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Secondary myelodysplastic syndrome/acute myeloid leukaemia following mitoxantrone-based therapy for breast carcinoma

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Summary Of 1774 patients with breast cancer given mitoxantrone (MTZ) with methotrexate (n = 492) or with methotrexate and mitomycin C (n = 1282), nine developed MDS/AML after a median of 2.5 years. Median duration of survival from diagnosis of MDS/AML was 10 months and six patients died. The crude incidence of developing MDS/AML after MMM or MM chemotherapy was 15 per 100 000 patient years follow-up, while the actuarial risk was 1.1% and 1.6% at 5 and 10 years respectively. MTZ-based regimens carry a 10 × higher risk of subsequent MDS/AML compared to that seen in the general population. © 2000 Cancer Research Campaign

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Significant improvement in the management of breast carcinoma has been achieved over the last few decades, mostly because of the use of combinations of surgery, radiotherapy and chemoendocrine therapy (Powles et al, 1995; Fisher et al, 1997). Adjuvant and neoadjuvant chemotherapy is delivered with the intention of controlling micrometastases. The 20-year follow-up of the first combination chemotherapy regimen reported by Bonadonna et al (1995) involved cyclophosphamide, methotrexate and 5-fluoro-uracil. Various other combinations have been tried, and use of anthracyclines is reported to improve the results (Brincker et al, 1983); mitoxantrone has been tried in place of doxorubicin and may have fewer side-effects (Powles et al, 1991).

A number of chemotherapy drugs, especially alkylating agents and some anthracyclines used in breast cancer treatment, are associated with increased risk of secondary acute myeloid leukaemia (sAML) or myelodysplasia (MDS), (Pedersen-Bjergaard and Rowley, 1994). This analysis was undertaken in breast cancer patients to ascertain whether there is a similar risk of secondary AML/MDS associated with mitoxantrone.

PATIENTS AND METHODS

The prospectively maintained database at the Royal Marsden Hospital was used to identify patients with breast carcinoma treated with mitoxantrone-based regimens in the period 1984–1995. Patients who developed leukaemia or MDS were identified in the Royal Marsden Hospital database and also by accessing data reported to the Thames Cancer Registry. Details from these sources were cross-checked and found to be consistent.

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Chemotherapy regimens

From 1984–1992, 1282 patients received MMM (mitoxantrone 7 mg m^{-2} every 3 weeks, methotrexate 35 mg m^{-2} every 3 weeks, mitomycin C 7 mg m^{-2} every 6 weeks). From 1992 onwards mitomycin was excluded from the regimen since there was an increased incidence of haemolytic-uraemic syndrome (Montes et al, 1993), and the subsequent 492 patients were treated (in 1992–1995) with MM (methotrexate 35 mg m^{-2} every 3 weeks, and mitoxantrone 11 mg m^{-2} every 3 weeks). Patients also received local radiotherapy to the chest wall, and tamoxifen 20 mg daily. Table 1 summarizes treatments and characteristics of patients in the MMM and MM groups.

Diagnosis of MDS/AML

MDS/AML was diagnosed using French-American-British (FAB) criteria (Bennett et al, 1982; 1985). Cytogenetic analysis was performed using conventional methods.

Statistical methods

Patients were considered to be at risk of developing MDS/AML from the initial date of treatment with MMM or MM until the last follow-up or death. The actuarial incidence was calculated by the life-table method of Kaplan and Meier (1958). A comparison of patients treated with MMM and MM was carried out using the Logrank test. Survival after diagnosis of MDS/AML was also ascertained by the life-table method.

The expected numbers of acute myeloid leukaemias and myelodysplastic syndromes in an age/sex matched population were calculated by applying the age- and sex-specific figures for leukaemias in England and Wales (supplied by the Office of Population Census and Surveys) assuming a Poisson distribution to the person-years at risk. The age-specific incidence figures for MDS were obtained from the data published by Williamson et al (1994). The relative risk of developing AML/MDS was calculated

Table 1 Patients treated with MM/MMM

	MMM	MM
Number of patients	1282	492
Male/Female	5/1277	1/491
Age (median (range))	54 (20–90)	54 (27–83)
Local RT	366	319
No RT	214	84
RT (no information)[a]	702	89
Number of courses	6	6
(median (range))	(1–15)	(1–11)

[a] RT (local radiotherapy) data not available before April 1988

using the standardized incidence ratio, and confidence intervals are exact (Breslow and Day, 1987).

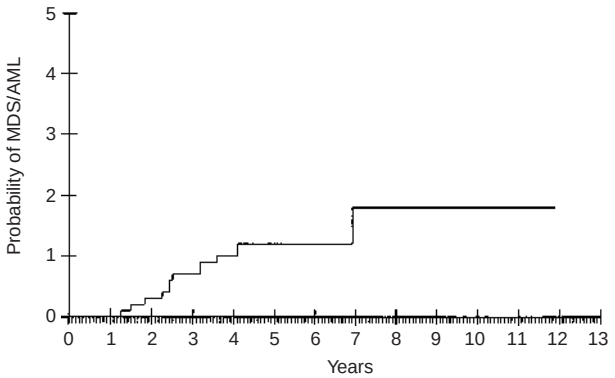

Figure 1 Incidence of MDS/AML after MZT-based chemotherapy.

