

## LATE TOXICITY AFTER THERAPY OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

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### 24.1 INTRODUCTION

A higher proportion of patients with gestational trophoblastic tumours or neoplasia (GTT or GTN), as opposed to other tumour types, are at risk of long-term toxicity because of the very high cure rate and young age at treatment. Consequently, prolonged surveillance of these patients post-treatment is essential to facilitate (1) detection of late side effects and (2) subsequent modification of therapy to minimize late risks. This chapter investigates several well-known late side effects of chemotherapy such as infertility and induction of second tumours as well as the psychological sequelae of both losing a pregnancy and having to receive therapy for cancer.

### 24.2 SECOND TUMOURS

There is often suspicion when a patient develops a second tumour that it is related to the initial therapy. However, before the era of chemotherapy, Moertel *et al.* (1) found that 2.8% of patients with a primary cancer subsequently developed a different primary tumour indicating that patients with malignancy may be generally more susceptible to developing this disease. This could be due to an underlying genetic defect in patients with many solid tumours (2) or to the associated immunodeficiency in patients who have leukemia or lymphoma. Unlike other cancers, GTN does not display somatic genetic defects although there may be a potential to modulate the immune system, since this cancer uniquely expresses paternal antigens in a maternal background.

Most anticancer agents act by causing chromosomal damage to neoplastic cells but also cause damage particularly to rapidly proliferating normal tissue. It is therefore not surprising that this damage may be carcinogenic and teratogenic. Continuous collation and analysis of clinical and laboratory data on cytotoxic drugs currently in use suggest that alkylating agents, anti-tumour antibiotics, cisplatin, procarbazine and etoposide are either identified as carcinogens or under strong suspicion, whilst the antimetabolites emerge as relatively safe (3-5). Many reports of second tumours associated with cytotoxic chemotherapy have described high total doses of alkylating agents given over a long period, in many cases continuously. It is not yet clear whether the second tumours seen after high-dose therapy and marrow grafting are related to the high-dose therapy or the large total amount of chemotherapy that these poor-risk patients had received.

Most patients who require chemotherapy for GTN fit into the low-risk prognostic group and are cured using single-agent chemotherapy with either methotrexate and folinic acid or Actinomycin D (6-8). Patients with high risk GTN receive combination chemotherapy which most frequently comprises etoposide, methotrexate and actinomycin D (EMA) alternating with cyclophosphamide and vincristine (CO) (9, 10). Furthermore, some may require the addition of cisplatin and/or paclitaxel containing combinations and rarely high dose chemotherapy (11). Consequently, this latter group of patients might be predicted to suffer more long term toxicity.

#### 24.2.1 SECOND TUMOURS FOLLOWING METHOTREXATE OR ACTINOMYCIN D

Methotrexate has been shown to cause chromosomal damage in rodents but has not been found to be carcinogenic, possibly because of the short life span of these animals (12, 13). In humans, apart from odd case reports, larger studies have failed to link methotrexate with an increased risk of tumours. Indeed, in a study of 205 patients with psoriasis receiving intermittent oral methotrexate, no increase in cancer risk was seen compared to a matched control group (14).

The first case-control study of second tumour incidence after therapy of GTN investigated 457 long-term survivors treated between 1958 and 1978 (15). Methotrexate and folinic acid (MTX-FA) was given to all but two patients, and 261 (57%) also received other drugs. After a mean period of 7.8 years since the beginning of treatment and a total of 3522 patient-years of risk, second tumours had developed in two women but would have been expected in 3.5. This study was then extended to include 1,377 patients treated up to 1990 with 15,279 patient years of follow-up (11 mean years post-treatment) (16). In this large group, 554 women treated with MTX-FA showed no significant increased risk of second tumours compared to matched controls (RR = 1.3; 95% CI, 0.6-2.1). A recent update in 1903 patients treated until 2000 with more than 32,000 patient years of follow-up has shown that in the 871 patients receiving MTX-FA alone the standardized incidence ratio (SIR) for cancer was actually lower than expected for the population (MTX-FA; SIR, 0.7; 95% CI, 0.5 to 1.1) (17). From this data, one can probably state with considerable confidence that single agent methotrexate does not appear to increase the chances of developing another cancer relative to the general age matched population. So what about actinomycin D? Similar results are not yet published for actinomycin D alone but in the latest analysis from Charing Cross there were 221 patients who received sequential MTX-FA followed by actinomycin D who showed a SIR of 1.4 (95% CI, 0.9 to 2.3) for developing cancer. This is unlikely to be a significant effect given the numbers of cases but further work is required (17).

