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RESULTS OF LOW-DOSE METHOTREXATE TREATMENT OF PERSISTENT GESTATIONAL TROPHOBLASTIC DISEASE IN SHEFFIELD 1980–1987

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Abstract

Between January 1980 and October 1987, 115 evaluable patients were treated in Sheffield for persistent gestational trophoblastic disease (GTD) with a low dose methotrexate regimen (LD-MTX). Each course comprised MTX 50 mg given by i.m. injection for 4 doses on alternate days. Courses were repeated every 2 weeks and serum β-hCG was used to monitor response. Overall, 80/115 (70%) of patients attained durable complete remissions (CR). Twenty-nine patients received the 'AVC' salvage combination of actinomycin-D 0.5 mg i.v. for 5 days, sequenced with cyclophosphamide 500 mg i.v. and vincristine 1 mg i.v., both given for 3 doses on alternate days. Sixteen (55%) patients attained a durable CR but 11 (38%) required further measures, 7 ultimately requiring hysterectomy. Two (7%) died during treatment. With 4 deaths overall (3 from metastatic GTD and 1 from infarction of the bowel), actuarial survival is 94% at over 7.5 years. A new Charing Cross prognostic scale weighted especially for hCG levels, number and sites of metastases, interval between pregnancy and start of treatment (score 0–6 each factor), was applied retrospectively to obtain a total score for each patient. Thus, 21/26 (81%) patients who scored >8, required additional treatment after LD-MTX, compared with 18/ 89 (20%) of lower scoring patients ($p<0.001$). Because of the frequent morbidity associated with prolonged chemotherapy as well as the development of drug-resistant GTD, it is concluded that the 'high-risk' patients should receive more intensive combination chemotherapy at the outset.

Key words: Uterine neoplasms; persistent trophoblastic disease, low-dose methotrexate.

Gestational trophoblastic disease (GTD) encompasses a spectrum of disorders from a disease with low malignant potential to one of the most highly malignant human tumours. Nonetheless, even in its systemic manifestations, GTD is one of the few malignancies where expectations of cure realistically approach 100%. It is also an 'ideal' tumor since the activity of disease virtually equates with the levels of urine and serum human chorionic gonadotrophin (hCG) (2, 6).

It has been recently estimated that GTD arises at an incidence of 1.5 : 1 000 pregnancies in the UK (5). Since 1973 Sheffield has, along with the Charing Cross Hospital and Ninewells Hospital, Dundee, provided a subnational registration service for patients with GTD. All evidence suggests that the problem of GTD in the UK, is continuing to show a progressive annual increase (5) and this has been clearly reflected in the rising number of annual registrations received in Sheffield. Despite this, the proportion of patients treated has remained under 10% (5, 16) and has settled around 5 to 6% in Sheffield. These rates are considerably lower than those reported from North America (12) where, in some centres, a policy of prophylactic chemotherapy has been advocated (18).

Sheffield has treated the great majority of patients with persistent GTD (invasive mole, choriocarcinoma) referred from within the catchment area of the North Midlands, North Wales and the North of England. All such patients have received first line chemotherapy with single-agent methotrexate, regardless of the type of disease or mode of presentation. The period from 1980 identifies a well-defined group of patients placed on lifelong follow-up, in whom the criteria for treatment and subsequent progress has been based on regular assays of the beta subunit of serum hCG (β-hCG). The outcome of treatment in these patients is described below.

Material and Methods

The Sheffield supraregional registration scheme was first established in 1973 and, up to the 1st of October 1987, 3875 patients had been registered, following the diagnosis

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Table 1

Mode of initial presentation

Suction/evacuation	60
Prostaglandin induction	12
Spontaneous abortion	20
Term delivery	12 (1 stillbirth)
Tubal ectopic	4
Abdominal hysterectomy	3
Metastatic disease only	2*
Partial hysterectomy	1
Missed abortion	1

* Both had undergone prostaglandin-induced delivery of hydatidiform mole, 2 years previously, and one had subsequently undergone hysterectomy. Four other patients had presented with molar pregnancies 2–5 years previously: 2 of these had required methotrexate for persistent, invasive mole.

