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Original article

Acute myeloid leukemia in patients previously diagnosed with breast cancer: Experience of the GIMEMA group

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Summary

Objective: To evaluate in a multicenter retrospective study, the clinical and laboratory characteristics and the outcome of patients with acute myeloid leukemia (sAML) previously diagnosed with breast cancer (BC) among an adult acute leukemia population.

Patients and methods: Between June 1992 and July 1996, 3934 new cases of adults with acute leukemia were recorded in *GIMEMA Archive of Adult Acute Leukemia* (2964 AML, 901 ALL, 69 acute leukemia expressing both myeloid and lymphoid surface markers).

Results: Two hundred patients (5.1%) presented with a history of previous malignancy (21 of them were affected by ALL and 179 by AML). Among sAML, 37 patients (29%) had a previous breast cancer. They consisted of 36 females and 1 male, median age 56 years, range 34–87. The median latency between the 2 malignancies was 54 months (range 5–379). Twenty-seven patients received chemo- and/or radiotherapy for breast cancer (7 only chemotherapy, 6 only radiotherapy, and 14 combined treatment). All patients were surgically treated but in 10 patients surgical debridement was the sole therapy for breast cancer. The drugs most frequently employed were alkylating agents (18 patients), topoisomerase II inhibitors (9 patients), antimetabolites (20 patients) (CMF, CEF and MMM combinations). At onset of sAML the median WBC count was 7.7×10^9/l (0.8–153) and the median platelet count was 33.5×10^9/l (3–305). Considering morphological features, FAB subtypes were 4 M0, 5 M1, 11 M2, 5 M3, 8 M4, 3 M5, and 1 M6. Cytogenetic study was performed on 28 patients and 12 of them presented abnormalities. It is noteworthy that chromosome 5 or 7 abnormalities (typically observed in those patients treated with alkylating agents) were present only in three cases. Thirty-four patients received chemotherapy for sAML, and twenty-five of them achieved a CR (74%), with a median duration of twenty-eight weeks (5–280+). The overall survival was 8 months (1–80+).

Discussion: The high number of sAML we observed in patients with a previous breast cancer, may be due to the fact that this malignancy is the most frequent neoplasm in women and by the high probability of cure with a consequent long disease-free survival. Our results suggest that the risk of sAML after recovery from breast cancer is increasing due to the rise in the number of patients cured from breast cancer, and in the future could be a relevant problem for haematologists.

Key words: acute myeloid leukemia, breast cancer

Introduction

Secondary leukemia in patients who received chemo- and/or radiotherapy for a previous malignancy is a well-documented event [1, 2]. In the majority of cases they are represented by secondary acute myeloid leukemia (sAML), but a secondary acute lymphoblastic leukemia is possible [3], although less common.

This occurrence is generally due to the leukemogenic activity of several drugs, above all alkylating agents or epipodophyllotoxins, utilized in the treatment of primary cancer [4, 5]. Radiation therapy is also considered to be potentially mutagenic [6].

sAML may develop in different groups of patients. It is particularly well studied in children cured from an acute lymphoblastic leukemia, and in patients treated for Hodgkin's disease (HD) [7–10]. The risk of a sAML after treatment of a previous breast cancer (BC) is a debated problem, with different opinions [12–24].

The purpose of our study is to analyze, in a multicenter retrospective study, the clinical, and laboratory characteristics and the outcome of sAML following a previous breast cancer among the entire adult acute leukemia population enrolled during a four-year period in the *GIMEMA Archive of Adult Acute Leukemia*.

Patients and methods

The study population comprised 3934 patients, aged 15–94 years, with newly diagnosed acute leukemia, registered in the *GIMEMA Archive of Adult Acute Leukemia* and observed in 62 Haematology Divisions in

tertiary care or University Hospitals during the period July 1992–June 1996. A total of 2964 patients were affected by AML, 901 by acute lymphoblastic leukemia (ALL) and 69 by acute leukemia expressing both myeloid and lymphoid surface markers.

Trained haematologists interviewed all patients at diagnosis of AML according to a standardized questionnaire. The form concerned statistical demographic data (race, age, gender), place and date of birth, residence at time of diagnosis, education, previous diseases, working activity at the time of diagnosis and previous activities of the patient. These data were available for all patients enrolled in the *Archive* Moreover, in 37 patients with sAML diagnosed after a previous history of BC, further information was obtained: type and date of onset of BC, treatment (chemotherapy, radiotherapy, surgery) and outcome of BC, latency between the BC and sAML, morphological, immunophenotypic, cytogenetic and molecular biology studies performed at onset of sAML, white blood cells (WBC), haemoglobin (Hgb) and platelet count at diagnosis of sAML, induction treatment, complete remission (CR) achievement and duration, and overall survival from sAML diagnosis.

