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Impact of the revised FIGO/WHO system on the management of patients with gestational trophoblastic neoplasia

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ABSTRACT

Objective. To study the effect of a change in disease scoring systems on the management of patients with gestational trophoblastic neoplasia (GTN) in our supra-regional treatment centre.

Methods. We reviewed disease characteristics and treatment outcomes in 632 GTN patients managed at our centre from 1973 to 2006. Two disease scoring systems were used sequentially, the Sheffield modification of the Charing Cross Scoring System (SCCSS) before 2000, and the revised FIGO/modified WHO system (FIGO 2000) thereafter.

Results. Using the SCCSS 573 (90.7%) patients were classified as low risk (LR) and 59 (9.3%) as high risk (HR). With FIGO 2000, 587 (92.9%) were LR and 45 (7.1%) HR. For LR patients, the complete response (CR) to first line single agent chemotherapy was 77% before 2000 and 61.6% from 2000 to 2006. For HR patients, the CR rates with first line chemotherapy were 79.5% and 75% respectively.
The higher threshold for assigning a patient as HR using FIGO 2000 had an impact on the success of treatment; only 7/19 patients (37%) who were scored 6 by FIGO 2000, and thus treated as LR with methotrexate/folinic acid, achieved a CR.

Conclusion. In our experience, the revised FIGO/modified WHO scoring system has down scored some patients who would have been considered as high risk with the previous scoring system. A trend to lower CR with first line chemotherapy and an increase in the need for second line chemotherapy was seen.

Introduction

Despite the fact that anatomical/clinical classifications and prognostic scoring systems of gestational trophoblastic diseases have been in use for many years there is no agreement on which is the best [1].

Bagshawe presented a weighted prognostic scoring system dependent on a range of parameters [2]. This subsequently formed the basis of the WHO (1982) [3] and the Charing Cross systems [4]. The Charing Cross System originally divided patients into 3 risk groups; low risk (0≤5), medium risk (6 to 9) and high risk (>9) [4]. In Sheffield, a modified Charing Cross scoring system was used for more than twenty years to stratify patients into low (≤7) or high risk (>7) groups [1].

However, Dubuc-Lissoir et al. [5] advised that such systems should only apply to patients with metastatic disease, since those with non metastatic GTN could fall into the high risk group and thus be over treated. Previously, a clinical classification developed by Hammond et al. [6], categorised GTN as either non metastatic or metastatic with the latter being subdivided into good and poor prognostic groups according to βhCG level, duration of symptoms, brain/liver metastases, prior chemotherapy failure and whether the pregnancy was term.

Recently it has been agreed that the anatomical FIGO staging should be retained and combined with a simplified WHO score in which ABO blood group risk factors are eliminated, the risk score for liver metastases increased, and placental site trophoblastic tumours excluded. This system has become known as FIGO 2000 [7].

Whatever stratification is used, a structured approach to clinical management is however essential [8].

In the UK, all patients diagnosed with a molar pregnancy are followed up with regular human chorionic gonadotrophin (hCG) urinalysis. In the majority of patients the trophoblastic disease remits following one or more uterine evacuations and there is no need for systemic therapy. In those where trophoblastic disease persists, the criteria for considering chemotherapy at our institution are as follows [9]:

- βhCG plateau for 4 measurements over 3 weeks.
- a rise in βhCG of 10% or greater for at least 3 values over 2 weeks.
- metastases in liver, brain or gastrointestinal tract or lung metastases larger than 2 cm on chest x ray.
- histological diagnosis of choriocarcinoma.
- raised βhCG level 6 months after molar pregnancy evacuation.

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Table 1
Charing Cross Prognostic Scoring System

Criterion	Score			
	0	1	2	6
Age (years)	≤39	>39		
Antecedent pregnancy	Mole	Abortion or unknown	Term	
Interval to treatment (months)	<4	4 to 6	7 to 12	>12
hCG (IU/l)	10^3	10^3 to 10^4	10^4 to 10^5	10^5
ABO blood group (Female×male)		A×O O×A O or A×unknown	B×A or O AB×A or O	
Number of metastases	Nil	1 to 4	4 to 8	>8
Sites of metastases	None detected, lungs, or vagina	Spleen, kidney	GI tract, liver	Brain
Largest tumour mass (cm)	<3 cm	3 to 5	>5 cm	
Previous chemotherapy			Single drug	2 or more drugs

Low risk: ≤0–5, medium risk: 6 to 9, high risk: >9 [4].
Sheffield modification: low risk: ≤7, high risk: >7 [1].

