one cycle of etoposide (100 mg/day, days 1-5), cytosine arabinoside (150 mg/day; days 1-5), cisplatin (25 mg/m^2; days 1-3) and dexamethasone (20 mg/day; days 1-5) (ESHAP regimen); (vi) 2 cycles of hydroxycamptothecin (6 mg/m^2; days 1-5), dacarbazine (60 mg/m^2; days 1-5) and methylprednisolone (80 mg/day; days 1-5); (vii) 2 cycles of gemcitabine (1.0 g/m^2; days 1 and 8), L-asparaginase (6000 U/m^2; days 1, 3, 5, 7, 9 and 11), oxaliplatin (100 mg/m^2; day 1) and methylprednisolone (80 mg/day; days 1-5); (viii) 2 cycles of gemcitabine (1.0 g/m^2; days 1 and 8), L-asparaginase (6000 U/m^2; days 1, 3, 5, 7, 9 and 11), cisplatin (25 mg/m^2; days 1-3) and dexamethasone (20 mg/day; days 1-5); and (ix) 3 cycles of hydroxycamptothecin (6 mg/m^2; days 1-5), mitoxantrone (5 mg/m^2; day 1), nedaplatin (80 mg/m^2; days 1) and dexamethasone (20 mg/day; days 1-5). However, the patient did not achieve CR and was admitted to The First Affiliated Hospital of Zhengzhou University in September 2011 for further treatment. At the time of admission, the bilateral supraclavicular and axillary lymph nodes were palpable, and CBC findings demonstrated a WBC count of 23.9x10^9 cells/l, which later increased to 70.3x10^9 cells/l, a hemoglobin level of 96 g/l and a platelet count of 106x10^9 cells/l, both of which reduced progressively. The peripheral blood smear identified numerous immature cells, and the bone marrow aspirate smears were predominantly composed of myeloblasts, which accounted for 86.8% of all nucleated cells. On FCM, this cell population displayed positive expression of CD34, CD33, CD13, CD7 and CD56, and negative expression of CD64, CD16, CD3 and CD79a. Consequently, the patient was diagnosed with AML French-American-British (FAB)-M2 subtype (9), and received a cycle of daunorubicin (45 mg/m^2; days 1-3) and cytarabine (150 mg/m^2; days 1-7) chemotherapy (DA regimen), and one of homoharringtonine (4 mg/day; days 1-7) and cytarabine (100 mg/day; days 1-7) (HA regimen) chemotherapy, accordingly.

However, half a month later, the patient presented hematochezia, and CBC findings revealed the following: WBC count, 52.8x10^9 cells/l; hemoglobin level, 41 g/l; and platelet count, 18x10^9 cells/l. The patient succumbed to hemorrhagic shock in December 2011.

Case 3. The patient, an 18-year-old female, was admitted to The First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China) due to a fever, and was diagnosed with T-cell lymphoblastic lymphoma at stage IV in April 2012. Following 6 cycles of chemotherapy, consisting of alternating 21-day courses of Hyper-CVAD regimen [cyclophosphamide (300 mg/m^2; q12h; days 1-3), vincristine (2 mg/day; days 4 and 11), doxorubicin (50 mg/m^2; day 4) and dexamethasone (40 mg/day; days 1-4 and 11-14)] and MA regimen [methotrexate (1 g/m^2; day 1) and cytarabine (1.5 g/m^2; q12h; days 2-3)], the patient achieved CR. Following admission to The First Affiliated Hospital of Zhengzhou University, mercaptopurine (50 mg/m^2; qd) and methotrexate administration (20 mg/m^2; q1w) was continued as maintenance treatment, as the patient refused allogeneic hematopoietic stem cell transplantation (allo-HSCT) and intravenous chemotherapy due to financial burden.

During follow-up on July 15th, 2013, the patient presented enlarged cervical and axillary lymph nodes, and the CBC findings were as follows: WBC count, 1.2x10^9 cells/l; hemoglobin

level, 82 g/l; and platelet count, $27x10^9$ cells/l. The bone marrow aspirate smears were predominantly composed of monoblasts, which accounted for 47.6% of all nucleated cells. On FCM, this cell population exhibited positive expression of CD34, CD38, CD117, CD11c, CD123, CD7 and HLA-DR, and negative expression of myeloperoxidase (MPO), cyclin (CYC)D3, CYCD79a, CYCD22, CD2, CD3 and CD5. The FCM results and the phenotype supported a diagnosis of AML FAB-M5 subtype (9). In addition, cytochemical staining demonstrated the cells to be positive for neuron specific enolase, which was inhibited by NaF.

The patient received sequential 7-day cycles of chemotherapy with the following: HA regimen (as in case 2); DA regimen (as in case 2); mitoxantrone (6 mg/m^2; days 1-3) and cytarabine (150 mg/m^2; days 1-7); and cytarabine (150 mg/m^2; days 1-7) and aclarubicin (40 mg/m^2; days 1-3). CR was achieved. Subsequently, the patient received allo-HSCT successfully, and was in good condition until the end of the follow-up period in August 2014.