The end of follow-up was December 1999.

Statistical analysis

Stratified analysis and adjusted ORs were computed by Mantel–Haenszel method. χ^2 test of Fisher's exact test was used for differences on frequencies among patients with sAML treated with and without chemo-radiotherapy

Results

During the study period, 200 of 3934 patients (5.1%) had a history of a previous PM. Of these, 179 had AML and 21 ALL. Among these, 40 had a previous BC (37 AML and 3 ALL). The clinical characteristics of AML patients following BC (21%) are described in Table 1. The percentage of a previous BC in adult females enrolled in the Registry during the study period was 2.5% (36 of 1417). The percentage of previous BC among sAML population was 20.6% (37 of 179).

No difference in the age was observed when comparing patients with sAML after BC with the entire AML population recorded in the study period in the GIMEMA Archive (56 years, range 34–87, vs. 57 years, range 15–94; P = NS).

sAML occurred after a median latency of 54 months (range 5–379) from BC. In patients treated with CMF the latency was 60 months (range 12–178), whereas in patients treated with protocols including topoisomerase II inhibitors ± alkylating agents the latency was 41.5 (range 19–156) (P = NS).

All patients were treated for BC, and all underwent surgical debridement of BC. In particular 10 patients received surgical resection only, while the other 27 patients underwent chemotherapy and/or radiotherapy as well (Table 2). Of these, 7 patients received only chemotherapy, 14 chemo-radiotherapy and 6 patients radiotherapy alone. In Table 3 are reported the types of chemotherapeutic trials performed. The drugs most frequently employed were alkylating agents (18 patients), topoisomerase II inhibitors (9 patients), antimetabolites (20 patients) (CMF, CEF and MMM combinations).

Table 1. Clinical and laboratory characteristics of patients with sAML following breast cancer.

Age (years)	
Median	56
Range	34–87
Latency between the two malignancies (months)	
Median	54
Range	5–379
WBC count at the onset of sAML ($\times 10^9$/l)	
Median	7750
Range	800–153,000
Haemoglobin level at the onset of sAML (mg/dl)	
Median	8
Range	5–13
Platelet count at the onset of sAML ($\times 10^9$/l)	
Median	33,500
Range	3000–305,000
FAB classification	
M0	4
M1	5
M2	11
M3	5
M4	8
M5	3
M6	1
Cytogenetic study (on 25 patients)	
No mytoses	3
Normal	10
t(15;17)(q22,q21)[a]	3
47XX,+8	2
44/45XX	1
45 XX,−7	1
41/42X,−X,−5,−7,−8,−13,−16	1
Del(16)	1
Inv(16)	1
Del(3q),−7	1
Del(5)	1

[a] The other two of the five cases with M3 sAML failed cytogenetic study, but were BCR/ABL positive at molecular biology study.

Six patients had a progression of BC at the time of AML diagnosis, and one patient showed a relapse.

Five patients had a myelodysplastic phase preceding AML development. At diagnosis of sAML, cytogenetic analysis was performed in 25 patients. Twelve patients presented cytogenetic abnormalities. Results of cytologic and cytogenetic analysis are reported in Table 1. Interestingly, a relatively high number of M0 and M3 subtypes was observed (4 and 5 cases respectively). All patients with M0 and 1 of 5 patients with M3 subtype were previously treated with alkylating agents, but none of them received topoisomerase-II inhibitors. Abnormalities of chromosome 5 or 7 were present in only four patients; two of them were treated with radiotherapy, one with chemotherapy and one only with surgery. The majority of patients received a combined treatment including both alkylating agents and topoisomerase-II inhibitors; therefore a separated analysis of cytogenetic abnormalities due to the different drugs was impossible.

Thirty-four patients received chemotherapy for sAML, but three died before starting any therapy. Twenty-five patients (74%) responded to chemotherapy and achieved a CR, six patients (17%) were resistant, and finally three

Table 2. Clinical and laboratory characteristics of patients at sAML diagnosis in relation to the previous treatments for breast cancer.

