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ORIGINAL ARTICLE

Secondary hematological malignancies after treatment of non-metastatic breast cancer

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Summary

Purpose: *To determine the frequency of secondary hematological malignancies in non-metastatic breast cancer (BC) patients who received adjuvant chemotherapy and radiotherapy.*

Methods: *Data of BC patients followed at Hacettepe University Institute of Oncology, Department of Medical Oncology between 2004 and 2010 were retrospectively analysed.*

Results: *There were 1,475 BC patients followed between 2004 and 2010 at our department; 1,319 (89.4%) of them had not metastatic disease. One thousand, one hundred eighty-three (89.7%) early-stage BC patients received at least one treatment modality (radiotherapy and/or chemotherapy). The number of patients receiving only chemotherapy or only radiotherapy were 228 (17.3%) and 117 (8.9%), respectively. Eleven (1%) out of 1,066 BC patients receiving adjuvant/neoadjuvant chemotherapy were also treated with granulocyte colony stimulating factor (G-CSF). The frequency of secondary hematological malignancies among adjuvant or neoadjuvant chemotherapy BC patients was 0.56% (6/1,066); it was 0.59% (7/1,183) among radiotherapy and/or chemotherapy-treated non-metastatic BC patients. Five patients developed acute myeloid leukemia (AML); 3 of them were AML-FAB M3 and 2 could not be subclassified. The 6th patient had multiple myeloma and the 7th had diffuse large B cell lymphoma (DLBCL). However, the latter did not receive cytotoxic chemotherapy for BC.*

Conclusion: *Treatment-associated secondary hematological malignancies, especially myeloid leukemias, are a growing problem due to high prevalence of BC and the dismal outcome of secondary leukemias. Further studies are needed to determine the risk for other hematological malignancies, possible responsible agents, and mechanisms.*

Key words: breast cancer, chemotherapy, hematological malignancies, non-metastatic, radiotherapy, secondary

Introduction

BC is the most frequent solid malignancy in women. Survival rates have been increased with the newer adjuvant chemotherapy regimens including alkylating agents, antimetabolites, anthracyclines, topoisomerase inhibitors, platinum derivatives, taxanes and radiotherapy modalities. On the other hand, long-term toxicity of the cytotoxic chemotherapy and radiotherapy is an increasing concern. Therapy-associated secondary AML and myelodysplastic syndrome (MDS) is a growing problem due to the high prevalence of BC and the dismal outcome of secondary leukemias. It occurs in 0.3-1.7 of BC patients receiving antineoplastic chemotherapy [1,2]. Colony stimulating factors (CSFs) are also shown to increase the risk of AML/MDS in some studies [3,4]. Reports on secondary hematological malignancies after BC mostly describe AML/MDS rather than lymphoid malignancies (Table 1). Rare cases of lymphoid malignancies were also reported in the literature [5,6]. To our knowledge, secondary multiple myeloma was not reported previously. In the present study we evaluated secondary hematological malignancies that occurred in non-metastatic BC patients followed at our center.

Methods

Data from 1,475 BC patients treated between 2004

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Table 1. Summary of studies of secondary hematologic malignancies (AML/MDS) in early breast cancer patients

Study	*Treatment*	*Risk (%)*	*Number of patients*	*Patients with AML/MDS*
Fisher et al. [1]	Melphalan	1.7	5,299	34
Curtis et al. [6]	Various agents[1]	0.7	13,744	24
Valagussa et al. [23]	CMF	0.2	2,645	3
Diamandidou et al. [24]	CAF	1.5	1,474	14
Laughlin et al. [25]	HDCT; CCNU-cyclophosphamide-cisplatin	0.7	350	2
Linassier et al. [26]	MCF	0.7	350	2
Chaplain et al. [13]	Mitoxantrone, anthracyclines and various	0.32	3,093	10
Saso et al. [15]	Mitoxantrone	1.6	1,774	9
Smith et al. [12]	AC (dose dense/ standard)	1.01/0.21	8,563	28
Kröger et al. [21]	Various high dose regimens[2]	0.3	364	1
Park et al. [2]	CEF, CAF, CMF[3]	0.15	1,934	3[4]
Beadle et al. [17]	Not given	0.09[5]	183,123	158
Patt et al. [18]	Anthracyclines, taxanes, cyclophosphamide and others[6]	1.8[7]	10,130	Not given
Hershman et al. [3]	Adriamycin, cyclophosphamide, and others + G-CSF/GM-CSF[8]	1.77	5,510	64
Tallman et al. [19]	Cyclophosphamide	0.00026[9]	2,638	5
Praga et al. [20]	Epirubicin, cyclophosphamide[11]	0.394[10]	7,110	28

