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Clinical analysis of 14 cases of breast cancer therapy-related acute myeloid leukemia

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Summary

Purpose: This study aims to summarize the clinical characteristics, treatment, and prognosis of breast cancer therapy-related acute myeloid leukemia (t-AML). *Materials and Methods:* Fourteen breast cancer patients with t-AML were enrolled, and their clinical characteristics, laboratory test results, treatment, and outcomes were retrospectively analyzed. Nine patients underwent bone marrow chromosome examination, of which five had balanced chromosomal translocations. Moreover, nine patients underwent fusion gene testing, and all nine cases were positive. *Results:* Three out of four patients with the M3 French–American–British subtype were in complete remission induced by treatment with tretinoin and daunorubicin; the fourth case stopped the chemotherapy. The remission rate of eight non-M3 patients with t-AML, who all received chemotherapy, was 50%. Breast cancer patients with t-AML were common in this study and had abnormal cytogenetics and molecular biology. *Conclusions:* Moreover, M3 breast cancer patients with t-AML achieved complete remission after chemotherapy, but non-M3 patients had a low remission rate.

Key words: Therapy-related; Acute leukemia; Breast cancer.

Introduction

Therapy-related acute leukemia (t-AL) is a well-recognized clinical syndrome that occurs as a late complication following cytotoxic therapy (chemotherapy or radiotherapy) for a variety of primary neoplastic or non-neoplastic diseases [1]. In 2008, the World Health Organization (WHO) classified this disease as a myeloid neoplasm in their classification of hematopathology. It is also called therapy-related myelodysplastic syndrome/myeloproliferative neoplasm (t-MDS/MPN), or therapy-related acute myeloid leukemia (t-AML). The chemotherapy drugs for treatment of t-AML/t-MDS, such as alkylating agents and topoisomerase II inhibitors, were classified as dependent subtypes [2].

Among all tumors that can lead to t-AL, lymphoma and breast cancer are the most common [3]. Authoritative data published by the Ministry of Health of China in 2012 showed that the incidence of breast cancer was highest among all malignant tumors in women and that breast cancer severely threatens the physical and mental health of women [4]. In the late 1950s, with the widespread use of alkylating agents, anthracycline, and biological agents, survivors of breast cancer significantly increased in number [5]. However, a number of studies indicate that the cumulative dose and frequencies of radiotherapeutics and chemotherapeutics (especially alkylating agents and topoisomerase II inhibitors) in patients with breast cancer leads to a higher risk of occurrence of t-AL, despite improving the survival of patients [6].

Some studies reported that the incidence of t-AL was 2–6% [3] after treatment for leukemia, but the incidence of t-AML/t-MDS/MPN has been reported to be 10–20% after treatment for AML [7, 8]. In addition, previous international studies have reported cases of breast cancer t-AML [9], but few cases have been reported in the present country; therefore, the authors retrospectively analyzed the characteristics, treatment, and prognosis of 15 patients with breast cancer t-AML at the First Affiliated Hospital of Guangxi Medical University from January 2003 to February 2015.

Materials and Methods

The clinical data of 14 female breast cancer patients with t-AML at the First Affiliated Hospital of Guangxi Medical University from January 2003 to February 2015 were collected. The patients were diagnosed with breast cancer by pathological examination. The definition of t-AML complied with the syndrome of acute leukemia after the breast cancer patients were treated with chemotherapy or radiotherapy. The median age of onset of t-AML was 46 years, ranging from 37 to 66 years. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Guangxi Medical University. Written informed consent was also obtained from all participants.

After marrow cells and peripheral blood cells were stained using the Wright-Giemsa method, cell morphology at different

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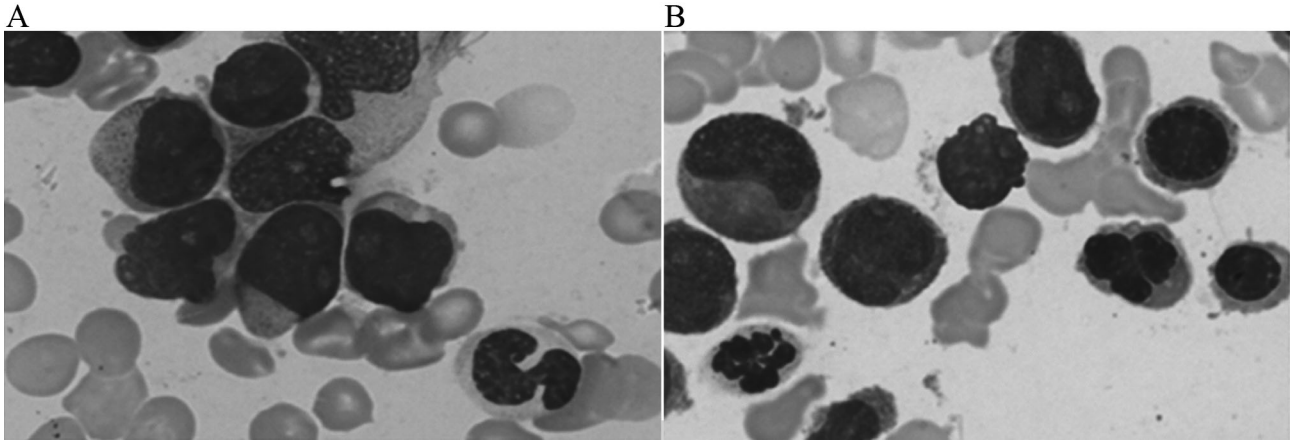