	Chemotherapy	Radiotherapy	Surgery	Chemo-radiotherapy	*P*-value
Number of cases	7[a]	6[b]	10[c]	14[d]	
Age	52 (39–68)	62 (42–74)	66 (42–87)	52 (34–76)	<0.03
WBC (× 10^9/l)	23.5 (1.2–153)	7.6 (0.9–88)	4.7 (0.8–29)	9.5 (1.3–138)	0.4
Hgb (g/dl)	10 (6–13)	9 (5–13)	8 (7–12)	8 (6–10)	0.3
Platelets (× 10^9/l)	48 (8–136)	31 (18–140)	35 (4–108)	30 (3–305)	0.7
Latency (months)	60 (22–178)	40 (5–235)	84 (6–379)	49 (12–156)	0.8
Cytogenetic abnormalities[e]	2	3	5	2	<0.04
CR	5	5	6	9	0.1
CR duration (weeks)	20 (5–75)	110 (23–250)	27 (8–80)	34 (6–74)	0.1
Survival (months)	7 (2–80)	23 (6–60)	7 (1–53)	9 (1–18)	0.1

The patients underwent the following treatments:

[a] Two FLAG (fludarabine, cytarabine and G-CSF), one daunorubicin and cytarabine, one ICE (idarubicin, cytarabine, etoposide), one MEC (mitoxantrone, etoposide, cytarabine), one GIMEMA 0288, one cytarabine + daunorubicin + mercaptopurine.

[b] Two FLAG, two AIDA (all trans retinoic acid, idarubicin), one ICE, one mitoxantrone and cytarabine.

[c] Three ICE, one daunorubicin and cytarabine, one AIDA, one all trans-retinoic acid + mitoxantrone + cytarabine, one idarubicine and cytarabine, one mitoxantrone and cytarabine, two died before treatment.

[d] Four ICE, two mitoxantrone and cytarabine, two daunorubicin and cytarabine, one MEC, one MICE (mitoxantrone, cytarabine, etoposide), one all trans-retinoic acid, one vincristine + cyclophosphamide + adriblastine, one etoposide and cytarabine, one died before treatment.

[e] *Chemotherapy group:* 1 case del(3q),−7; 1 case inv(16); *radiotherapy group*. 1 case 47XX(+8); 1 case del5(q13;q33); 1 case 45XX−7; *surgery group*. 1 case 41/42X,−X,−5,−7,−8,−13,−16; 1 case del(16); 2 case t(15;17)(q22;q21); 1 case 47XX(+8); *chemo-radiotherapy group*: 1 case 44/45XX; 1 case t(15;17)(q22;q21).

Table 3. Kind of previous chemotherapy for breast cancer.

Treatment	Number of patients (plus RT)
CMF	8 (5)
CEF	6 (4)
MMM	1 (1)
CMF + MMM	1 (1)
CEF + MMM	1 (1)
CEF + CAP	1 (1)
CMF + CEF	1 (–)

Two patients underwent chemo- and radiotherapy not specified
Abbreviations. CMF – cyclophosphamide–fluorouracil–methotrexate, CEF – cyclophosphamide–epirubicin–fluorouracil, MMM – mitoxantrone–methotrexate–mitomycin; CAP – cyclophosphamide–adryamicin–CDDP.

Table 4. Kind of treatment for sAML and outcome.

Treatment	Number of cases	CR	DI	Resistant
ICE	9	7	1	1
FLAG	4	4	–	–
3 + 7	3	2	–	1
AIDA	3	3	–	–
Mitoxantrone + ara-C	3	2	1	–
ATRA	2	1	–	1
MEC[a]	2	2	–	–
Etoposide + ara-C	2	2	–	–
Adriamycin	2	–	1	1
ATRA[b] + mitoxantrone + ara-C	1	1	–	
Ara-C + idarubicin	1	1	–	–
MICE[a]	1	–	–	1
DAM	1	–	–	1
Total	34[b]	25 (74%)	3 (9%)	6 (17%)

[a] These protocols differ for drugs dosage.

[b] In this patient, with a M0 sAML, ATRA was added for the presence of a myelodysplastic picture.

[c] Three patients died before starting any treatment.

Abbreviations: CR – complete remission, DI – death in induction; ICE – idarubicin, cytarabine, etoposide; FLAG – fludarabine, high-dose cytarabine, G-CSF, 3 + 7 – daunorubicin, cytarabine; AIDA – all trans-retinoic acid, idarubicin; ARA-C – cytarabine; ATRA – all trans-retinoic acid, MEC – mitoxantrone, etoposide, cytarabine; MICE – mitoxantrone, cytarabine, etoposide; DAM – cytarabine, daunorubicin, mercaptopurine.

patients (9%) died during induction. Results of treatment administered are reported in Table 4. The median duration of CR was 28 weeks (range 5–250+). The median overall survival was eight months (1–80+).

