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Breast cancer

Secondary acute leukemia following mitoxantrone-based high-dose chemotherapy for primary breast cancer patients

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Summary:

The incidence of secondary myelodysplasia/acute myeloid leukemia (AML) was retrospectively assessed in an international joint study in 305 node-positive breast cancer patients, who received mitoxantrone-based high-dose chemotherapy (HDCT) followed by autologous stem cell support as adjuvant therapy. The median age of the patients was 57 years (range 22–67). In all, 268 patients received peripheral blood stem cells, and 47 patients received autologous bone marrow. After a median follow-up of 57 months (range 10–125), three cases of secondary AML (sAML) were observed, resulting in a cumulative incidence of 0.94%. One case of sAML developed 18 months after HDCT (FAB M3) The karyotype was translocation 15;17 and, after induction therapy, the patient underwent autologous stem cell transplantation, and is in complete remission (CR) of both breast cancer and AML. The second patient developed AML (FAB M4eo with inversion 16) 5 months after HDCT. This patient achieved CR after induction therapy, but died of infectious complication. A third patient developed AML (FAB M4) 6 months after HDCT. She achieved CR after induction therapy, but relapsed and expired 28 months after diagnosis of AML. sAML after mitoxantrone-based HDCT is a possible, but rare complication in breast cancer patients.

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Secondary myelodysplasia (MDS) or acute myeloid leukemia (AML) in breast cancer patients is a rare but well-known long-term complication of prior chemotherapy or radiation therapy as adjuvant therapy.[1–3] Specific risk factors are the combinations of chemotherapy and radiation therapy, the cumulative dose of alkylating agents and the duration of therapy.[2] Two different types of treatment-related leukemia can be distinguished. The first type results from prior therapy with alkylating agents or radiation therapy, and occurs after a latency period of 5–7 years. This type of AML is often preceded by a preleukemic period of MDS. Nearly 90% of the patients with alkylating agent-related MDS or AML show clonal chromosome aberrations including monosomy or deletions on chromosomes 5 and/or 7 or complex aberrations involving chromosomes 3, 12, 17, and 21.[4] The second type of therapy-related leukemia is induced by topoisomerase II-targeted drugs like etoposide, anthracyclines or, recently, anthracenediones.[5–7] This type of AML usually occurs after a median of 2 years and is not preceded by a myelodysplastic syndrome. According to the French–American–British (FAB) classification, more frequently, M4 or M5 subtype is observed and cytogenetic analysis showed a high frequency of rearrangements of the chromosome band as 11q23, translocation (t)(8;21), t(15;17), inversion 16 (inv(16)) or t(8;16), as in *de novo* AML.[5,8] Recently, several studies indicated that adjuvant chemotherapy consisting of the anthracenedione mitoxantrone, a topoisomerase II-targeted drug, may induce secondary AML (sAML) in up to 8% of patients[7,9,10–15] (see Table 1). Few studies investigated the risk of secondary MDS/AML after high-dose chemotherapy (HDCT) in breast cancer patients, suggesting a similar incidence as conventional chemotherapy.[16–19] Mitoxantrone is part of several high-dose chemotherapy regimens followed by autologous stem cell transplantation in breast cancer patients.[20–23] In the present study, we evaluate the incidence of secondary MDS/AML in 305 breast cancer patients after mitoxantrone-based high-dose conditioning regimens, followed by autologous stem cell transplantation in a joint analysis of the Solid Tumor Working Party of the European Group for Blood

Table 1 Literature of mitoxantrone-based chemotherapy and incidence of secondary MDS/AML in breast cancer patients

Study	*Patient number*	*Patients with MDS/AML*	*Actuarial incidence*	*Therapy*
Saso (9)	1774	9	1.6%	Mitoxantrone and MTX or mitoxantrone/MTX and mitomycin C
Linassier (7)	350	2	0.7%	Mitoxantrone based
Chaplain (15)	449	7	2.2%	Mitoxantrone-based chemotherapy
	263	6	3.5%	$\geqslant 13\,mg/m^2$ Mitoxantrone
Kumpulainen (10)	196	16	8.1%	Mitoxantrone/5-fluorouracil/cyclophosphamide
Cremin (14)	59	3	5%	Mitoxantrone based
Mitchell (12)	577	3	0.5%	Mitoxantrone based
Andersson (24)	71	5	7%	Mitoxantrone/prednimustine/MTX, 5-Fluorouracil and Tamoxifen
Kröger (present study)	305	3	0.9%	Mitoxantrone-based high-dose chemotherapy

Table 2 Conditioning regimens for high-dose chemotherapy

Study group	*High-dose conditioning regimen*	*Patient (n)*
GABG	Mitoxantrone $40\,mg/m^2$, thiotepa $600\,mg/m^2$, cyclophosphamide $6000\,mg/m^2$	133
UCSF	Mitoxantrone $24–60\,mg/m^2$, thiotepa $600\,mg/m^2$, cyclophosphamide $6000\,mg/m^2$	118
EBMT	Mitoxantrone $45\,mg/m^2$, cyclophosphamide 120 mg/kg, melphalan $140\,mg/m^2$	54

GABG = German Adjuvant Breast Cancer Study Group; UCSF = University of California, San Francisco; EBMT = European Group of Blood and Marrow Transplantation.

and Marrow Transplantation (EBMT), the German Adjuvant Breast Cancer Study Group (GABG), and the University of California, San Francisco (UCSF).

