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Original Paper

Chemotherapy for Gestational Trophoblastic Tumours Hastens Menopause by 3 Years

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Chemotherapy may induce acute ovarian failure, but in women who retain gonadal function throughout chemotherapy, the late effects upon ovarian function are unknown. A retrospective controlled survey was performed to ascertain whether chemotherapy for gestational trophoblastic tumours (GTT) results in premature menopause. Questionnaires were sent to 1,489 women diagnosed between 1971 and 1990 with GTT, including 1089 who had received chemotherapy and 400 who had not received chemotherapy (controls). Responses were obtained from 972 chemotherapy-treated patients and 327 controls. 124 women were not evaluable for menopause date as they had undergone hysterectomy as part of the treatment for GTT or had developed permanent amenorrhoea during chemotherapy. Overall, 172 women reported that they were postmenopausal, including 157 women who had received chemotherapy. The median age at menopause for the evaluable population was 50 years (range 25–56 years). The age at menopause was significantly earlier in the treated arm (median 50, range 25–56 years) than in the controls (median 53, range 40–57 years) (logrank test $\chi^2 = 12.6$, $P = 0.0004$). Menopause occurred significantly earlier in women treated with combination chemotherapy (median 49, range 25–56 years) compared with single agent methotrexate (median 51, range 25–56 years) (logrank test $\chi^2 = 8.3$, $P = 0.004$). However, the age at completion of chemotherapy in the treated arm did not influence the age of menopause (proportional Hazards $\chi^2 = 1.99$, $P = 0.16$). Chemotherapy for GTT induces menopause 3 years earlier than it occurs in women with GTT who do not receive chemotherapy. Although the difference is statistically significant, the magnitude is modest and most women can be reassured that neither fertility nor postmenopausal osteoporosis will be greatly affected. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THERE ARE an increasing number of women surviving long term following curative cytotoxic chemotherapy and gonadal function in these women has become a focus of concern. Many studies have focused on ovarian failure, pregnancy and risk to offspring following chemotherapy. Most women who are successfully treated with combination chemotherapy before the age of 25 years retain their normal ovarian function [1–5]. Although there have been reports of women whose menses returned after chemotherapy subsequently developing amenorrhoea, it remains unknown whether women who receive chemotherapy are at risk of an early menopause.

A large cohort of women have been treated with chemotherapy for gestational trophoblastic disease in our unit and remain in contact through monitoring assays for human chorionic gonadotrophin (hCG). A control group of women were recruited who were registered for hCG follow-up following the diagnosis of hydatidiform molar pregnancy, but who had not required chemotherapy for persistent trophoblastic disease. We undertook a postal questionnaire survey of these women enquiring about the age of menopause.

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PATIENTS AND METHODS

Between 1958 and 1990, 1,377 women were treated with cytotoxic chemotherapy for gestational trophoblastic disease in our unit. Questionnaires were sent to 1,089 women known to be long-term survivors still resident in the U.K. who were on hCG monitoring follow-up. The questions were designed to detect the date of menopause and the occurrence of second malignancies and have been presented elsewhere [6]. Women were asked about their health, hospital admissions and obstetric history since they completed the chemotherapy, whether they had reached menopause and if so at what age.

In addition to the 1,089 women who were long-term survivors resident in the U.K. following chemotherapy for gestational trophoblastic tumours (GTT), questionnaires were sent to 400 women who were registered with our unit for hCG follow-up following hydatidiform moles who did not receive chemotherapy. These control patients were selected from the hydatidiform mole registration database which was established in 1973 and was computerised in 1984. Control patients were chosen from the same years as the treated patients if a valid address and post code were available on the computer, as the majority of these women are only monitored for 6–24 months and so may have changed address since last follow-up. This control group was chosen in order to minimise the effects of other fertility-related variables on the age at menopause, although we recognise that this control group may differ from the general population.

Chemotherapy regimens have evolved from methotrexate as a single agent in 1958 to sequential administration of different single agent cytotoxics to combination chemotherapy. Since 1974, the chemotherapy regimen has depended upon the prognostic risk group of the patient [7]. In most cases, the treatment has been standardised since the current high risk chemotherapy regimen was introduced in 1979. The methods by which treatment was tailored to prognostic factors, the full drug protocols and the results of therapy are described fully elsewhere [8–10].