Table 2

Treatment regimens

Low-dose methotrexate

MTX(50 mg i.m. q. 48 h ×4
Folinic acid: 7.5 mg, 30 h after each MTX
Treatment cycled every 2 weeks, with
treatment-free intervals of 1 week,
to complete remission +2 further months of therapy

'AVC' salvage combination

Actinomycin-D: 500 μg i.v., daily ×5 2-week interval, then:
Cyclophosphamide: 500 mg i.v.
Vincristine: 1 mg i.v.
Both, given on alternate days ×3 10-day interval, et. seq.

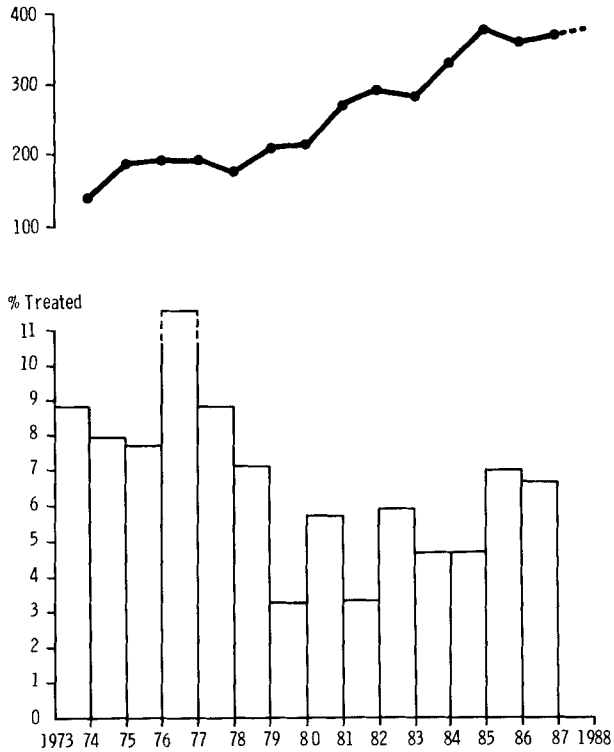

Figure. Gestational trophoblastic disease registered in the Sheffield catchment area January 1973–October 1987. Total registered: 3875. Total treated with chemotherapy: 225 (5.8%). Total deaths: 6 (0.1%). Upper diagram: Annual number of registrations. Lower diagram: Percentage treated each year.

of gestational trophoblastic disease (GTD). Over the 14-year period, the annual rate of registration approximately trebled (Figure). Out of this population, 3646 patients underwent no further treatment following the complete evacuation of hydatidiform mole while 225 (5.8%) received additional treatment with chemotherapy; 209 (93%) of these patients were treated at Weston Park Hospital.

Patients. For the purposes of this study, the period from the 1st of January 1980 was chosen since from this time lifelong follow-up was established and all records are thus complete and up to date. At the same time, the introduction of an assay for the beta subunit of human chorionic gonadotrophin (β-hCG) enabled great accuracy in the monitoring of treatment progress. Thus, during the period of time up to the 1st of October 1987, 129 patients received low-dose methotrexate for persistent GTD. Of these, 115 are considered evaluable, since 11 patients were treated elsewhere and 3 patients with atypical histology were excluded. The clinical modes of presentation in the 115 patients are given in Table 1.

Pathology. Requests for slides of pathological material were made to the referring centres, wherever possible and were reviewed by one of us (ASH). Classification of the tumours was made along the guidelines recommended in a WHO report (24) and gave the following results: complete (classical) mole, 81 patients (70%); partial mole, 5 (4.5%); classical mole + choriocarcinoma, 3 (3%); choriocarcinoma, 21 (18%) and unknown histology in 5 patients.