#### 24.2.2 SECOND TUMOURS FOLLOWING COMBINATION CHEMOTHERAPY

In 1987 Ratain *et al.* (18) suggested that etoposide could induce leukaemias in patients treated for non-small cell lung cancer. Since then many others reported an increased incidence of acute myeloid leukemias after either etoposide or tenoposide given to patients with acute lymphoblastic leukemia, germ cell tumours, small cell lung cancer, neuroblastoma and non-Hodgkin's lymphoma (19-24). Interestingly, these leukaemias frequently show characteristic chromosomal translocation involving 11q23. The risk of secondary acute myeloid leukemia (AML) has been shown to be related to increasing dose and more frequent schedule of administration of podophyllotoxins. A cumulative risk at six years of 12% was found in children receiving therapy twice weekly or weekly, whilst it was 1.6% or less in those receiving less frequent tenoposide or etoposide (19). Among 1990 patients who received etoposide, usually three-weekly for germ cell tumours, 16 (0.8%) developed leukemia (22). A more recent overview of 5 germ cell tumour trials has shown that while total cumulative dose is important when given over many months, short term high dose administration of etoposide does not appear to increase leukaemogenic risk (25). However, while an overview of 12 NCI studies where topoisomerase II inhibitors were used in various cancers has confirmed an increased leukaemogenic risk, it failed to show any link between total dose given and / or duration of treatment (26).

In view of the above, it seems likely that women with GTN treated with etoposide-containing combination drug chemotherapy would be more likely to develop leukaemias. Indeed, in our study of 1377 patients treated for GTN between 1958-1990, those receiving combination drug therapy showed a significant increase in the rate of acute myeloid leukaemia compared to an age matched population (RR = 16.61, CI 5.40—38.9,  $p < 0.000$ ) (16). Whilst this risk of leukaemia persists in the modern analysis, surprisingly, the overall risk of developing a second cancer is not increased by EMA/CO chemotherapy. Indeed, in the extended analysis of patients treated up to 2000, in the 255 patients who received EMA/CO either alone or after MTX/FA with or without actinomycin D, the SIR for all cancers was 0.9 (95% CI, 0.4 to 2.2) (17).

The explanation for the increased leukaemia risk is clear but why is the overall risk of second cancers unchanged. The recent data suggests that this is because there is a reduced risk in other types including those originating in the lung, ovaries and breast. As seen previously, the duration of chemotherapy is associated with risk of second cancers and keeping treatment under 6 months seems sensible (16, 17).

Cisplatin has been introduced into the management of some patients with GTN since 1977 (27). This agent is known to cross-link DNA and there is increasing evidence that it may induce second tumours in patients previously exposed to the drug. Studies in ovarian and testicular cancer have shown that cisplatin is leukemogenic in a dose-dependent fashion (28, 29). It may also induce other second tumours including bowel and breast cancers (30, 31). Cyclophosphamide used in the EMA/CO regimen also has

leukemogenic potential, which is significantly enhanced by combination with other agents inhibiting topoisomerase II (32, 33). Our present data is still not sufficient to determine the effects of cisplatin or the more recently introduced paclitaxel on second cancer risks (17).

The above findings have helped us to modify our clinical practice. We now treat all former middle risk GTN patients with single agent methotrexate and those patients who become resistant to this drug are given actinomycin-D rather than etoposide containing combination drug therapy if their hCG is  $\leq 300$  IU/L. For those requiring combination chemotherapy, either because of high risk disease or methotrexate resistance with an hCG  $> 300$  IU/L, we try to limit the duration of therapy to less than 6 months. Using this approach, we have not recently seen any new patients with second leukaemias (8, 17).