Table 3
Treatment regimens at Weston Park Hospital

Risk		Regimen
Low risk	First line "low dose methotrexate"	Methotrexate 50 mg intramuscular alternate days×4. Folinic acid 7.5 mg* oral 24 h after methotrexate. 7 day intervals between cycles.
	Salvage "AE"	Dactinomycin 0.5 mg/day IV×3. Etoposide 100 mg/m^2/day IV×3. 7 day intervals between cycles.
High risk	First line "MAE"	Arm A: methotrexate 300 mg mg/m^2/IV. Folinic acid 15 mg 6 hourly commencing 24 h after methotrexate (eight doses, the first intravenous). Alternating with arm B ("AE" as above) with 7 day intervals between each arm.
	Salvage "CEC"	Cisplatin 25 mg/m^2/IV daily×3 Etoposide 100 mg/m^2/IV daily×3 Cyclophosphamide 600 mg/m^2/IV day 1. 7–10 day intervals between cycles.

IV: intravenous.
Hancock et al. [18].
* Increased to 15 mg from 2000.

The aim of this study was to review the management of our patients with GTN according to the two slightly different prognostic scoring systems.

Materials and methods

Patients

Sheffield is one of three supra-regional screening centres (and one of two treatment centres) in the UK for the management of gestational trophoblastic diseases. All patients were initially managed locally by a gynaecologist and by uterine evacuation(s). Patients with evidence of persistent GTN were admitted to our unit for assessment including history, physical examination, serum βhCG level, chest x-ray, computerised tomography (CT) scan of the chest and an ultrasound scan of the abdomen and pelvis. Histological diagnosis was centrally reviewed.

Risk stratifications

Before 2000, patients requiring chemotherapy were assigned a risk score using the Sheffield modification of the Charing Cross Prognostic Scoring System (SCCSS) (Table 1). Patients with a score of 7 or less were classified as low risk (LR) and suitable for single agent chemotherapy with methotrexate while those with a score more than 7 were considered as high risk (HR) and given combination chemotherapy. After 2000, the revised FIGO/WHO system (FIGO 2000) was used with LR defined as a score 6 or less and HR as more than 6 (Table 2).

Chemotherapy regimens

First line chemotherapy in patients with LR disease was intramuscular methotrexate on days 1, 3, 5 and 7 with alternate day oral folinic acid (MTX/FA) on days 2, 4, 6, and 8 repeated every 14 days while for HR patients a regimen of intermediate dose methotrexate alternating with dactinomycin plus etoposide (MAE) was used. Patients with central nervous system (CNS) involvement also received intrathecal methotrexate and a higher dose of intravenous methotrexate (1 g/m^2). Patients continued on chemotherapy for 6 weeks after achieving a biochemical complete response (CR) (at least 2 additional cycles) (Table 3).

A complete remission (CR) on chemotherapy was defined as three consecutive weekly normal βhCG levels (<2 IU/l). A change of chemotherapy was indicated if a CR was not achieved or in the event of unacceptable toxicity. Follow up was life long, initially with monitoring of serum βhCG and then urine hCG at increasing intervals thereafter.

Table 2
FIGO 2000 classification for gestational trophoblastic neoplasia

FIGO 2000 classification for GTN [7]				
A. Staging				
Stage I	Disease confined to the uterus.			
Stage II	GTN extends outside the uterus, but is limited to the genital structures (adnexa, vagina, and broad ligament).			
Stage III	GTN extends to the lungs, with or without known genital tract involvement.			
Stage IV	All other metastatic sites.			
B. Scoring	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4 to <7	7 to <13	≥13
Pre-treatment serum hCG (IU/ml)	<10^3	10^3 to <10^4	10^4 to <10^5	≥10^5
Largest tumour size (cm) (including uterus)	<3	3 to <5	≥5	–
Site of metastasis	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	–	1 to 4	5 to 8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

Source: FIGO Oncology Committee (2002). GTN: gestational trophoblastic neoplasia; hCG: human chorionic gonadotrophin. FIGO: the International Federation of Gynaecology and Obstetrics.
Low risk≤6, High risk>6.