Staging. Endocrine investigations included assays for urinary hCG and serum β-hCG, serum prolactin, thyroid function and oestradiol. The full blood count, serum electrolytes, urea, creatinine and liver function were also measured. Imaging investigations included pelvic ultrasonography and whole-body computed tomography as well as plain radiography of the chest. Patients with multiple pulmonary metastases and β-hCG levels exceeding 10^5 IU/l, also underwent lumbar puncture for measurement of β-hCG levels within the cerebrospinal fluid and a CSF: blood ratio of $<1:60$ was regarded as negative.

Treatment. The guidelines of the WHO report (24) were followed in determining the requirements for treatment of individual cases. In addition, local practice prescribed treatment for any patient with persistently raised β-hCG levels after a maximum of 2 dilatation-curettages (D&C). Details of the 1st-line low-dose methotrexate regimen (LD-MTX) as well as the salvage 'AVC' combination, are given in Table 2.

Although both urinary hCG and β-hCG were monitored throughout treatment, decisions on the duration of therapy were based exclusively on the monitoring of β-hCG

Table 3

Charing Cross Hospital prognostic scoring system

Criterion	0	1	2	6
Age (years)	<39	>39		
Antecedent pregnancy	Mole	Abortion or unknown	Term	
Interval to treatment (months)	<4	4–7	7–12	>12
hCG: IU/l	10^3–10^4	$<10^3$	10^4–10^5	$>10^5$
ABO blood group (female×male)		A×O	B×A or O	
		O×A	AB×A or O	
		O or A×		
		Unknown		
No. of metastases	Nil	1–4	4–8	> 8
Sites of metastases	ND	Spleen	GI tract	Brain
	Lungs	Kidney	Liver	
	Vagina			
Largest tumour mass	<3 cm	3–5 cm	>5 cm	
Previous chemotherapy	Nil		Single drug	Multiple

Low risk: 0–5
Medium risk: 6–9
High risk: >9

Table 4

Response to low-dose methotrexate (LD-MTX) and salvage therapy with actinomycin-D, vincristine and cyclophosphamide (AVC)

Response to low-dose MTX	
Receiving treatment	115
Attaining CR	83
Requiring no further treatment	80 (70%)
Failing LD-MTX	35 (30%)
Response to AVC	
Receiving treatment	29
Attaining CR	19 (65%)
Requiring no further treatment	16 (55%)
Failing AVC	13 (45%)
Outcome of 13 patients failing AVC	
Total abdominal hysterectomy	7 (54%)
(3: after receiving etoposide)	
(2: relapsed after initial response to AVC)	
(1: progressively rising hCG levels)	
Referred to Charing Cross Hospital	2*
Responded to etoposide	1
Lobectomy for persisting lung nodule	1
Died of progressive disease	1
Died in treatment, but responding	1

* Both, successfully salvaged and remain well and free of disease.

levels. Complete remission (CR) was considered to have been achieved when β-hCG levels fell within the normal range (6 IU/l, or less). LD-MTX was continued either to a minimum of 6 courses, or to CR with an additional 2 courses. Since 1985, however, it has been the policy to extend treatment to 8 weeks beyond CR (in practice, 4–5 additional courses).

Treatment was changed to the 'AVC' combination in any patient, either who developed sustained plateauing of raised β-hCG levels, or in whom there was a sustained and progressive rise in these levels. Treatment with AVC was then continued to CR, followed by at least one additional course.

On completion of chemotherapy, arrangements were made to obtain serum β-hCG levels every 2 weeks for 6 weeks and, thereafter, monthly for 6 months. Subsequently, patients were followed up with urinary hCG levels which, after 3 years, were obtained annually.

Prognostic scoring. Analyses of prognostic factors in persistent GTD have been carried out in detail, at the Charing Cross Hospital, London (4, 14, 24). In 1983, a simplified prognostic scoring system was introduced (Table 3). In order to evaluate how far this system could be retrospectively applied to the patients treated in Sheffield, all patients were scored for the various prognostic factors and a cumulative total was obtained for each case.