CMF: cyclophosphamide + methotrexate + 5-Fluorouracil, HDCT: high dose chemotherapy, CAF: cyclophosphamide + adriamycin + 5-Fluorouracil, MCF: mitoxantrone + cyclophosphamide + 5-Fluorouracil, AC: adriamycin + cyclophosphamide, CEF: cyclophosphamide + epirubicin + 5-Fluorouracil.
[1]Regimens used in breast cancer patients in whom acute non-lymphocytic leukemia /MDS occurred; melphalan, thiotepa+ methotrexate + 5-Fluorouracil, adriamycin + mitomycin-C + vinblastine, thiotepa + 5-Fluorouracil. Total risk for hematologic malignancies (NHL + MDS + AML) is 3%.
[2]Carboplatin + cyclophosphamide + thiotepa, melphalan + thiotepa, melphalan + mitoxantrone + cyclophosphamide, cyclophosphamide + methotrexate + epirubicin + paclitaxel + melphalan, ifosfamide + carboplatin + etoposide, busulfan + melphalan + thiotepa, carboplatin + cyclophosphamide + paclitaxel, melphalan, epirubicin + cyclophosphamide
[3]In this report 2 patients developed AML and 1 MDS; these 3 patients received CEF and CAF.
[4]In addition, 3 patients developed non-Hodgkin's lymphoma and they had received CEF and CMF.
[5]This study is a population-based cohort from Australia. The calculated adjusted risk rate for AML was 2.56 times higher in patients with prior breast cancer diagnosis compared to normal population. The frequency of chemotherapy administration or chemotherapy agents used were not mentioned.
[6]Chemotherapeutic regimens were not given in detail.
[7]The calculated absolute risk for AML development in adjuvant chemotherapy of breast cancer patients was 1.8% vs. 1.2% in patients who did not receive adjuvant chemotherapy.
[8]In this trial 5,510 patients received adjuvant chemotherapy and 906 received colony stimulating factors (CSFs). The risk of MDS/AML was 1.04 in patients who received chemotherapy but not CSFs (48/64 patients) and 1.77 in patients who received chemotherapy plus CSFs (16/64 patients).
[9]The estimated risk was calculated as person-years of follow-up.
[10]The incidence of AML/MDS was 0.394%. The 8-year cumulative risk for AML/MDS was 4.97% in patients who received epirubicin ≥720 mg/m^2 and cyclophosphamide ≥6300 mg/m^2; the risk was 0.37% in patients who received lower doses of those agents.
[11]One of 28 patients received additional taxane and 5-Fluorouracil because of recurrence prior to diagnosis of AML/MDS.

and 2010 at the Department of Medical Oncology of Hacettepe University Institute of Oncology were retrospectively analysed. Non-metastatic BC patients were selected from this patient population. All non-metastatic BC patients who had received neoadjuvant or adjuvant chemotherapy were analysed and cumulative doses for each chemotherapeutic agent were calculated. Patients were also evaluated for adjuvant radiotherapy and CSF administration. Non-metastatic BC patients who developed hematological malignancies after the BC diagnosis were identified and analysed for disease characteristics.

Results

A total of 1,475 BC patients were followed at our unit between 2004 and 2010. One hundred and fifty-six (10.6%) of these BC patients had metastatic disease and the remaining 1,319 (89.4%) had non-metastatic disease at the time of diagnosis. Two hundred and fifty-three (19.2%) of the non-metastatic BC patients did not receive adjuvant or neoadjuvant chemotherapy. The median age at diagnosis for non-metastatic BC patients was 48.2 years (range 20-91). Survival data could not be drawn because not enough events were seen yet for such an analysis.