When comparing patients treated by surgery alone to those who received chemo- ± radiotherapy, a significantly higher median age ($P < 0.03$), as well as a high number of cytogenetic abnormalities ($P < 0.04$) was observed in surgical patients (Table 2); nevertheless due to the small number of patients, the significance of these data need to be confirmed. No significant differences were found for latency between two malignancies (BC and sAML), WBC count, and Hgb level, CR and survival duration (Table 2).

Clinical and laboratory parameters such as age, sex, WBC and platelet count, Hgb level, CR achievement, CR duration and survival of 37 patients with sAML following BC were compared with those of 90 patients with sAML following other malignancies. No statistical differences were found. Only a trend in a higher CR rate (74% vs. 51%, $P < 0.08$) was observed for sAML following BC.

Discussion

The risk of a myelodysplastic syndrome or of a sAML following chemotherapy for breast cancer is much debated [11–26]. There are contradictory data about the possibility that chemo and/or radiotherapy could favour the onset of a secondary leukemia. Already Rosner et al. in 1978, in a review of literature, observed that sAML occurred after BC with a sevenfold increased frequency over the expected number [11]. In the following years some population-based studies confirmed that this risk, compared with that observed in normal population, ranged from 2.7 to 24 times higher [12–14]. On the contrary, in other recent studies an increased risk in BC patients with respect to the normal population was not found [15, 16].

In most cases alkylating agents have been considered the most relevant leukemogenic agents, and among these, melphalan presented a higher leukemogenic role than cyclophosphamide [17].

In a recent prospective study by Levine et al., four cases of sAML were observed in 351 BC patients treated with a protocol including topoisomerase II inhibitors drugs (CEF), whereas none of the 359 patients treated with CMF developed a sAML [18]. Considering our series, CMF was administered in 10 patients and CEF in 9 patients. Although the median latency between BC and sAML was different in these two groups with a lower latency for patients who received topoisomerase II inhibitors, in accordance with data reported in literature (60 months in CMF patients; 41 months in patients treated with CEF or MMM) no statistical difference was found. This is probably due to the fact that in all cases treatments included alkylating agents, and that in most cases radiotherapy was also added.

Other reports emphasize the possible role of mitoxantrone in leukemogenesis [19–22]. Although some authors reported a high proportion of acute promyelocytic leukemia following BC treatment with mitoxantrone [22, 23], in our series we observed that only one out five promyelocytic leukemia patients previously received mitoxantrone.

The leukemogenic role of radiotherapy in the treatment of patients with BC was studied as well, but its role is unclear [12, 24–26].

In our study on sAML, we found that BC was the most frequent PM. It is well-known that BC, cancer of the uterus, and prostate cancer are very common in the normal population of Italy. The observation of a higher number of sAML in this group of patients, however, is probably related to the high proportion of patients that are cured for this disease with the recent therapies and the earlier stage of disease at the diagnosis of BC due to preventive medicine.

Our study is retrospective, starting from the diagnosis of AML, and is not population-based due to the absence of a common national registry for BC. Therefore, we are not able to calculate the relative risk of sAML in BC with respect to the normal population.

Interestingly enough, none of our patients previously treated with topoisomerase II inhibitors for BC showed the chromosome 11 abnormalities generally found in topoisomerase II inhibitors-related leukemia [27]. This may be due to the addition of radiotherapy, which is more often associated with deletions or unbalanced mutation [28].

It is noteworthy that 27% of our patients (10 of 37) did not receive any chemo-radiotherapy. Therefore, for these patients it may be hypothesized that sAML developed after a previous BC, occurring in the context of a predisposition to neoplastic disease related to genetically determined inherited alterations. This hypothesis is supported by the various studies which report a 7–30 times higher risk in those BC patients treated only surgically, with no chemo/radiotherapy [11, 29].

A common etiological mechanism or at least a predisposing condition favoring the onset of sAML with a previous BC can be envisaged, and in experimental studies with the Wistar rats a methylcholanthrene intraperitoneal injection can equally induce an acute leukemia or a BC [30].

As opposed to the observation of other authors regarding sAML following Hodgkin's disease [31], in our study the use of alkylating agents in the previous treatments for BC, administered in 18 of 21 patients who received chemotherapy, did not modify the response to chemotherapy for sAML. Furthermore, the CR rate of 74%, higher than in other studies, suggests a wide sensitivity to chemotherapy of sAML following BC.

In conclusion we think that large prospective studies on patients with BC, observed for long-term follow-up, associated with molecular biology studies performed on BC tissues and, possibly, on leukemic cells at onset of sAML, are necessary to answer the remaining questions regarding the development of secondary leukemia and to confirm the possible biological predisposition of BC patients to sAML.

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*Appendix

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