Materials and methods

Patient population and data collection

In all, 305 patients with node-positive breast cancer had received mitoxantrone-based HDCT followed by autologous stem cell transplantation as adjuvant therapy between July 1990 and December 1998. All centers of the EBMT received a questionnaire for the transplanted patients. The patients of the GABG and the UCSF were treated in phase II or III protocols and monitored closely. A total of 305 patients were evaluable to calculate the incidence of secondary myelodysplastic syndromes or leukemias. All patients were high-risk patients with at least more than three involved lymph nodes, either stage II/III or IIIB. The different conditioning regimens are listed in Table 2. Most of the patients received four to six cycles of anthracycline-based induction chemotherapy prior to HDCT. Patients with stage IIIB generally received in the San Francisco study two to four premastectomy cycles of chemotherapy, followed by one to two more cycles prior to HDCT. In all, 251 patients received a locoregional radiotherapy of the chest wall or breast including the regional lymph nodes (supraclavicular and axillary), but detailed analysis of radiotherapy was not available in all patients. In 54 patients, no data of radiotherapy were available. Usually patients with positive hormonal receptor status received 20–30 mg tamoxifen for a planned 5 years post HDCT. The median age of the patients at the time of stem cell transplantation was 46 years (range 22–67). The stem cell source was bone marrow in 47 patients and peripheral blood stem cells in 258 patients.

Statistical analysis

The time to MDS/AML is the interval from HDCT to diagnosis of MDS/AML. Patients who did not develop MDS/AML were censored at the date of death or at the date of last follow-up for surviving patients. The time to MDS/AML and the cumulative probability of developing MDS/AML was estimated by the Kaplan–Meier method.

Results

After a median follow-up of 57 months (range 10–125), three out of 305 patients developed secondary leukemia in this retrospective study. Thus, the cumulative incidence of secondary leukemia is 0.94%. All patients developed AML without preceding MDS within 2 years after HDCT. The Kaplan–Meier probability of developing MDS at 2 (242 at risk), 4 (145 at risk), 6 (49 at risk), and 8 years (19 at risk) was 1% (95% CI: 0.094–1.06%). One of the three cases of sAML developed in a 31-year-old woman with inflammatory breast cancer 18 months after HDCT (FAB M3) The karyotype was t(15;17) and, after induction therapy with daunorubicine and ATRA and consolidation with high-dose cytosine arabinoside, the patient underwent autologous stem cell transplantation after conditioning with busulfan (16 mg/kg) and etoposide (40 mg/kg). The patient is still in complete remission (CR) of both breast cancer and AML 63 months after stem cell transplant for breast cancer and 42 after stem cell transplant for AML. The second 52-year-old patient with more than 10 involved lymph nodes

Table 3 Characteristics of secondary acute leukemia

Patient/age	*Induction chemotherapy*	*Mitox. dose*	*AML (FAB)*	*Cytogenetic*	*Treatment*	*Outcome*	*Time from HDT to AML*
1.31 years	4 × ADM/paclitaxel plus 3 × CMF	60 mg/m^2	M3	t(15;17)	Daunorubicin/AraC and auto SCT	CCR 3 years +	18 months
2.52 years	4 × Epi/Cyclo	40 mg/m^2	M4(eo)	Inv(16)	Mitoxantrone/AraC	Died of infection	5 months
3.60 years	4 × Epi/Cyclo	40 mg/m^2	M4	Not done	Daunorubicin/ARA C	Died of relapse	6 months

Epi = epirubicin; Cyclo = cyclophosphamide; ARA-C = cytosin arabinoside; CCR = continuous complete remisssion; Inv(16) = inversion 16; SCT = stem cell transplantation.

received HDCT after 4 cycles of induction chemotherapy with epirubicine and cyclophosphamide. sAML (FAB M4eo with inv 16) developed 5 months after HDCT. This patient received anthracycline-based induction therapy and consolidation therapy with high-dose cytosine-arabinoside and achieved CR, but died of infectious complications. A third 60-year-old woman developed AML (FAB M4) 6 months after HDCT. She achieved CR after ARA-C and daunorubicin therapy, but relapsed and expired 28 months after diagnosis of AML. All patients had received peripheral blood progenitor cells as the stem cell source for HDCT (Table 3).