### 24.2.3 GENETIC FACTORS LINKED TO THERAPY-INDUCED SECOND TUMOURS.

Recent advances in high through-put screens using genomic, proteomic and metabonomic technologies have heralded a new era. These approaches should enable us to select treatments, predict response, outcome and also longterm side-effects of therapies. Indeed, the use of next generation sequencing, methylated DNA arrays, RNAseq, metabonomics and protein/reverse-phase protein arrays have already yielded interesting results in several human diseases (34-40). For example, expression of certain genes can predict response to particular drugs in lung cancer (37). So is there any evidence that these approaches might identify genes linked with risk of second cancers? Recent work in children with leukaemia has shown that several gene clusters may predict risk of therapy induced secondary acute myeloid leukaemias suggesting that we might be able to identify patients where we may wish to use less of certain cytotoxic drug classes (35). This raises the hope that we might be able to use these techniques to identify metabolic, genetic or epigenetic signatures predictive of subsequent second tumours or other late side-effects from chemotherapy given to women with GTN.

## 24.3 EFFECT OF THERAPY ON GONADAL FUNCTION

### 24.3.1 FERTILITY

Women treated for GTN are almost all in the reproductive age group and many desire to bear children after recovering from therapy. Cytotoxic drugs are well-recognized as a potential cause of sterility. Permanent ovarian failure has been reported in over 50% of women treated for Hodgkin's disease (41, 42). The factors associated with the gonadotoxic effect of chemotherapy include age, and dose, type and duration of therapy. It is clear among women treated for Hodgkin's disease, that many of those treated below the age of 30 maintain

menses during and following treatment. Human ovaries acquire their quota of oocytes before birth, following which there is no further proliferation of germ cells. This might explain why the ovary appears more resistant to the effects of chemotherapy than the testis. It might also suggest that antimetabolite cytotoxic drugs that require proliferation to be effective may cause less sterility than drugs such as alkylating agents that damage DNA of resting cells. Once the ovary is damaged by chemotherapy with follicle destruction and ovarian fibrosis, the hormonal effects are far greater than after cytotoxic damage to the male gonad. There is an elevation of serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) with a decrease in serum estradiol. This leads to temporary or permanent amenorrhea and symptoms associated with the menopause.

It has been known since the 1970s that pregnancies can occur after chemotherapy of trophoblastic neoplasms (43). A large study of women treated for GTN between the years of 1957 to 1990, analyzed the obstetric records of 1211 long-term survivors. These women were followed up for a mean of 12.3 years and of 93% who wished to conceive post-treatment, 83% had at least one live birth(44). This compares very favourably with the general population. Strikingly, there was no significant difference in conception rate or pregnancy outcome between those women treated with methotrexate as a single agent, and those receiving multi-agent chemotherapy (including combinations of actinomycin D, cyclophosphamide, 6-mercaptopurine, vincristine, and, after 1979, etoposide and cisplatin) ( $\chi^2=0.21$ ,  $P=0.90$ ). It is, however, our clinical impression that women treated with combination chemotherapy after the age of 35 years are at increased risk of therapy- induced ovarian failure (17).

Others have also found that etoposide fails to significantly impair fertility. Adewole *et al.* (45) found that 77% of 74 women who received etoposide and wished to conceive succeeded in having at least one live birth. When correcting for two patients with a previous history of infertility he found only six (8.1%) of the patients had true post-chemotherapy infertility problems.

Patients with GTN sometimes require the addition of cisplatin to achieve cure. The specific effects of this agent on fertility in women with GTN have not yet been assessed. However, cisplatin-based therapy has been used for years in the management of young women with ovarian germ cell tumours (GCT). In an early report we found that menstruation restarted in 16 of 17 women who had a remaining ovary and uterus after therapy (46). In a more recent analysis, 28 of 35 women with prior treatment for their ovarian GCT attempted to conceive and of these, 21 succeeded in having one or more pregnancies (47). Thus, the fertility rate following cisplatin-containing chemotherapy appears to be about 75% in women with ovarian GCTs. It should be noted, however, that these patients will often have had more extensive pelvic surgery than patients with GTN and so may have other causes for subsequent infertility problems.

With the introduction of the taxanes into the management on GTN is there any evidence that these drugs will behave differently with regard to fertility? Thus far comparatively little is known.