Statistical analysis. Calculations of actuarial survival were derived, according to the methods of Kaplan & Meier (11).

Results

The maximum follow-up for the 115 patients is 7.8 years and minimum follow-up 1 month, from completion of treatment. The actuarial survival beyond 7.5 years was 94%. Only 3 of 83 patients who achieved CR with LD-MTX, have subsequently relapsed, these being at intervals of between 2 and 8 months. Thus, 80 (70%) patients achieved complete eradication of GTD with LD-MTX alone, while 35 (30%) patients required further therapy (Table 4). Twenty-nine patients received chemotherapy with AVC (Table 4). This figure includes 28 patients treated initially in Sheffield as well as one patient whose disease had progressed following suboptimal treatment with LD-MTX at a district hospital centre. Despite AVC salvage, 2 patients died and 11 (38%) patients required further treatment, as outlined in Table 4. All 11 of these

ultimately attained durable remissions although, in the majority, this was achieved at the expense of prolonged additional chemotherapy ultimately terminating in excisional surgery to remove resistant disease foci.

Of the 7 patients who did not receive treatment with AVC, 6 were successfully salvaged: 2 following total abdominal hysterectomy for uterine rupture and 4 who received a combination of etoposide and actinomycin-D which has now replaced AVC as the second-line salvage regimen (Table 7). The 7th patient, who was not salvaged, died of widely metastatic disease unresponsive to any treatment. Details of the 4 patient deaths during the study period are described in Table 5. These 4 deaths include that of a patient in 1980, whose disease had recurred 2 years following apparently successful treatment with LD-MTX in 1978. The actuarial survival for the 115 patients, excluding the latter patient, is thus 95% at nearly 8 years. Mention should, however, be made of 3 other deaths, 2 of which occurred prior to 1980. One patient treated in 1974, died of a haemorrhage into a cerebral metastasis while the other, initially treated in 1977, required prolonged chemotherapy for resistant GTD but was eventually salvaged with multi-agent chemotherapy at the Charing Cross Hospital. Following this, however, she succumbed to acute leukaemia. An additional patient died in 1986 from widespread pulmonary metastases, before she could be transferred to Sheffield from the referring hospital.

The results of treatment were retrospectively analysed in relation to the cumulative prognostic scores assigned to each patient and derived from Table 4. Although there was some suggestion that a medium-risk category could be defined (Table 6), the clearest separation was between a 'low-risk' population with a maximum score of 7, and a 'high-risk' group which scored 8 and above. The 'cure' rate for the former, with LD-MTX, was 80% as compared with less than 20% for the latter.

The reasons for treatment failure in low-scoring patients could not be confidently ascertained. In 7 patients, no individual factors could be clearly identified, while 4 patients probably received insufficient treatment with LD-MTX. Of the remainder, 2 experienced a uterine rupture while on treatment; one patient aged 45, presented with true choriocarcinoma and a history of a hydatidiform mole which had been completely evacuated 5 years earlier; yet another patient presented with choriocarcinoma following a term delivery. Control of disease proved difficult and she eventually required a total hysterectomy to eradicate residual tumour.

When analysed according to the presence or absence of pulmonary metastases, 36 patients presented initially with pulmonary involvement of which 17 (47%) required additional treatment, compared with 19/79 (24%) who did not ($p<0.05$) Despite the relatively high incidence of pulmonary disease, only one particularly high-risk patient (total prognostic score >16) developed a cerebral metastasis after prolonged chemotherapy for resistant choriocarcino-