Discussion

Mitoxantrone is an anthracenedione derivate that intercalates into DNA and RNA. It damages DNA by interacting with topoisomerase II. Like anthracyclines, it arrests the cell cycle in G2 and S phases.[25] As part of a combination chemotherapy or alone, it is used as an active agent in the treatment of breast cancer patients. Recently, several reports have shown an increased incidence of secondary MDS/AML up to 8% after adjuvant chemotherapy containing the anthracenedione derivate mitoxantrone.[7,9–14,24] Since mitoxantrone was mainly used as part of a combination chemotherapy followed by radiation therapy, the responsibility of the combination chemotherapy in the genesis of treatment-related AML cannot be excluded. In a French population-based study with 3093 women, the risk of leukemia was significantly increased in women who received adjuvant mitoxantrone-based chemotherapy and radiotherapy, with a standardized incidence ratio of 28.5. In that study, a dose-dependent effect was seen for mitoxantrone and the incidence of leukemia was lower in patients treated with anthracyclines than in those treated with mitoxantrone >13 mg/m^2.[15]

In a smaller study, a standardized incidence ratio of 38 for breast cancer patients treated adjuvant with a combination of mitoxantrone, 5-fluorouracil, and cyclophosphamide was reported.[10] The high incidence of AML with an incidence ratio of 339 in the study by Andersson *et al*[24] was ascribed to prednimustine, a known leukemogenic alkylating agent, but a synergistic or additive effect of mitoxantrone cannot be excluded. Regarding this risk of developing sAML after standard mitoxantrone treatment, one might expect a higher incidence after a mitoxantrone-based HDCT regimen. In our study, we observed two cases of sAML, which occurred as described for topoisomerase II-induced leukemias within the first 2 years after treatment and without preceding MDS. The karyotype abnormalities found in these two patients were t(15;17) and inv(16). Besides the balanced translocation 11q23, inv(16), and t(15;17) are found with a high frequency in topoisomerase II-induced sAML, especially after treatment with mitoxantrone.[7,8,26] In a French study, two out of 10 patients with sAML after mitoxantrone-based chemotherapy for breast cancer showed an inv(16), and one patient the translocation t(15;17).[7] Furthermore, Carli *et al* found in four out of nine patients (44%) with sAML after mitoxantrone-based chemotherapy for breast cancer, a FAB M3 subtype with classical translocation t(15;17).[26]

After autologous transplantation for non-Hodgkin lymphoma, there is some concern about the high probability of secondary MDS or AML, which is 14–18% at 5 years.[27–29] There are only a few reports of MDS/AML following HDCT for breast cancer. In 864 patients who received a high-dose regimen consisting of BCNU, cyclophosphamide, and cisplatinum, a 4-year probability of developing MDS/AML of 1.6% has been reported.[17] In a Spanish trial involving 229 patients after a median follow-up of 36 months, no single case of secondary MDS/AML was observed.[19] In that trial, cytogenetic aberrations were found in some patients (5%), after HDCT, but these aberrations were only transient and disappeared without developing into MDS or AML. Recently, in a retrospective EBMT study, only one case of treatment-related AML with 11q23 translocation was observed in 364 patients with primary breast cancer after HDCT.[16] Another retrospective analysis including 379 patients with breast cancer after HDCT reported a probability at 5 years for developing a secondary MDS/AML of 0.032%.[30]

While, in general, the prognosis of sAML occurring after topoisomerase II inhibitor treatment is poor,[31] there are controversial reports about the prognosis in patients with balanced translocations t(8;21), t(15;17) or inv(16) after topoisomerase II inhibitor treatment. Some investigators reported these cytogenetic abnormalities as favorable with the same response, and survival as *de novo* AML,[32,33] but others reported a poor outcome.[7,31,34] One patient in our study with AML M3 t(15;17) received a second autologous transplant and is now more than 3 years disease-free from both breast cancer and AML. The outcome of therapy-related acute promyelocytic leukemia (APL) has been recently reported to be similar to *de novo* APL.[35] The other patient with AML M4eo inv(16) achieved CR, but

died during treatment of infectious complications. Only the death of the third patient was due to relapse of AML. In our study, no case of MDS has been observed. However, because no cytogenetic monitoring was performed, anemia or thrombocytopenia occurred, so that overlooking of MDS cannot be excluded from this retrospective study.

We conclude that anthracendione-based high-dose treatment with mitoxantrone in combination with cyclophosphamide ± thiotepa and local radiation therapy induces sAML in some rare cases. The incidence of sAML is lower in comparison to standard mitoxantrone doses used as adjuvant therapy. A single high dose of mitoxantrone might not be as leukemogenic as smaller doses given at fixed intervals. Since all patients also received anthracycline-based induction chemotherapy, the contribution of anthracyclines to the development of sAML cannot be excluded. Since, in our patients, no MDS was preceded and two of them showed t(15;17) and inv(16), respectively, the development of AML is likely attributed to the topoisomerase II inhibitors than to the alkylating agents used in the HDCTregimen. The low incidence of about 1% is in contrast to the reported high incidence after autologous transplantation for non-Hodgkin's lymphoma. There is no obvious increase in leukemia in comparison to the standard dose of mitoxantrone, but longer follow-up is needed to determine the late incidence of AML.

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