However, the available evidence in animals and patients suggests that these agents like the older drugs have little effect on fertility (48, 49). High dose therapy appears more likely to induce fertility problems though (50) and so in the rare patients who undergo this there might be a case for considering ovarian tissue harvesting and cryopreservation before the procedure (51). The issue here is that patients will have been heavily pre-treated by this stage and so the safety and benefit of ovarian tissue cryopreservation is unclear.

#### 24.3.2 TERATOGENICITY

Patients with GTN are advised to avoid pregnancy for one year after completing chemotherapy, for three reasons: (1) the physiological rising titre of hCG during pregnancy prevents early detection of recurrent disease, which is most likely to occur in the first year of follow-up; (2) cytotoxic drug-induced genetic damage to the eggs might be repaired in the first year of follow-up minimizing subsequent teratogenic effects; (3) the potential increased risk of GTN relapse driven by a new pregnancy. The transient period of anovulation post-therapy, as well as some psychological loss of confidence towards pregnancy (see below), suggests that patients may be relatively unlikely to become pregnant soon after completion of their chemotherapy.

Nevertheless, a review of 1532 patients treated for trophoblastic disease (52) found that 230 of these women did become pregnant within 12 months of completing therapy (22% having received single-agent, and 10% multi-agent chemotherapy). Interestingly, relapse rates were not significantly different in these patients, compared to those who did not become pregnant (2 and 2.5% vs. 5 and 5.6% in the single- and multi-agent groups, respectively). Moreover in a more recent series of 1204 patients treated with either low or high risk chemotherapy between 1998-2012, 255 pregnancies occurred within 12 months of chemotherapy. Curiously, the incidence of relapse was actually only 1.7% in the early pregnancy group as compared to 5.2% in the 963 patients who did not conceive early(53).

In terms of pregnancy outcome: both the Blagden and Williams papers show a full term baby rate of between 71-73%, with no significant increased risk of congenital abnormalities, miscarriage, ectopic pregnancy, second molar pregnancy or stillbirth as compared to the general U.K. population (52, 53). Consequently, this study indicates that early pregnancy following chemotherapy for GTN does not increase the rate of relapse and is not associated with an increased risk of fetal malformation. Although there were no maternal deaths associated with recurrent disease during pregnancy, one woman did present with breathlessness due to progressing lung metastases late in pregnancy. In view of the potential for life-threatening complications due to late presentation, we still advise our younger patients to avoid a pregnancy during the first year of follow-up post-treatment for GTN. However, for more mature women who are keen to get on with having their families they can be reassured of a likely favourable outcome.

Other studies have also examined the question of chemotherapy-

induced teratogenicity in GTN. Woolas similarly reported an overall 1.7% incidence of congenital abnormalities in 680 women treated for GTN who had become pregnant (44). However, the stillbirth rate was significantly greater when compared to the general population. Ross found no excess of malformations in 78 infants born to women treated for trophoblastic diseases (54). The rate of congenital abnormality in 112 babies born to a sample of 85 women treated with EMA-CO was found to be 2.6% (9). Thus, women treated for GTN can be reassured that their fertility is unlikely to be impaired and they are not at increased risk of having a congenitally-malformed child.

Children born to mothers who had received chemotherapy may be at increased risk of developing cancer though this has not become apparent from studying progeny of women treated for GTN. There were 455 women who answered the question in our questionnaire 'Have any of your children born since receiving chemotherapy had a serious illness?' Only 1% after low-risk, 0.9% after middle-risk and 0.6% after high-risk therapy answered "yes" and none reported any malignancies.

### 24.3.3 AGE OF MENOPAUSE

The menopause is considered to have occurred when menstrual cycles have ceased for more than one year and there is no evidence of ovarian steroid hormone production. The average age of menopause of women in developed countries is considered to be 52 years. Alkylating agents have been shown in mice to cause oocyte destruction, but for there to be a major effect on the reproductive lifespan, over 80% of the oocytes need to be destroyed (55). Mathematical models have been produced based on total follicle counts of ovaries obtained from women suddenly dying or removed at surgery (56). They suggest a bi-exponential decline, with the faster decline occurring when numbers had fallen to 25000 at the age of 37.5 years. The model predicts that a 50% reduction before age 30 years resulted in menopause being reached at 44 years and 0.6 year later for every subsequent year until age 37.5, after which it is reached at 48 years.