Table 5

Details of couses of death

Age (years)	Year	Clinical Details	Cause
31	1980	Re-presented 2 years after successful treatment with MTX for invasive mole, with widespread lung metastases	GTD
25	1981	Invasive mole with multiple lung metastases. Partial response to low-dose MTX. No response to any subsequent chemotherapy	GTD
22	1982	Re-presented 18 months after successful MTX therapy of invasive mole. New presentation with liver metastases of choriocarcinoma following a term delivery. No response to chemotherapy	GTD
45	1985	Re-presented 3 years after complete evacuation of a hydatidiform mole, with lung metastases from choriocarcinoma. Ultimately required treatment with the 'AVC' regimen to which she responded. Died from mesenteric artery thrombosis at a time when platelet count exceeded 800×10^9/l.	Therapy

Table 6

Prognostic factors: Role of the Charing Cross System

Score	No. treated	No. re-treated	
0–5	83	14 (17%)	
			$p<0.001$
6–9	19	12 (63%)	
			p NS
>9	16	13 (81%)	
0–7	89	18 (20%)	
>8	26	21 (81%)	$p<<0.001$

Note: 9/13 (69%) of patients whose treatment with AVC was not successful, scored >8.

Table 7

Treatment modifications from May 1987

'Low-risk' group Max. score 7
Low-dose methotrexate

'High-risk' group score >8
Methotrexate: 300 mg/m^2 i.v. in 12 h
Folinic acid: 15 mg, 6-hourly ×8 doses, commencing 24 h after start of MTX 7-day interval, then:
Actinomycin-D: 500 μg i.v. daily ×3
Etoposide: 100 mg/m^2 i.v. daily ×3 7-day interval, et seq.

Methotrexate-resistance
Actinomycin-D: 500 μg i.v. daily ×3
Etoposide: 100 mg/m^2 i.v. daily ×3 7-day interval, et seq.

ma (she was successfully salvaged after craniotomy and multi-agent chemotherapy at the Charing Cross Hospital). Thus, the incidence of cerebral metastasis appearing during treatment is 3% of those presenting with pulmonary metastases or 0.9% overall. Two patients have presented with liver metastases since 1980: one died shortly after commencing treatment and the other, not included in the present analysis, is currently proceeding through treatment with multi-agent chemotherapy and is demonstrating an excellent response to this.

Discussion

In an entirely unselected and non-stratified patient population, the results of LD-MTX as initial therapy in persistent GTD have been highly satisfactory, with 70% of patients attaining permanent eradication of disease. The toxicity of LD-MTX is low (4) and in this practice no patient has withdrawn from treatment as a result of intolerance. It has also been previously shown that the great majority of patients wishing to conceive subsequent pregnancies may do so (19) and this has also been the experience of this centre, although in keeping with the Charing Cross Hospital policy, we advise patients to avoid pregnancy for 12 months from the conclusion of treatment.

The outcome of the 30% of patients who required additional treatment has been more problematic. Although only 2 patients treated since 1980 have died as a direct consequence of progressive metastatic disease (one of these, before any effective treatment could be initiated), treatment has often been prolonged and resulted in considerable physical and psychological morbidity. Patients who responded to the AVC regimen usually did so promptly, with over 50% in CR by the completion of one course, and all but one in CR at the end of the second cycle. In the remainder, the development of resistant disease precluded a successful outcome, a factor to which the relatively lengthy intervals between courses of AVC may have contributed. The morbidity associated with intensive salvage chemotherapy, e.g. alopecia, gastrointestinal symptoms, myelosuppression, etc., has usually been predictable and short-lived. Nonetheless, the majority of patients who failed to enter CR with AVC, have ultimately required hysterectomy with the resulting termination of reproductive capacity. Furthermore, although there is no evidence of a significantly increased risk of second tumours with treatment (20), the occurrence of acute myelogenous leukaemia in a patient who received very extensive chemotherapy in 1977, indicates the need to restrict the length of exposure to treatment to the minimum necessary to secure permanent eradication of disease.