Adjuvant radiotherapy and/or neoadjuvant or adjuvant chemotherapy were administered to 1,183 (89.7%) patients. Of the non-metastatic BC patients 1,066 (80.8%) had received adjuvant or neoadjuvant chemotherapy. Also, 960 (72.8%) of the non-metastatic BC patients had received adjuvant radiotherapy. Adjuvant radiotherapy was delivered to 843 (79.1%) of the 1,066 BC patients who had received adjuvant or neoadjuvant chemotherapy. Two hundred and twenty-three (16.9%) patients had received only adjuvant/neoadjuvant chemotherapy and 117 (8.9%) only adjuvant radiotherapy. The number of patients who had received chemotherapy, G-CSF and radiotherapy are summarized in Table 2.

Cumulative chemotherapy doses for each agent

Table 2. Number of patients in this study according to treatment modalities

Group of patients	*Patients, n*	*%*
All patients	1,475	
Early-stage breast cancer patients	1,319	100
Adjuvant / neoadjuvant chemotherapy (includes patients receiving both chemotherapy and radiotherapy)	1,066	80.8
Adjuvant radiotherapy (includes patients receiving both chemotherapy and radiotherapy)	960	72.8
Both adjuvant radiotherapy and adjuvant / neoadjuvant chemotherapy	1,183	89.7
Adjuvant radiotherapy only	117	8.9
Adjuvant /neoadjuvant chemotherapy only	223	16.9
G-CSF	11	1 (in patients receiving chemotherapy)

administered are summarized in Table 3. Only 11 (1%) out of 1,066 BC patients receiving adjuvant chemotherapy were also treated with G-CSF.

Table 3. Total cumulative doses of cytotoxic agents administered to all non-metastatic breast cancer patients in this study

Cytotoxic agent	*Total dose adjusted (mg/m^2)*
Adriamycin	149,885
Epirubicin	46,570
Docetaxel	64,575
Cyclophosphamide	1,097.440
Vinorelbine	100
Paclitaxel	699.600
5-fluorouracil	179,160
Cisplatin	1,770
Methotrexate	5,760
Etoposide	2,160
Carboplatin*	10*

*Carboplatin dose was given as AUC (area under the curve)

The frequency of secondary hematological malignancies among non-metastatic BC patients treated with adjuvant or neoadjuvant chemotherapy was 0.56% (6/1,066); it was 0.59% (7/1,183) in patients treated with radiotherapy and/or chemotherapy. The characteristics of the patients with secondary hematological malignancies occurring in non-metastatic BC patients are summarized in Table 4. There were 5 AML patients; 3 of them were AML-FAB M3 and 2 were unclassified. One patient developed multiple myeloma and the other one DLBCL. The patient with multiple myeloma had received both adjuvant chemotherapy and radiotherapy for BC but the patient with lymphoma had received only adjuvant radiotherapy for BC.

Discussion

In this retrospective study the frequency of sec-

Table 4. Characteristics of the non-metastatic breast cancer patients in the present study who developed secondary hematological malignancy

Patient no.	*Age* (years)*	*Time intervals† (years)*	*Hematological malignancy*	*Breast cancer/ TNM stage*	*Chemotherapy*	*Radiotherapy*	*Hormonotherapy and/or Trastuzumab*	*Outcome*
1	69	4^+	AML (FAB M3)	IIIC	(DD) AC×4→ Paclitaxel ×4	+	Trastuzumab/Anastrozole	Dead
2	74	2^+	NHL-DLBCL	IIA	–	+	Tamoxifen	Alive
3	57	1.5^+	M. Myeloma	IIB	CAF ×6	+	Trastuzumab/Anastrozole	Alive
4	45	4^+	AML-unclassified	IIB	CAF ×6	+	Tamoxifen	Alive
5	50	2.5^+	AML-unclassified	IIIA	CEF ×6→ Docetaxel ×1	+	–	Alive
6	45	3^+	AML (FAB M3)	IIIA	CEF ×3→ weekly Paclitaxel ×12	+	Tamoxifen	Alive
7	46	8^+	AML (FAB M3)	IIIC	CAF ×6→ Docetaxel ×4	+	–	Dead