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Table 4
Patients' characteristics

Number (*N*) of patients	Before 2000		2000–2006		Total number
	465		167		632
	N	%	*N*	%	
Risk groups					
LR	426	91.6	151	90	577
HR	39	8.4	16	10	55
Histology					
Hydatidiform mole	401	86.2	140	83.8	541
Choriocarcinoma	64	13.8	27	16.2	91
FIGO staging					
I	371	79.8	138	82.6	509
II	7	1.5	–	–	7
III	76	16.3	25	15	101
IV	11	2.4	4	2.4	15
N of vaginal evacuations					
One evacuation	375	80.6	161	96.4	536
Two or more evacuations	90	19.4	6	3.6	96
Status					
Alive	449	96.6	165	98.8	614
Dead	15	3.2	2	1.2	17
Lost to follow up	1	0.2	–	–	1

LR: low risk, HR: high risk.

Analytical methods

We reviewed the demographic and treatment data from patients with GTN who presented to the Sheffield Trophoblastic Disease Centre at Weston Park Hospital, Sheffield between 1973 to 2006 using an electronic database, supplemented by information from patient records. All patient data were anonymized prior to statistical analysis. Survival was calculated from the first day of treatment until death or the last recorded date of follow up. SPSS statistical package version 15 was used. The Kaplan–Meier method was used for survival analysis.

Results

Patients' characteristics

A total of 632 patients were managed in our centre between 1973 to 2006. This represents 5.3% of all registrations of gestational trophoblastic disease over this time period. Patients with placental site trophoblastic tumour were excluded from this analysis. The median age at presentation of our patients was 27 (range 15 to 58 years).

Before 2000, 465 patients with persistent GTN were managed in our centre. There were 426 patients (91.6%) classified as LR and 39 (8.4%) as HR as stratified by the SCCSS. Four hundred and one patients (86.2%) had hydatidiform mole and 64 (13.8%) had choriocarcinoma. Most (371) patients (79.8%) were FIGO stage I (Table 4).

From 2000 to 2006, a further 167 patients with persistent GTN were managed in our centre. There were 151 (90%) LR patients, and 16 (10%) HR as stratified by FIGO 2000. One hundred and forty patients had hydatidiform mole (83.8%) and 138 patients (82.6%) were FIGO stage I (Table 4).

Response to chemotherapy

We studied the response to chemotherapy in 2 separate time periods corresponding to the use of the different scoring systems; before 2000 and from 2000 to 2006. The median number of chemotherapy cycles was 6 cycles of MTX/FA regimen (range 1 to 16) for LR patients and 7 of MAE (range 1 to 10) for those classified as HR.

1973 to 2000

Before 2000, complete responses (CR) were achieved in 329 (77%) LR patients and 31 (79.5%) HR patients (Table 5). Second line chemotherapy regimens were required in 105 patients (22.6%) of the total 465 treated with chemotherapy These were for incomplete response (92 LR and 8 HR patients) or unacceptable toxicity to first line chemotherapy (5 LR patients). In the case of LR patients, AE

Table 5
Response to chemotherapy before 2000 and from 2000 to 2006

Total *N* of patients treated with first line chemotherapy	Before 2000		2000 to 2006	
	465		167	
	Low risk	High risk	Low risk	High risk
N of patients according to risk	426	39	151	16
First line chemotherapy, *N* (%)				
MTX/FA	426 (100)	–	151(100)	–
MAE	–	39 (100)	–	16 (100)
Response, *N* (%)				
CR	329 (77)	31 (79.5)	93 (61.6)	12 (75)
Plateau (static βhCG)	79 (18)	3 (7.7)	42 (27.8)	4 (25)
PD (rising βhCG)	13 (4)	2 (5.1)	5 (3.3)	–
Unacceptable toxicity	5 (1)	3 (7.7)	11 (7.3)	–
N of patients treated with second line chemotherapy	97	8	58	4
Second line chemotherapy, *N* (%)				
AE	55 (56.7)	–	40 (69)	–
MAE	8 (8.2)	–	5 (8.6)	–
CEC	–	6 (75)	–	–
EP/EMA	–	2 (25)	1 (1.7)	4 (100)
AVC	34 (35.1)	–	–	–
IVA		–	11 (19)	–
BEP			1 (1.7)	
Response, *N* (%)				
CR	90 (92.8)	6 (75)	51(87.9)	3 (75)
PLATEAU	2 (2.1)	1 (12.5)	2 (3.4)	–
PD	5 (5.1)	1 (12.5)	5 (8.7)	1 (25)
TAH (+chemotherapy) for resistant GTN	26	2	10	3