In brief, the low risk treatment consists of four doses of methotrexate 50 mg on alternate days with folinic acid 6 mg 30 h after each methotrexate injection, followed by a 6 day rest period. The medium risk regimen consists of the low risk regimen plus hydoxyurea 1 g on day 1 and mercaptopurine 75 mg on the same day as the folinic acid, alternating with courses of either etoposide 250 mg/m^2 on days 1 and 3 or courses of actinomycin-D 0.5 mg daily for 5 days. The high risk regimen consists of methotrexate 300 mg/m^2 day 1 followed by folinic acid and etoposide 100 mg/m^2 plus actinomycin-D 0.5 mg on days 1 and 2 (EMA), alternating every week with vincristine 0.8 mg/m^2 plus cyclophosphamide 600 mg/m^2 (CO). Patients received repeated courses until the hCG levels had returned to within the normal range for 6–10 weeks. There was no long-term daily drug administration and no maintenance therapy.

Statistics

The time to menopause was calculated from the date of birth until reported date of last menstruation or censored at the date of answering the questionnaire for premenopausal women. The menopause-free survival was plotted according to the method of Kaplan and Meier [11]. The logrank method was used to test for the significance of differences in menopause-free survival distributions [12].

RESULTS

Questions regarding menopause were completed by 972 women treated with for GTT, representing 89% of questionnaires sent. Responses were obtained from 327 women in the control arm (82% of questionnaires sent). For 124 women it was not possible to evaluate the date of menopause as the women had either undergone a hysterectomy as part of their treatment for GTT or had developed permanent amenorrhoea whilst receiving chemotherapy for GTT. 42 of these women received hormone replacement therapy, whilst 66 have not been prescribed hormone replacement. Overall, there were 1,175 women evaluable for menopausal status. The median age of these patients at the time of answering the questionnaire was 38 years (range 18–74 years) and the median interval from GTT diagnosis to questionnaire completion was 11 years (range 1.4–34 years). Although the control patients were younger at the time of GTT diagnosis (median age 24.8 years compared with 27.3 years for the treated women, Mann–Whitney U test $P < 0.0001$), the interval between diagnosis and the time of answering the questionnaire was greater for the control women (median 11.9 years compared with 10.2 years for the treated women, Mann–Whitney U test $P < 0.0001$). The clinicopathological details of the cohort of patients are shown in Table 1.

Overall, 172 evaluable women reported that they were postmenopausal, including 157 women who had received chemotherapy. The median age at menopause for the evaluable population was 50 years (range 25–56 years). The age at menopause was significantly earlier in the treated arm (median 50, range 25–56 years) than in the control arm (median 53, range 40–57 years) (Figure 1, logrank test $\chi^2 = 12.6$, $P = 0.0004$). Furthermore, the nature of the chemotherapy influenced the age of menopause. Menopause

Table 1. *Clinicopathological details of patients included in this report*

	All patients responding	All patients evaluable for menopausal status	Treated patients evaluable for menopausal status	Control patients evaluable for menopausal status
Total	1299	1175	848	327
High risk chemotherapy	180	147	147	0
Medium risk chemotherapy	358	299	299	0
Low risk chemotherapy	434	402	402	0
No chemotherapy	327	327	0	327
Combination chemotherapy	538	446	446	0
Single agent chemotherapy	434	402	402	0
Premenopausal		1003	691	312
Postmenopausal		172	157	15

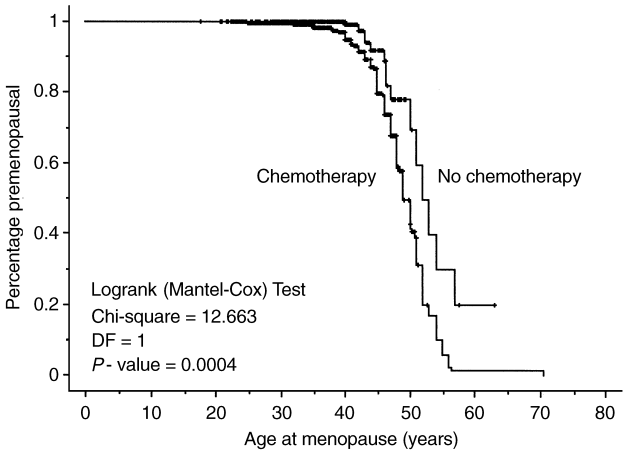

Figure 1. Kaplan–Meier plot of age at menopause of women evaluable for menopausal status divided according to whether they received chemotherapy or not.