RESULTS

In the period 1984–1995 1774 patients received MMM chemotherapy (n = 1282, median age 54 years, range 20–90) or MM (n = 492, median age 54 years, range 27–83) in adjuvant or neoadjuvant setting. Median follow-up was 5 years.

Five patients developed AML and four developed MDS after treatment with MTZ-based chemotherapy, giving an incidence of 15 per 100 000 years follow-up. The median age was 60 years (range 45–68). Details of the cases of MDS and AML are shown in Table 2. On average, MDS/AML developed 2.5 years (range 1.3–7) following MTZ-based chemotherapy (Table 2). There was no difference in incidence between prior MM or MMM chemotherapy (3/492 versus 6/1282; P = 0.9). The risk of developing MDS/AML at 5 and 10 years was calculated as 1.1% (95% CI: 0.6–2.2%) and 1.6% (95% CI: 0.7–3.6%) respectively (Figure 1). The relative risk of developing MDS/AML was 10.1 times greater than in an age- and sex-matched normal population (95% CI: 3.5–16.7). For MDS alone the risk was 8.6 times greater, and for leukaemia alone it was 14.1 times greater than in the normal population (Table 3).

Women with AML/MDS had received the following total drug doses: Mitoxantrone 80 mg (range 60–162 mg), methotrexate 310 mg (range 265–400 mg), in six cases with mitomycin 45 mg (range 39–51 mg). In addition to MTZ-based chemotherapy, all patients had surgery and additional chest wall irradiation, while five patients in this group had adjuvant therapy with tamoxifen. An abnormal cytogenetic clone was present in eight cases, while one patient had no clonal abnormality. Five individuals had abnormalities involving chromosomes 5 and/or 7, and three had

Table 2 Details of secondary MDS/AML patients

Case	Age (years)	Diagnosis	Ca. Breast T/T[a]	Regimen	Time to AML/MDS (years)	Total chemotherapy doses[d]			Cytogenetics	Outcome (months)
						Mitoxantrone	Methotrexate	Mitomycin		
A	64	AML M7	S, CT+RT, Tamox	MMM	3.6	68 mg (46.9)	270 mg (186.2)	39 mg (26.9)	45, XX, –7	Dead 2
B	50	AML M1	S, CT+RT	MMM	4.2	60 mg (37.5)	300 mg (187.5)	45 mg (28.1)	47, XX, +mar	Dead 1
C	71	MDS/RA	CT, S, CT+RT, Tamox	MMM	3.2	79 mg (45.1)	310 mg (177.1)	45 mg (25.7)	46, XX	Dead 10
D	46	AML M2	CT, S, CT+RT	MM	1.3	162 mg (93.1)	400 mg (229.9)	nil	46, XX, t(8;21)(q22;q22)	In CR1 60
E	75	MDS Hypoplas	HAD[c], S, HAD+RT	MM FEC[b]	2.5	96 mg (59.6)	320 mg (198.8)	nil	46, XX, del(1)(p32p34), del(5)(q13q33), der(7)t(7;12)(q3;q13), der(12)t(7;12)(q22;q13)	Dead 17
F	58	AML M3	CT, S, CT, RT, Tamox	MM	1.8	126 mg (70)	300 mg (166.7)	nil	46, XX, t(1;2)(p22;q21), t(15;17)(q22;q21)	In CR1 18
G	66	MDS RARS	CT, S, CT, RT, Tamox	MMM	2.4	77 mg (38.5)	265 mg (132.5)	50 mg (25)	45, XX, del(3)(p12),–7, –9 add(17)(p1), –8, +mars/ 45, XX, idem, del(5)(q3)	Dead 8
H	62	MDS	S, RT, Tamox	MMM	7	93 mg (51.7)	320 mg (177.8)	51 mg (28.3)	46, XX, –7, +mar	Alive 12
I	77	AML M2	S, RT, Tamox, VAC/VEC	MMM	2.4	80 mg (53.3)	400 mng (260.6)	40 mg (26.6)	45, XX, add(5)(q15), der(11) add(11)(p15)add(11)(q23), –18, del(20)(q13)	Dead 27days

[a] S = surgery, CT = chemotherapy, RT = radiotherapy; [b]FEC-5FU, epirubicin, cyclophosphamide, VAC/VEC = vincristine, adriamycin (epirubicin), cyclophosphamide, Tamox = tamoxifen; [c]HAD-hydroxyandrostenedione; [d]Total dose in mg, mg m^{-2} in parentheses

Table 3 Relative risk (RR) of developing MDS/AML compared to an age- and sex-matched population

	No. of cases	RR	95% CI	Significance
MDS/AML	9	10.1	3.5–16.7	$P < 0.01$
MDS	4	8.6	0.2–17.0	$P < 0.1$
AML	5	14.1	2.8–25.4	$P < 0.05$

complex abnormalities. Other chromosome abnormalities included t(8;21), t(15;17) with t(1;2), and one patient had an unidentified additional abnormality (Table 2).