Case 4. The patient, a 69-year-old female, who had suffered from cervical lymphadenopathy for 6 months, was admitted to The First Affiliated Hospital of Zhengzhou University in July 2009, and was diagnosed with stage III anaplastic large cell lymphoma. The patient had undergone 6 cycles (each 21 days) of chemotherapy with 3 different regimens: (i) 4 cycles of CHOP regimen (as described in case 2); (ii) 1 cycle of ESHAP regimen (as described in case 2); and (iii) 1 cycle of hydroxycamptothecin (6 mg/m^2; days 1-5), dacarbazine (60 mg/m^2; days 1-5) and methylprednisolone (80 mg/day; days 1-5). Although the patient achieved CR, the disease progressed a year later, as revealed by the enlargement of the bilateral cervical lymph nodes.

The patient subsequently received 1 cycle (21 days) of ifosfamide (2 g/day; days 1-3), mitoxantrone (5 mg/m^2; day 1) and dexamethasone (20 mg/day; days 1-5), in addition to involved-field radiotherapy of the cervical region (210 cGy x 10), between August 22nd and 31st, 2011. During follow-up on January 8th, 2013, the CBC findings were as follows: WBC count, $1.7x10^9$ cells/l; hemoglobin level, 69 g/l; and platelet count, $35x10^9$ cells/l. The bone marrow aspirate smears were predominantly composed of myeloblasts, which accounted for 82.8% of all nucleated cells. On FCM, the cell population exhibited positive expression of cytoplasmic (c)MPO, CD38, CD33, CD117 and CD56, and lacked the phenotype of mature cells. Furthermore, fluorescence *in situ* hybridization demonstrated the cells to be negative for eight-twenty-one, whilst Wilms tumor 1 expression was positive according to the results of polymerase chain reaction analysis. Therefore, the patient was diagnosed with AML FAB-M2 subtype (9), for which sequential chemotherapy was administered, consisting of the following: 1 cycle of HA regimen (as in case 2; 7-day cycle); 1 cycle of DA regimen (as in case 2; 7-day cycle); 2 cycles of aclarubicin (14 mg/m^2; days 1-4), cytarabine (6 mg/m^2; q12h; days 1-14) and recombinant human granulocyte colony-stimulating factor (200 μg/m^2; days 0-14) (14-day cycle); and 1 cycle of mitoxantrone (10 mg/m^2; days 1-3), etoposide (100 mg/m^2; days 1-5) and cytarabine (200 mg/m^2; days 1-7) chemotherapy (7-day cycle). However, the treatment was ineffective.

At 2 days after the final chemotherapy cycle, the patient presented a headache and nuchal rigidity, and computed tomography of the head indicated subdural effusion and cerebral hernia. The patient succumbed to cerebral hernia in September 2013.

Discussion

t-MDS/AML is a well-recognized clinical syndrome that occurs as a late complication following cytotoxic therapy used in the treatment of a variety of primary malignancies, including lymphoma, acute lymphoblastic leukemia, multiple myeloma and breast carcinoma (10,11). First identified by Crosby *et al* in 1969 (3), t-MDS/AML accounts for 10-20% of all cases of AML at present (4). Despite its rarity, its incidence has increased in recent years (12-14). Depending on the causative therapeutic exposure, two types of t-MDS/AML are recognized: Alkylating agent/radiation-related and topoisomerase II inhibitor-related (13,15). The former is associated with a longer latency period (5-8 years), presents with t-MDS, and exhibits an unbalanced loss of genetic material, typically involving chromosomes 5 and/or 7. By contrast, the topoisomerase II inhibitor-related type exhibits a shorter latency period (2-3 years), and is typically associated with overt leukemia without preceding MDS and frequent rearrangements involving the mixed lineage leukemia gene at the chromosome 11q23 (11,16-18). However, differentiation of patients with respect to the type of therapy that they had received for a previous malignancy is often not feasible as, in recent years, the majority of these patients are likely to have been exposed to alkylating agents and drugs targeting topoisomerase II (16). Therefore, the current WHO classification no longer subcategorizes therapy-associated myeloid neoplasms (4).

The 4 cases reported in the present study had received chemotherapy comprising alkylating agents and/or topoisomerase II inhibitors, with or without radiotherapy. The latency period ranged from 15 to 42 months, which is consistent with the data reported in previous studies, in which the latency period was observed to range from several months to several years, depending on the intensity of dose or overall dose of the preceding cytotoxic therapy, and on exposure to specific agents (19-22). A previous study determined the median time to develop of t-MDS/AML to be 3-5 years, and the risk of developing the disease was observed to be markedly reduced following the first decade after treatment (11). These observations are consistent with the data reported in the present study.

According to previous studies, the pathogenesis of t-MDS/AML is associated with: i) Abnormalities in DNA regulatory sequences, including chromosome breakage, rearrangement and complete or partial loss (7,10,23,24); and ii) the susceptivity of the hematopoietic progenitor cells (25).