Figure 1. — Results of bone marrow cytomorphologic examination (×100, Wright staining). (A) The monocytes are out of shape, with multiple nucleus and abnormal growth of cells body (No. 6 patient). (B) The red cells have hypersegmentation of nucleus and megaloblastoid change (No. 11 patient).

stages was observed under an optical microscope. Flow cytometry was used to detect the surface antigens of the marrow cells.

A single karyotype was separated from the marrow cells and incubated for 24 hours, followed by preparation of chromosome specimens. The G-banding method was used to analyze the karyotypes with the International System for Human Cytogenetic Nomenclature (ISCN) 2009 [10]. Marrow specimens were tested for leukemia-related genes at the Wuhan Kangshengda Medical Laboratory Institute.

All patients were followed up via telephone and at an out-patient clinic through March 1, 2015.

Results

Fourteen breast cancer patients with t-AML were identified. They represented 1.31% (14/1068) of the patients with adult primary acute leukemia treated in the present hospital during the study period. According to the French–American–British (FAB) classification, there were two cases of M2, four cases of M3, four cases of M4, and four cases of M5. All patients had no relevant environmental or toxicity exposure before the disease onset. The median period of latency from the use of cytotoxic drugs or radiotherapy to the onset of t-AML was five years (1.5-12 years).

Breast cancer pathological type results showed that there were five cases of infiltrating ductal carcinoma (35.7%), five cases of adenocarcinoma (35.7%), three cases of infiltrating lobular carcinoma (21.4%), and one case of medullary carcinoma (7%). The radiotherapy and chemotherapy details for patients post breast cancer surgery are as follows: one patient received radiotherapy, eight patients received chemotherapy, and five patients received radiotherapy plus chemotherapy. Additionally, eight patients had taken alkylating agents and Pt, and ten patients had taken anthracyclines.

In 14 patients, the initial clinical manifestation included 14 cases of anemia (100%), ten cases of bleeding (67%), seven cases of infection (47%), four cases of sterna pain (27%), two cases of gingival invasion (13%), three cases of swelling of the liver, spleen, and lymph nodes (20%); and one case of infiltration of the central nervous system (7%).

Eight of 14 (57%) patients had dysplasia of the bone marrow indicated by bone marrow cytomorphologic examination results, mainly presenting as a granuloid and erythroid hematopoietic disorder. Primarily, granulocytes or monocytes were seen, with increased irregular karyolobism and abnormal growth of the corpus, erythrocyte megaloblastic changes, nuclear budding, and cenocytes (Figure 1, patient No. 6 and 11).

Ten patients underwent immunological examination for leukemia, and ten cases were CD33+, ten were CD13+, nine were CD117+, seven were CD64+, seven were CD15+, three were CD14+, and ten were CD34-. Four patients had lymphocytic CD7 expression.

In this study, ten patients underwent bone marrow chromosome examination and the characteristics identified were as follows: 46, XX in four cases, 46, XX, t(15;17)(q22;q21) in three cases, 46, XX, t(8;21) (q22;q22) in two cases, and 46, XX, t(4;11) (q21;q23) in one case. Ten patients underwent fusion gene detection and gene mutation detection, and there were four cases with *PML-RARα*, two cases with *AML1/ETO*, one case with *MLL*, one case with *FLT3/ITD*, one case with *CEBPA* gene, and two negative cases. The *NPM1* gene was not detected.