N: Number; **MTX/FA**: Methotrexate/folinic acid; **MAE**: Methotrexate, dactinomycin, etoposide; **EP/EMA**: Etoposide, cisplatin/etoposide, methotrexate, dactinomycin; **AE**: Dactinomycin, etoposide; **CEC**: Cisplatin, etoposide, cyclophosphamide; **AVC**: Dactinomycin, vinblastine, cyclophosphamide; **IVA**: Intravenous dactinomycin; **BEP**: Bleomycin, etoposide, cisplatin; **CR**: Complete remission; **PD**: Progressive disease; **TAH**: Total abdominal hysterectomy.

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(dactinomycin, etoposide) was the most common second line regimen. In resistant HR patients cisplatin based regimens were most commonly used. The CR rates for second line chemotherapy were 92.8% (90/97 patients) and 75% (6/8 patients) for LR and HR respectively.

Twenty four patients (18 LR, 6 HR) required 3rd line chemotherapy including CEC (cisplatin, etoposide and cyclophosphamide; 6 patients), AVC (dactinomycin, vinblastine and cisplatin; 4 patients), IVAE (ifosfamide, vinblastine, dactinomycin and etoposide; 1 patient), carboplatin/paclitaxel (4 patients), MAE (3 patients), or oral etoposide (6 patients). One patient underwent high dose chemotherapy and peripheral blood stem cell support.

Fifty six patients (12%) required a total abdominal hysterectomy; 28 (6%) for uncontrolled bleeding at initial presentation and 28 (6%) for resistant disease (26 LR and 2 HR).

Since 2000

From 2000 to 2006, a total of 167 patients were treated with chemotherapy; 151 LR and 16 HR (Table 5). Complete response (CR) was achieved in 93 LR patients (61.6%) and 12 HR (75%). Second line chemotherapy was required in 62 out of 167 patients (37.1%) treated from 2000. This was for incomplete response (47 LR and 4 HR patients) and/or unacceptable toxicity to first line chemotherapy (11 LR patients were changed to single agent intravenous dactinomycin). The CR rates for second line chemotherapy were 87.9% (51/58 patients) and 75% (3/4 patients) for LR and HR respectively (Table 5). In total, 6 patients (3 LR and 3 HR) required 3rd line chemotherapy involving either CEC (4) or IVAE (2). One patient underwent high dose chemotherapy and peripheral blood stem cell support. Eighteen patients (10.8%) required a total abdominal hysterectomy; 5 (3%) for uncontrolled bleeding at initial presentation and 13 (7.8%) for resistant disease (10 LR and 3 HR) (Table 5).

Nineteen of the 167 patients who were treated in our centre from 2000 to 2006 had a score of 6 on the FIGO 2000 system. They were considered LR and treated initially with MTX/FA. Only seven patients (37%) had CR and 12 (63%) required second line chemotherapy with AE regimen. They received between 2 to 8 courses (median 5) prior to being changed. Ten of the 12 patients who required second line chemotherapy (83.3%) achieved a CR. A median of 10 AE cycles were required in these patients (range from 5 to 19 cycles). The other 2 patients were fully salvaged with 3rd line chemotherapy as well as total abdominal hysterectomy (TAH) for resistant disease.

Response to chemotherapy in relation to different scoring systems

When comparing the two scoring systems in relation to patients' management, before 2000, 10 patients were managed as high risk according to the SCCSS. Overall CR rate and survival for these patients was 100%. They would have been considered LR using FIGO 2000.