AML: acute myeloid leukemia, DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin's lymphoma, AC: adriamycin + cyclophosphamide, CAF: cyclophosphamide + adriamycin + 5-Fluorouracil, CEF: cyclophosphamide + epirubicin + 5-Fluorouracil, TC: docetaxel + cyclophosphamide, DD: dose dense
*Age at diagnosis of breast cancer
†Time interval between diagnosis of breast cancer and secondary hematological malignancy

ondary hematological malignancies among non-metastatic BC patients treated with adjuvant or neoadjuvant chemotherapy was 0.56% (6 /1,066). We selected non-metastatic BC patients for evaluation because of the differences in survival, and the variety of treatment schedules between non-metastatic and metastatic patients. The frequency of secondary hematological malignancies in radiotherapy- or chemotherapy-treated non-metastatic BC patients was 0.59% (7/1,183). Five of 7 patients developed AML (3 had AML-M3). However, the remaining 2 patients with AML could not be sub-classified. All these 5 patients had received both radiotherapy and chemotherapy as adjuvant treatment. One of the 7 patients with secondary hematological malignancy was diagnosed as multiple myeloma. This patient had received both radiotherapy and chemotherapy as adjuvant treatment. The last patient developed DLBCL and had received only radiotherapy as adjuvant treatment.

The large body of information on secondary hematological malignancies in BC patients deals with AML and MDS. Secondary lymphomas are reported only rarely in BC patients [5,6]. Cytotoxic chemotherapy and radiotherapy might have an impact on the risk of non-Hodgkin's lymphomas [7]. There is no data on secondary multiple myeloma risk in BC patients. Exposure to ionizing radiation is the single strongest factor shown to increase the risk of multiple myeloma [8]. Data on the relationship between cytotoxic chemotherapy and the risk of multiple myeloma is lacking.

The most studied culprits of treatment-related AML/MDS in BC patients are alkylating agents, topoisomerase inhibitors, growth factors and radiation treatment. Candidate mechanisms of chemotherapy and radiotherapy that could induce secondary leukemias might be polymorphisms in DNA repair and/or xenobiotic-metabolising enzymes. Some early reports suggest that deficiency of glutathione S-transferase (GST), a xenobiotic metabolising enzyme, might increase the risk of treatment-induced hematological malignancies in BC patients [9]. In a retrospective study, peripheral blood and bone marrow DNA samples from patients with AML (n= 213) and MDS (n=128), 44 of whom suffered from therapy-induced AML/MDS were analysed [9]. GSTM1 and GSTT1 genotypes (double null genotype) which metabolise various drugs, as well as reactive oxygen species were examined with multiplex PCR. Combined deletions of both GSTM1 and GSTT1 were more frequent in the group of AML/MDS patients secondary to chemotherapy and/or radiotherapy of BC. Double null genotype was more frequent in this group compared to healthy controls (55 vs. 8%, p =0.0003). This genotype might bear an increased risk for development of a secondary treatment-induced hematological malignancy in BC patients.

Insufficient detoxification of anticancer drugs, such as cyclophosphamide, might be suggested to represent the underlying mechanism. Chemotherapy-associated AMLs are known to exhibit different characteristics from *de novo* leukemias [10]. AMLs associated with alkylating agents generally occur after 5 to 7 years from drug exposure. They are usually preceded by MDS and seen in M1 and M2 subtypes (FAB classification). M4 or M5 subtypes are generally seen as AML/MDS related with topoisomerase-II inhibitors treatment. They occur after a shorter interval (2-3 years) from drug exposure. Translocation of the long arm of chromosome 11 (11q23) is frequently associated with topoisomerase-II inhibitors treatment-associated leukemias [10-15]. However, abnormalities of chromosomes 7q, 20q, 1q and 13q without chromosome 11q23 translocation were shown in patients with AML or MDS treated with topoisomerase-II inhibitors [16]. Secondary leukemias are known to exhibit a worse course compared with *de novo* leukemias. In our study 3 of 5 leukemia patients survived and are followed with no evidence of disease.