For treatment, the t-AML (M3) remission + induction program was ATRA plus daunorubicin and the t-AML (not-M3) remission + induction program was IA, DA, and HA

Table 1. — *Clinical characteristics and treatment of 14 breast cancer patients with t-AML.*

No.	Age (year)	Period of latency (year)	FAB type	Bone marrow chromosome	Fusion gene	Induced regimen and effect	Survival time (month)
1	51	1.5	AML-M3	*46, XX*	PML-RARα	ATRA+DNR(CR)	10
2	46	4	AML-M3	*46, XX, t(15; 17)(q22; q21)*	PML-RARα	ATRA+DNR(CR)	Missing
3	45	10	AML-M3	*46, XX, t(15; 17)(q22; q21)*	PML-RARα	ATRA+DNR (CR)	15
4	40	6	AML-M3	*46, XX, t(15; 17)(q22; q21)*	PML-RARα	Abandoning treatment	1
5	53	12	AML-M2	*46, XX, t(8; 21)(q22; q22)*	AML1/ETO	DA(CR)	5
6	43	1.5	AML-M5	*46, XX*	—	DA(NR)	2
7	40	7	AML-M5	—	—	IA(CR)	Missing
8	44	5	AML-M4	*46, XX*	FLT3/ITD	IA(NR)HA(NR)	6
9	51	2.5	AML-M5	—	Negative	IA(NR)	4
10	50	12	AML-M4	*46, XX*	Negative	IA(NR)HA(NR)	Missing
11	66	2.5	AML-M4	—	—	Abandoning treatment	6
12	37	5	AML-M4	—	—	DA(CR)	Until now PFS 24 months
13	50	4	AML-M2	*46, XX, t(8; 21)(q22; q22)*	AML1-ETO/CEBPA	IA(CR)	Until now PFS 18 months
14	57	6	AML-M5	—	—	Abandoning treatment	6

AML: acute myelocytic leukemia; CR: complete remission; NR: no remission; PFS: progression-free survival; DA: daunorubicin (DNR) plus aracytidine (Ara-C); HA: homoharringtonine (HHT) plus aracytidine (Ara-C); IA: darubicin plus aracytidine (Ara-C); ATRA: all-trans retinoic acid; "—": not examined.

(Table 1).

Through the end of follow-up (March 1, 2015), there were nine deaths, three cases with missing follow-up, and two survivors. The mortality rate, survival rate, and missing rate were 64.3%, 14.3%, and 21.4%, respectively. Except for one patient with t-AML (M3) who abandoned treatment and died after one month, three of the four patients with t-AML (M3) were in complete remission after treatment with ATRA and DA. However, one patient was not followed up after leaving the hospital and two patients who could not undergo the maintenance treatment died of leukemia recurrence after ten and 15 months, respectively.

In the ten patients with not-M3 t-AML, two abandoned chemotherapy. The others received chemotherapy and the remission rate was 50% (4/8). In four patients without remission, one patient was lost to follow up and three patients died. Furthermore, two of four patients with complete remission maintained treatment and were alive until now, with survival times of 24 and 18 months, respectively. One case was treated irregularly and died of recurrence of leukemia after five months and one case failed to be followed up. Patients with t-ALL who had complete remission after the VDLP regimen did not maintain chemotherapy or failed to be followed up.

Discussion

With increases of the cure rate for breast cancer patients, the incidence of t-AML in the breast cancer survivors gradually rose. In this study, 1,068 patients were diagnosed with AML (0.97%), of which 14 cases were breast cancer treatment related t-AML (1.31%), and the median latent period was 60 months. Previous studies reported that acute myelocytic leukemia was common after primary acute leukemia and t-AML was the most common type, around 90% to 95% of cases, with only 5% to 10% of t-ALL cases [11]. Howard *et al.* [12] followed up 376,825 women with breast cancer for a median of 8.9 years, and there were 411 cases of t-AL (0.1%), among which there were 363 cases of t-AML (88.3%) and 48 cases of t-ALL (11.7). The median latent time ranged from 48 to 60 months.

Because of repeated cytotoxic treatment, and with an increase in age, the immune function of patients becomes weaker and bone marrow hematopoiesis function decreases which results in poorer outcomes for patients with t-AL. The present authors found that three out of four patients with t-AML (M3) were in complete remission after treatment with retinoid and daunorubicin. However, economic problems limited patients from continuing treatment and two patients finally died of recurrence of leukemia and one patient dropped out.

Presently, there is still controversy about the treatment of t-AML. Only t-APL (AML-M3) has a good response. Aldoss and Pullarkat [13] reported that t-AML (M3) had similar outcomes to primary AML-M3, which supports the use of the same regimen for t-AML (M3). This finding is similar to the present results. Takeyama *et al.* demonstrated that 85 of 256 patients with TRL/MDS (46%) were in complete remission. The median remission duration was 8.2 months and overall median survival was only 9.7 months [14]. The present study showed that the chemotherapy remission rate was only 50% (4/8) in non-M3 t-AML patients, which is similar to Takeyama *et al.*'s result. Other studies suggested azacitidine be used to treat patients with t-AML with an effective rate of 38%, which is not significantly different from patients with primary AML (45%), but the overall sur-

vival of patients with t-AML (14%) was significantly shorter than that of patients with AML (33.9%) [15].