Patient outcomes are shown in Table 2. All five patients with AML were treated with chemotherapy. Two are alive, and three died of chemotherapy-related problems. Four patients with MDS were over 60 years-of-age and were managed with supportive care alone; three have died. In one patient the MDS evolved into AML.

DISCUSSION

There has been significant improvement in survival and cure expectancy for patients with breast cancer due to combined modality treatment using surgery, chemotherapy and radiation. Selection of the optimum form of combination chemotherapy for breast cancer should take into account associated long-term risks. The CMF regimen is a standard regimen for adjuvant treatment and its long-term benefit has been established. However, there is a potential risk of secondary leukaemia associated with most of these drugs (Henderson et al, 1990).

Aul et al (1992) have shown that the risk of developing MDS/AML increases with age; the average annual incidence in all age-groups in the period 1986–1990 was 4.11 per 100 000 per year, with a considerable rise of incidence in the older population. The average incidence in the population > 70 years-of-age was 22.81 per 100 000 per year (33.88 for men and 18.02 for women), while the incidence of AML is 6.7 per 100 000 per year. Another study has confirmed an increased incidence of MDS in older patients (Williamson et al, 1994).

We assessed the incidence of MDS and AML occurring in a cohort of patients with breast cancer treated with mitoxantrone-containing regimens. The current report is one of the largest analyzing risk of secondary acute myeloid leukaemia after mitoxantrone in breast cancer patients. With a median follow-up of 5 years, there were nine cases of AML/MDS among 1774 patients giving a crude incidence of 15 per 100 000 years of follow-up.

Bonadonna et al (1993) noticed a cumulative risk of 0.23% +/– 0.15% at 15 years, and a relative risk 2.3 × greater compared to the normal population after a median follow-up of 12 years in patients receiving CMF. However, the Eastern Cooperative Oncology Group (ECOG) found a crude incidence rate of 26 per 100 000 years of follow-up for a secondary haematological malignancy after treatment with standard adjuvant chemotherapy, which with standard dose cyclophosphamide was not much higher than that seen in the general population (Tallman et al, 1995).

To improve tumour response rates and prolong survival, anthracycline-based regimens have been introduced, with results at least as good as those seen with CMF. However, the risk of secondary AML with doxorubicin-containing regimens has been found to be 1.5% (0.7–2.9%) at 10 years (Diamandidou et al, 1996) and the risk was significantly higher after chemoradiotherapy than after chemotherapy alone (10 year actuarial risk of 2.5% vs 0.5%). Mitoxantrone may be less toxic and has also been used more recently in combination chemotherapy for breast cancer (Powles et al, 1991).

To our knowledge there is no association between mitomycin and methotrexate and hematological malignancies (Rustin et al, 1996), and there are few reports concerning a possible leukaemogenic effect of mitoxantrone (Philpott et al, 1993; Mitchell et al, 1996). Therapy-related or secondary leukaemias often show cytogenetic abnormalities, and there are characteristic differences which may be specific for particular chemotherapy agents; alkylating agents are associated with abnormalities of chromosomes 5 and 7 while topoisomerase-II inhibitors are associated with chromosome 11 abnormalities. (Ellis et al 1993; Smith et al, 1996).

In our study, 67% of patients had predominantly unbalanced chromosome aberrations that are associated with prior radiotherapy and/or alkylating agent treatment, but not with mitoxantrone therapy. However, all the patients with MDS/AML had also received radiotherapy and hence it is possible that in our patients the risk of MDS/AML was more likely to be associated with the combination of chemotherapy and radiotherapy (Johansson et al, 1996).

Two patients in this series who had balanced translocations had a family history of cancer. One had a sister with brain cancer, while the other had a mother with lung cancer and a sister with breast cancer. Because of their family backgrounds, these patients may be in a high-risk category and more prone to developing a secondary malignancy; MDS/AML in this situation is more likely to represent a second primary rather than a secondary haematological malignancy (Thirman and Larson, 1996). An increased family incidence of haematological malignancies in these cases may also indicate a role for oncogenes and tumour suppressor genes in the development of MDS/AML (Skuse and Ludlow, 1995).

CONCLUSION

Our study has shown an increased incidence of MDS and AML after MTZ-based chemotherapy, compared to that seen in the general population. However, it is difficult to estimate how much of this is due to the MTZ-based chemotherapy rather than to the population being at higher risk because of family history, age or additional treatment with chemo/radiotherapy.

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