There is, therefore, a clear requirement to identify patients who should receive more intensive chemotherapy at the outset, both to achieve a rapid response and to avoid the occurrence of resistant GTD. Efforts to subdivide patients into differing categories of risk have been based on the identification of factors likely to predict for the development of resistant disease. Factors relating to the success of chemotherapy in eliminating persistent GTD have been well investigated (3, 7, 9, 12, 13, 17, 23, 24) and all reports have reached broadly similar conclusions with particular weight attached to the time interval between the antecedent pregnancy and the start of treatment, the bulk of tumour (assessed by hCG levels, number of metastases), the mode of pregnancy (term or molar) and the influence of preceding chemotherapy. Factors predicting the likelihood of requiring chemotherapy following evacuation of a molar pregnancy may also help to identify problematic patients (5, 10, 22). Since prostaglandin induction appears to encourage vascular invasion and hence, metastatic spread (21), this method of evacuation is not recommended. It is, therefore, of some interest that 2 patients in this report had presented 2 years after the medical termination of molar pregnancy, with resistant metastatic disease.

The Charing Cross Hospital scoring system has, retrospectively, enabled the identification of a clear 'high-risk' patient group which, in this practice, accounts for under 25% of all patients. However, an intermediate-risk category was not defined as a distinct group and, moreover, despite high cumulative scores, 20% of the high-risk group still responded satisfactorily to LD-MTX. Similarly, 20% of the low-risk patients have required additional therapy for reasons which cannot be readily defined, although inadequate treatment with LD-MTX was contributory in a proportion. It must be said, however, that the clinical practice in Sheffield differs from that of the Charing Cross Hospital in 2 important respects. In the first place all patients are, for practical purposes, previously untreated. In the second place, in the absence of a policy of cranial prophylaxis, we have not observed the relatively high incidence of intracerebral metastases previously reported (1).

The treatment of high-risk patients has been greatly enhanced through discovery of the potent activity of etoposide (VP16-213) in GTD (15). In one centre, oral etoposide is now the first-line treatment of all low and intermediate-risk patients (25). At the Charing Cross Hospital, the incorporation of etoposide in chemotherapy regimens has allowed for considerable simplification of the management of high-risk patients. The 5-drug 'EMACO' regimen replaced the earlier, considerably more toxic, 'CHAMOCA' combination (4, 14) and is reported to result in cure rates approaching 100% in previously untreated patients (16). One of the main tenets of this regimen is in ensuring that treatment intervals are kept to the minimum possible, to prevent the emergence of resistant disease.

Since May 1987, treatment in Sheffield has been modified to take into account these factors. All high-risk patients will now receive combination chemotherapy with the 3 most effective drugs, methotrexate, actinomycin-D and etoposide, as detailed in Table 7. Patients with metho-

trexate-resistant GTD now receive actinomycin-D and etoposide, also detailed in Table 7. Thus far, one high-risk patient with multiple pulmonary and liver metastases has been treated: β-hCG levels are approaching normal after a rapid response to treatment. Four patients with methotrexate-resistant disease have now been treated with actinomycin-D and etoposide and all have demonstrated a prompt response to treatment.

Surgery has a major role in the salvage of localised drug-resistant disease, e.g. confined to the uterus, or in the removal of isolated metastatic lesions at thoracotomy or craniotomy (8, 16, 23) but has little part to play in the primary management of GTD except for the emergency treatment of uterine rupture or persistent haemorrhage, by total abdominal hysterectomy.

In the treatment of invasive mole and frank choriocarcinoma, the prospects for cure approach 100%, given the right selection of treatment at the outset. In the experience of this centre, the use of the LD-MTX regimen has resulted in cure rates of 70%, overall. Despite this, more than 80% of high-risk patients are likely to require additional treatment and the management of almost half of these has posed considerable problems. The retrospective use of a prognostic scoring system devised by the Charing Cross Hospital has enabled the identification of the poor-prognostic group and it is proposed that these patients will, in future, be treated with an intensive combination of actinomycin-D, methotrexate and etoposide, in order to ensure rapid eradication of disease as well as the avoidance of resistant disease.

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