In a population-based study from Australia, AML risk was 4.73-fold higher in patients with prior hematological malignancy and 2.56-fold higher in BC [17]. Patt and colleagues reported the data of AML frequency from the Surveillance, Epidemiology, and End Results-Medicare (SEER) data on older non-metastatic BC patients between 1992 and 2002 [18]. There were 64,715 patients; 10,130 had received adjuvant chemotherapy and 54,585 had not. The median patient age was 75.6 years (range 66 -104) and the median follow-up time was 54.8 months (range 13-144). The absolute risk of developing AML at 10 years after any adjuvant chemotherapy was 1.8 vs. 1.2% for women who had not received chemotherapy. The adjusted hazard ratio of adjuvant chemotherapy vs. none for AML was calculated as 1.53 (95% CI 1.14-2.06). However, the increased risk seems small and the study is very strong regarding the large patient number.

Six adjuvant trials of ECOG containing cyclophosphamide chemotherapy, conducted between 1978 and 1987, were reviewed to determine the risk of secondary MDS or AML [19]. The patient number was 2,638 and the mean follow-up duration 7.3 years. The calculated person-years follow-up was 19,200. Three patients developed MDS (2 with a characteristic cytogenetic abnormality). Two patients developed acute leukemia; however, one had adult T-cell leukemia associated with human T-lymphotrophic virus type 1 (HTLV-1) and the second one developed AML after receiving additional cyclophosphamide for metastatic BC. The estimated incidence rate for MDS was 3 per 19,200, and 5 per 19,200 person-years of follow-up when all 5 patients were included.

Nineteen randomized trials with epirubicin with 7,110 early BC patients were reviewed in another study to determine the incidence rates and probable risk factors (chemotherapy dose, patient age, radiotherapy, tamoxifen and G-CSFs usage) for subsequent AML or MDS [20]. In that trial 92% of the patients also received cyclophosphamide and the 8-year cumulative probability was 0.55%.

Certain chemotherapeutics, like anthracyclines and mitoxantrone, used for the treatment of BC were found to be related with a higher risk for AML and MDS [4]. However, we do not have any data yet for some of the novel agents like taxanes and biological agents used for adjuvant treatment in BC. The risk of AML and MDS was increased with the use of topoisomerase-II inhibitors and the risk was higher with mitoxantrone-based chemotherapy than with anthracycline-based chemotherapy (relative risk [RR] = 15.6; 95% CI 71-34.2 vs. RR = 2.7; 95% CI 1.7-4.5) in a case-control study among women treated for BC between 1985 and 2001 [4]. However, alkylating agents were not found to increase the risk [4]. In the above mentioned retrospective study by Tallman et al. standard dose of cyclophosphamide did not increase the risk of AML/MDS to higher levels than in the general population [19]. Parallel with this data, the risk was found to be higher in patients treated with cumulative cyclophosphamide doses $\geq$ 6300 mg/m^2 and epirubicin $\geq$720 mg/m^2 than with lower doses in the retrospective study of Praga et al. [20]. The 8-year cumulative probability of developing AML/MDS was 4.97% for the former and 0.37% for the latter.

The incidence of AML/MDS was elevated in patients treated with more intense regimens of cyclophosphamide in the retrospective study by Smith et al., in which they reviewed the 6 completed adjuvant of NSABP BC trials with regimens containing both doxorubicin and cyclophosphamide [12]. The cumulative incidence of AML/MDS at 5 years was 1.01% (95% CI 0.63-2.62) in 2400 mg/m^2 of 2 or 4 cycles of cyclophosphamide-containing regimens and 0.21% (95% CI 0.11-0.41) in standard 600 mg/m^2 of 4 cycles of cyclophosphamide-containing regimens. In our study only one AML patient received dose-dense regimen (adriamycin 60 mg/m^2 on day 1 plus cyclophosphamide 600 mg/m^2 on day 1, every 14 days, for 4 cycles) followed by paclitaxel 175 mg/m^2 on day 1, every 14 days, for 4 cycles. The cumulative dose of cyclophosphamide was 2400 mg/m^2 in this patient. The remaining 4 patients received a cumulative dose of 3600 mg/m^2 and one patient received 1800 mg/m^2 of cyclophosphamide in this study.