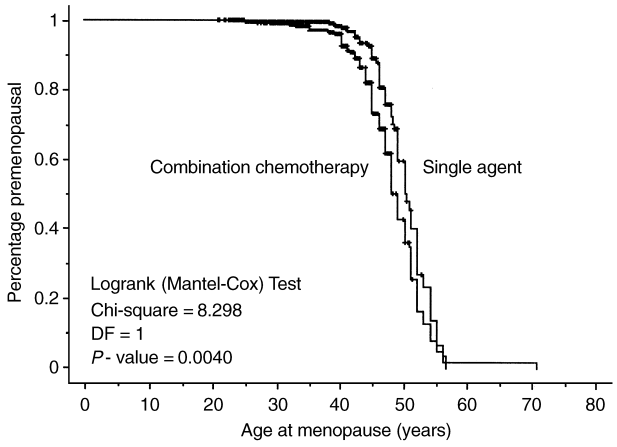

Figure 2. Kaplan–Meier plot of age at menopause of treated patients evaluable for menopausal status according to treatment with single agent methotrexate chemotherapy or combination chemotherapy.

occurred significantly earlier in women treated with combination chemotherapy (median 49, range 25–56 years) compared with single agent methotrexate chemotherapy (median 51, range 25–56 years) (logrank test $\chi^2 = 8.3$, $P = 0.004$) and in the high risk chemotherapy (median 47, range 27–55 years) than the medium (median 49, range 25–56 years) or low risk groups (median 51, range 25–56 years)(logrank test $\chi^2 = 26.9$, $P < 0.0001$) (Figures 2, 3 and Table 2). Single agent methotrexate chemotherapy led to significantly earlier menopause compared with the untreated control group (logrank test $\chi^2 = 4.7$, $P = 0.03$) but there was no significant difference in the age at menopause between low risk and medium risk treatments (logrank test $\chi^2 = 2.7$, $P = 0.1$).

The age at diagnosis in the treated women (median 27.3 years) was significantly higher than in the control women (median 24.8 years) (Mann–Whitney U test $P < 0.0001$). However, the age at completion of chemotherapy in the treated arm did not influence the age of menopause (proportional hazards $\chi^2 = 1.99$, $P = 0.16$).

DISCUSSION

Pretreatment fertility in men with testicular tumours and Hodgkin's disease is impaired [13], but pretreatment amenorrhoea is uncommon in women with Hodgkin's disease [14]. None the less, it has been suggested that premenopausal women with breast cancer are more frequently having anovulatory cycles [15] and this suggests that these women are subfertile prior to therapy. In contrast, all women with GTT who make up this cohort are fertile by definition prior to treatment.

Table 2. Median ages and range of menopause for all groups

Group	Median age of menopause years (range)
All evaluable respondents	50 (25–57)
Control (no chemotherapy)	53 (40–57)
All chemotherapy	50 (25–56)
Single agent methotrexate	51 (25–56)
Combination chemotherapy	49 (25–56)
High risk chemotherapy	47 (27–55)
Medium risk chemotherapy	49 (25–56)
Low risk chemotherapy	51 (25–56)

Cytotoxic drugs disrupt ovarian follicular structures resulting in fibrotic 'streak' ovaries. Serum levels of 17-oestradiol and progesterone fall and luteinising hormone (LH) and follicle stimulating hormone (FSH) rise. Gonadal toxicity was widely recognised in men treated with chlorambucil and cyclophosphamide in the 1970s. In women, ovarian failure has been reported with the use of cyclophosphamide [16], vincristine [17, 18], high-dose methotrexate [18] and etoposide [19], although the effects may be reversible. Combination chemotherapy regimens for Hodgkin's disease and adjuvant combination chemotherapy for premenopausal breast cancer have been found to induce ovarian failure. In these cases the patients' age at the time of treatment and the chemotherapy regimen used were the major determinants of ovarian failure [14, 20–22].