In the present report, all the patients presented t-MDS/AML of III/IV stage. The patients of cases 1 and 4 had experienced radiation therapy, and those of cases 2 and 4 had been treated with ≥4 chemotherapy regimens and had received ≥8 cycles of chemotherapy. In previous retrospective studies of patients with lymphoma receiving autologous stem cell transplantation (ASCT), multivariate analyses suggested that high-dose therapy, including total-body irradiation (TBI), was associated with an increased risk of developing t-MDS/AML (24,26-28).

By contrast, in a case-control study of 56 patients with t-MDS/AML, TBI at doses of 12 Gy was not observed to increase the risk of developing t-MDS/AML (29). In their review, Armitage *et al* (26) concluded that, unlike subtotal nodal irradiation or TBI, involved-field radiotherapy is unlikely to be associated with a significant risk of developing t-MDS/AML. In addition, previous studies identified the following independent risk factors for the development of t-MDS/AML: i) Prior exposure of the patient to radiation therapy; ii) ASCT preceded by ≥4 chemotherapy regimens; and iii) apheresis lasting >5 days in order to harvest a sufficient number of stem cells (15,28,30-32). Therefore, the advanced stage of the primary tumor at the time of diagnosis, previous exposure to radiation therapy, and ≥4 regimens and ≥8 cycles of chemotherapy, may be considered the most significant risk factors for developing t-MDS/AML.

According to previous studies, >90% patients that developed t-MDS/AML presented an abnormal karyotype, and the cytogenetic abnormalities often correlated with the length of the latency period and the previous exposure to cytotoxic therapy (7,11). Lillington *et al* (24) and Micallef *et al* (23) analyzed the karyotype of patients at the time of diagnosis of t-AML, and detected complex karyotypes in ~75% patients, particularly complete or partial loss of chromosomes 5 and/or 7; mutations and internal tandem duplications in the nucleophosmin and Fms-related tyrosine kinase 3 genes were less frequent (10).

The ages of the patients in the present report ranged from 18 to 84 years (mean, 58 years old). The primary diagnosis of the patient of case 1 was Hodgkin's lymphoma, while the other patients presented T-cell non-Hodgkin's lymphoma. All cases were aggressive and of advanced stage. When t-AML subsequently developed, all 4 patients experienced anemia, whilst 1 patient (case 1) presented hemorrhage, 1 (case 4) exhibited fever, 2 (cases 2 and 3) presented lymphadenopathy, and none displayed hepatosplenomegaly. Compared with *de novo* AML, t-AML is characterized by the following clinical features: i) t-AML occurs more commonly in older patients; ii) the majority of patients with t-AML present bone marrow failure to variable extents, including anemia, hemorrhage, fever and tissue infiltration; iii) infections are common among patients with t-AML, who may display low temperature or high fever, although certain patients may not exhibit an obvious infection site; iv) 5% of the patients present hepatosplenomegaly and/or lymphadenopathy; and v) in serious cases, patients may develop septic shock or sepsis, which is a common cause of mortality from t-AML (10,14,33).

Conventional chemotherapy is less effective as a treatment for t-AML than for *de novo* AML, and is associated with poor prognosis, as t-AML exhibits multidrug resistance (34,35). The median survival time of patients with t-AML is 6-12 months (8). In the present report, the majority of patients died within 1 year of t-AML development, with the exception of the patient in case 3, who is currently experiencing complete remission following allo-HSCT. Therefore, allo-HSCT remains a promising option for the treatment of t-AML, although it has been previously reported that ASCT may increase the incidence of t-AML (15,32,36,37). However, patients with therapy-related acute promyelocytic leukemia (APL) who receive homogeneous APL therapy containing all-trans retinoic acid and idarubicin regimens may have a better prognosis compared with cases of non-promyelocytic AML. Studies have reported that the rates of CR, 4-year event-free survival and overall survival for these patients are 97, 65 and 85%, respectively (33,38). By contrast, elderly patients, those with AML FAB-M1 or -M2 subtype caused by alkylating agents, and those presenting -5 or 5q- and -7 or 7q- chromosomal rearrangements, tend to have a poorer prognosis (23,39).

In order to reduce the incidence and improve the CR rate of t-AML, novel strategies have been explored, including chimeric antigen receptors (CARs), which are recombinant receptors that combine the specificity of an antigen-specific antibody with the functions of activating T-cells. Recent studies regarding the use of CAR T-cells for the treatment of relapsed and refractory lymphoma and leukemia indicate promising results for cancer immunotherapy in the future (39-41).

With the population of cancer survivors growing, attention must be focussed on the prevention of t-MDS/AML. It is important to further the understanding of the mechanisms of t-MDS/AML and to apply this knowledge to clinical strategies in order to reduce the incidence of the condition. Furthermore, it is necessary to emphasize and control the indication and dosage of alkylating agents and topoisomerase II inhibitors for clinicians, and to explore new drugs that are able to protect stem cells. Immunotherapy eliciting specific cellular immune responses against cancer cells, such as CAR T-cell therapy, may have a major impact in cancer therapy, and increasing its variety and enhancing its effectiveness requires collective efforts.

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