Allogeneic transplantation allows 20–50% patients to have long-term disease free survival [16, 17]. Spina *et al.* analyzed 29 patients with allogeneic transplantation and their two-year overall survival and disease free survival was 37% and 34%, respectively [16]. Patients who have a poor prognosis and general condition are suggested to undergo transplantation at the proper time. The 14 breast cancer patients with t-AML in this study did not receive allogeneic transplantation, and only two patients (M2 and M4) are still alive. In summary, the prognosis of patients with t-AML is poorer than patients with primary AL, regardless of treatment.

Related studies indicated that alkylating agents, such as cyclophosphamide [18] and platinum [19], have a dose dependent risk of causing t-AML. The mean period of latency of t-AML has been reported to be five to seven years after completion of treatment, and t-AML mostly had primary manifestations of MDS and then acute leukemia [1]. In this study, eight of 14 patients with t-AML were treated with alkylating agents, and the median period of latency was four years, which is similar to previous reports.

Anthracyclines used for treatment of breast cancer are DNA topoisomerase II inhibitors, without primary MDS manifestations. The latency period before t-AML has been reported to range from one to ten (median: two to three) years, and the risk of leukemia increases with an increase of cumulative dose [6]. Ten patients from this study were treated with anthracycline drugs and their median period of latency was about five years, which is not consistent with previous studies. This might be because the few patients in the present study do not represent the general population, and some patients in this study also used other chemotherapeutics, such as 5-fluorouracil [20] and docetaxel [21], which are possibly related to t-AL. Whether they can cause t-AML when combined with alkylating agents and topoisomerase II inhibitors needs to be studied further.

Some studies have reported that radiotherapy led to t-AML [22, 23]. One of our patients with radiotherapy and five patients with a combination of radiotherapy and chemotherapy suffered from t-AML. However, this study had few patients with radiotherapy; the relationship between radiotherapy and therapy-related acute leukemia requires more patients for further study.

A previous study [24] confirmed that the clinical manifestation is not different between t-AML and primary AML. Both t-AML and AML present with anemia and bleeding as the first major symptoms and infection and infiltration as the second major symptoms. Bone marrow dyshematopoiesis is commonly seen in patients with t-AL, especially after use of alkylating agents to treat t-AML. In this study, eight patients (57%) developed bone marrow dyshematopoiesis, which is consistent with previous reports.

Praga *et al.* [6] found that in 7,110 patients treated with epirubicin-containing regimens, 25 patients developed t-AML and types M4, M2, and M5 were commonly seen, and three patients developed t-ALL. In this study, there were four cases of M5 and three cases of M4, which is consistent with the Praga *et al.* study. The rates of M3 and M2 were 27% and 13%, respectively, which is a significant difference from the Praga *et al.* study. This obvious difference might be correlated to the small number of patients. Additionally, many studies [25] have reported that lymphoid expression is found in AMLs, with CD7 as the major expression. Their prognosis is poor compared with primary AML. In this study, ten patients with t-AML underwent immunologic examination and the authors found four cases with CD7 expression, in which one case was in complete remission after chemotherapy.

For abnormal chromosomes, t-AML/MDS is more frequently seen than AML/MDS with an incidence of 76–90% and 48–66%, respectively. t-AML induced by alkylating agents commonly presents with an abnormal chromosome 5 or 7. t-AML induced by topoisomerase II inhibitors usually involves 11q23 or 21q22, which is a balanced translocation [24]. Marrow chromosome examination was performed in nine breast cancer patients with t-AML in this study, all of whom had used alkylating agents and topoisomerase II inhibitors. Five cases (55.6%) had an abnormal karyotype with balanced translocations. An abnormal chromosome 5 or 7 was not found.

Nardi *et al.* reported [23] t-AML/MDS induced by radiotherapy had a balanced translocation. After four breast cancer patients received radiotherapy, two underwent chromosome examination, and one case that was treated with alkylating agents and topoisomerase II inhibitors had a balanced translocation; thus, whether abnormal chromosomes are correlated with radiotherapy cannot be determined.

From the molecular biological study of t-AML, it is generally believed that *FLT3/ITD* is a gene indicating a poor prognosis of t-AML. In this study, only one case was found to have the *FLT3* gene. This patient did not achieve complete remission after chemotherapy using darubicin plus aracytidine and homoharringtonine plus aracytidine.

In conclusion, with an increase in the cure rate of breast cancer, the incidence of breast cancer t-AML has also increased. The results of this study are consistent with those of most previous studies. However, because of economic limitations, unfortunately, some patients give up treatment at the beginning or during chemotherapy, ultimately leading to disease progression.. Clinical physicians should pay attention to prevention, early detection and diagnosis, and early treatment as principles to help patients prolong their survival time.

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