Patients are exposed to higher doses of cytotoxic drugs with high-dose chemotherapy and autologous stem cell transplantation and the risk of AML or MDS might be expected to be higher in this group of patients. However, the results from the study by Kröger et al. did not confirm this hypothesis [21]. A low rate of AML (0.27%, 1/364 patients) was reported after adjuvant treatment of BC patients with high-dose chemotherapy followed by autologous stem cell transplantation in a median follow-up of 4 years (range 1-108 months) [21]. This unique patient developed a M4 subtype of AML, after epirubicin and high-dose cyclophosphamide, while translocation of t(9;11)(p22;q23) was shown by cytogenetic analysis.

CSFs administration in BC patients is another suggested factor, increasing the risk of AML/MDS. However, controversial results appear in the literature over this issue. In the case-control study of Le Deley and colleagues performed to determine the risk factors for AML and MDS among women treated for BC (182 MDS or AML patients and 534 matched controls) G-CSF support had increased the risk (RR = 6.3, 95% CI 1.9-21) even when adjusted for chemotherapy doses [4]. In the trial from SEER database in older BC patients by Patt et al. G-CSF usage did not increase the risk of AML in the first year of follow-up [18]. Hershman and colleagues studied from the same database 5,510 BC patients who had received adjuvant chemotherapy [3]. There were 906 patients who were treated with G-CSF or GM-CSF. The frequency of AML or MDS in these patients was higher than in patients who never received these growth factors (1.77 vs. 1.04%). The hazard ratio for AML or MDS among those treated with G-CSF or GM-CSF compared with those who were not was 2.14 (95% CI 1.12-4.08). Dose-dense adjuvant chemotherapy of BC with doxorubicin and cyclophosphamide requiring G-CSF support was shown to be associated with increased risk of AML/MDS [12]. In our study only one patient received dose-dense chemotherapy with G-CSF. G-CSF was used in 1% of our non-metastatic BC patient group who received adjuvant/neoadjuvant chemotherapy.

Ionizing radiation exposure is known to be associated with genomic insult and increased risk of AML/MDS. The risk of non-lymphocytic leukemia was increased by 2.5 times in patients who were exposed to breast irradiation [11,12]. A population-based retrospective study with low risk BC patients (n=1,828) without further treatment after surgery and high risk patients (n = 846) who received radiotherapy ± tamoxifen was reported from Denmark [22]. The risk of nonlymphocytic leukemia increased from 0.1% in non-irradiated patients to 0.9% in irradiated patients (p= nonsignificant). Another study showed that radiotherapy created a 3.9-fold risk for AML/MDS (95% CI 1.4-10.8) among early BC patients [4]. In our study, all of the 7 patients with secondary hematological malignancy occurred after BC

adjuvant radiotherapy. The patient with DLBCL had received adjuvant radiotherapy for BC, but not chemotherapy. In that early-stage BC patient the only possible culprit known for secondary DLBCL occurrence was radiotherapy. However, coincidence cannot be ruled out and the time interval between the occurrence and radiotherapy was short (2 years). The patient with multiple myeloma had received both adjuvant radiotherapy and chemotherapy for BC. Radiotherapy is known to be risk factor for both lymphoma and multiple myeloma [7,8].

In conclusion, thanks to modern chemotherapy and radiotherapy practices a significant survival improvement has been obtained in early and metastatic BC patients. Secondary hematological malignancies which are one of the important long-term toxicities of the chemotherapeutic agents [23-26] must be considered before deciding to administer adjuvant treatment, especially in patients in whom the benefit of chemotherapy is controversial. This risk must also be kept in mind during the follow-up of BC patients. Further studies are needed to evaluate the risk of secondary hematological malignancies including lymphomas and multiple myeloma for both adjuvant chemotherapy and radiotherapy, especially with the use of novel chemotherapy agents in BC patients.

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