This present study addresses the late effects of chemotherapy upon ovarian function in women with normal pretreatment ovarian function. Both single agent and combination chemotherapy resulted in early menopause, although age at the time of treatment was not a significant determinant in this cohort. In females, proliferation of germ cells is completed during intrauterine life and numbers fall progressively.

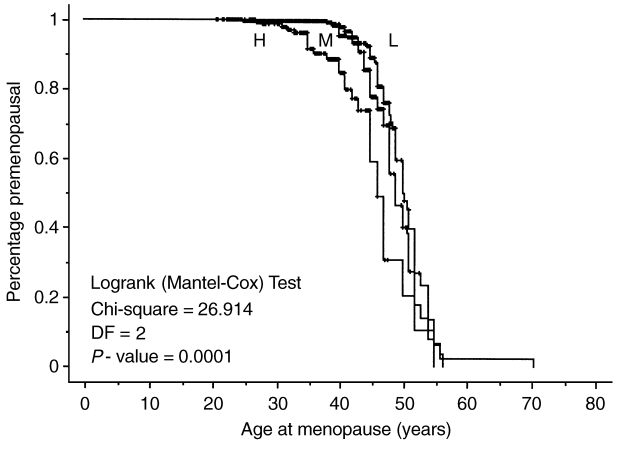

Figure 3. Menopause free survival (Kaplan–Meier) of treated women evaluable for menopausal status according to treatment protocol received. The logrank test results compare the age at menopause in the high-risk (H) group with that in the low (L) and medium (M) risk groups together.

Thus, younger women have greater reserves of follicles and might be expected to be more resistant to chemotherapy-induced ovarian failure. Patients receiving combination chemotherapy had menopause 2 years earlier than those treated with single agent therapy and patients receiving the high risk protocols had earlier menopause than those receiving the medium risk and low risk regimens. These results suggest that chemotherapy contributes to premature ovarian failure and early menopause and that alkylating agents that are included in the high risk schedule (cyclophosphamide) may be particularly culpable in this respect. The omission of an alkylating agent from combination chemotherapy for Hodgkin's disease led to the development of the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen. ABVD has been found, in a randomised trial, to be as effective as MOPP (mustine, vincristine, procarbazine, prednisolone), but without causing amenorrhoea [22]. None the less, even the use of single agent methotrexate for GTT was associated with menopause 2 years before that recorded by the control group, although this therapy has been shown not to induce second malignancies [6] and further investigation is required to substantiate this effect.

Potential sources of bias in our data may relate to the lower questionnaire response ratein the control arm (82% compared with 89% in the treatment arm). This is because many women in the control arm are no longer on hCG monitoring and so the residential addresses are less up to date. In addition, no women in the control arm had had hysterectomies prior to menopause, whilst over 100 women in the treatment arm were not evaluable for the date of menopause as they had hysterectomies as part of the management of GTT. None the less, the median age of menopause in the control group was similar to that reported in a longitudinal survey of the onset of menopause from the Massachusetts Women's Health Study. A cohort of 2570 women aged 45–55 years were followed for 5 years and the median age of natural menopause was 51.3 years [23]. The control group of women with GTT that did not require chemotherapy may not be an accurate reflection of the general population, as there will be no infertile women and since molar pregnancy is more common in older women, the group will have included more women who have late pregnancies.

Chemotherapy has a modest effect upon the age at menopause in women treated for GTT, which in the majority of women will be of little practical importance. For older women who wish to conceive, physicians may choose to warn their patients of the shortened window of fertility following treatment of GTT. We advise all women treated with chemotherapy for GTT not to become pregnant for 1 year following completion of chemotherapy, as early pregnancy will mask serological diagnosis of relapse. Thus, the optimal timing of pregnancy needs to be considered and should not be delayed too much as these findings demonstrate that these women are at risk of early menopause. Furthermore, the early ovarian failure caused by chemotherapy may necessitate treatment with hormone replacement therapy and women and their primary care physicians should be aware of this late complication of chemotherapy.

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