Many women develop temporary ovarian failure during cytotoxic chemotherapy. Based on the comments above one could assume that provided over 20% of oocytes remain there would be recovery of ovarian function. However, despite recovery there is likely to be a reduction in the number of menstrual years. To assess this we have over the years sent out questionnaires to our GTD patients who either remained untreated or received chemotherapy for GTN.

A survey between 1971 and 1990 including 1089 patients who had received chemotherapy and 400 who had not received chemotherapy (controls) provided responses 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 GTN 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  $\chi^2 = 1.99$ ,  $P = 0.16$ ). Consequently, combination drug chemotherapy for GTN induces menopause 3 years earlier than it occurs in women with GTD who do not receive chemotherapy (57).

A more recent analysis has confirmed that multiagent chemotherapy hastens the age of the menopause (17). These findings, though expected, have several implications. Women who receive any form of chemotherapy should be told of the risk of an early menopause. This information could alter the age at which they intend to become pregnant. However, becoming menopausal three years early is unlikely to increase the risk of osteoporosis and cardiovascular disease in these women.

#### **24.4 PSYCHOLOGICAL SEQUELAE**

Emotional disturbance is commonly seen after pregnancy loss due to miscarriage. Interestingly, Ngan and Tang found that among women who had a molar pregnancy, those who required chemotherapy were less disturbed by the pregnancy loss than those who did not receive chemotherapy (58). This may be due to those requiring chemotherapy being more preoccupied with their disease, chemotherapy and fear of death.

Many women are surprised that they become most depressed soon after completing chemotherapy. Their lives have been controlled by the need to get through chemotherapy and once finished they feel lost and have difficulty organizing their lives again. This is probably due to feeling physically weakened by the treatment, due to the disruption to their lives, delayed grief over their pregnancy loss and expectation of euphoria once treatment is finished. Warning patients that they may become depressed or not happy on completing chemotherapy often relieves the distress.

Table 24.1 gives the findings from our questionnaire that was sent to 1089 women after successful chemotherapy for GTN. Thirteen per cent who answered a question on anxiety and depression wrote that they had sought or wanted help for anxiety or depression secondary to treatment for GTN. Four per cent felt isolated and wanted, but did not receive, counseling. Patients treated for GTN at the Charing Cross Hospital are only followed by urine or serum hCG levels after completing chemotherapy and do not return to the clinic. A more recent study examining a range of quality of life issues in women treated 5-10 years previously for GTN revealed that 51% would appreciate a counseling program today and 74% would have

appreciated counseling at the time of therapy (59). Consequently, GPs need to remain aware that their patients need continued support and a prospective analysis of counseling during initial treatment for GTN is required.

Berkowitz found that 80% of patients with gestational trophoblastic disease had a change in their outlook on life (60). This was less commonly seen among Chinese women (58). Decreased sexual activity has been noted often because of the fear of getting pregnant again and 44% of those who required chemotherapy reported more tense sexual relationships (60). However, 87% of these American women felt that their marital relationships were either unchanged or closer as a result of their experiences with GTN, whilst marital problems were reported in only 1% of the Charing Cross patients. Our more recent collaborative retrospective study of both US and UK populations 5-10 years post chemotherapy has shown that our patients enjoy a good quality of life, with physical, social and emotional functioning comparable to, or better than, comparative population norms (61) and (59). This is essentially excellent news and our patients should continue to be reassured of their likely favourable outlook. However, prospective studies are still needed to fully assess quality of life issues and the benefits of counseling.

**Table 24.1** Anxiety or depression following chemotherapy for GTT

Ever sought or wanted help	280/974	29%
Due to treatment at Charing Cross	123/931	13%
Fear of cancer/recurrence	25/123	
Fear of treatment (not cancer)	20/123	
Isolation, need for counselling	34/123	
Adverse effect on marriage	10	
Fear of subsequent pregnancy	8	
Attempted suicide	1	
Contemplated suicide	1	

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