From 2000 to 2006, our patients were scored using FIGO 2000. 4 LR patients on the FIGO 2000 system would have been placed in the high risk category by SCCSS because of an increased score. These 4 patients were treated as LR with MTX/FA; one patient had CR and the other 3 had an incomplete response but were successfully salvaged with AE. A median of 6 cycles (range 5 to 15) were required for these 3 patients.

Survival

At a median follow up of 18 years (range 1 to 35 years), 15 out of a total of 465 patients seen before 2000 died of resistant GTN (3.2%); 10 LR and 5 HR. Three patients died pre 1980, 8 in the 1980s and 4 in the 1990s. The 5 and 10 year survival rates for LR patients pre 2000 were both 98%. For HR patients over the same time frame, the 5 and 10 year survival rates were 87%.

Since 2000, and with a median follow up of only 5 (range 1 to 7) years, 2 out of a total of 167 patients (1.2%), both with an HR disease, died of resistant GTN. The 5 year survival rates were 100% and 88% for LR and HR respectively.

Discussion

Over the years various anatomical, clinical and prognostic scoring systems have been used [1–2,4–5,7]. In 1967, the International Union Against Cancer (UICC) developed combined clinical and morphological criteria [10]. At the same time the Registration Committee of the Japan Society of Obstetrics and Gynecology adopted a morphological classification whereby treatment was determined by whether the patient had invasive mole or choriocarcinoma. [11]. An anatomical staging system was proposed by Song et al. [12] and promoted by the Fèdèration International d'Gynècologie et d'Obstètrique (FIGO) Oncology Committee in 1982 [13].

Subsequently, several prognostic factors were identified: urinary hCG levels greater than 100,000 IU/ml in 24 h, duration of disease more than 4 months from the onset of symptoms or antecedent pregnancy, brain or liver metastases and previous failed or inadequate therapy [6,14]. The prognostic scoring system described by Bagshawe in 1976 [2] took into account the relative importance of both these and some additional prognostic factors. He derived a weighted prognostic scoring system, which formed the basis of the WHO, and Charing Cross scoring systems [3,4].

The Lewis classification divided GTN patients into 3 risk groups based on recognition that the hCG level and duration of disease are less important risk factors than the site(s) of metastases and prior unsuccessful chemotherapy [15]. In 1983, a Dutch working group stratified patients into low and high risk groups with the latter based on failure of previous chemotherapy, metastases in more than one site, antecedent term pregnancy, more than 12 months interval from antecedent pregnancy and start of chemotherapy [16]. Review of the importance of the individual prognostic factors in different classifications has been presented by Miller and Lurain [17]

To take into account some of the above difficulties, the original FIGO staging system was modified in 1992 to include certain risk factors, namely hCG level higher than 100,000 IU/l and interval from termination of antecedent pregnancy to diagnosis of more than 6 months. [1].

Recently it has been agreed that the anatomical FIGO staging should be retained and combined with a simplified WHO score in which ABO blood group risk factors are eliminated, the risk score for liver metastases increased, and placental site trophoblastic tumours excluded. This system has become known as FIGO 2000. Two risk groups were suggested: low risk (LR) ≤6, treatable by single agent chemotherapy and high risk (HR) >6, mandating multi-agent chemotherapy [7].

A retrospective study of 201 patients with persistent GTN was conducted in our centre [18] according to the criteria used in the FIGO 2000 to identify the numbers of patients in each risk group, the treatment they would receive, chemotherapy resistance patterns, and outcome. The scoring systems were broadly comparable and chemotherapy resistance was always greater in the high risk groups (at least 33%), particularly when patients were divided into just two risk categories. Such categorisation led to fewer patients (less than 15%) falling into high-risk groupings, but outcome was not compromised and it seemed that the proposal of combining the revised FIGO staging and modified WHO scoring systems, with two risk groupings only, was realistic and practicable. This is similar to the Sheffield modification of the Charing Cross system [1].

In this report we reviewed our experience in the management of patients with persistent GTN before and after the introduction of FIGO 2000. It was observed that there was an increased need for second line chemotherapy in patients with a low risk score under the new system, with a need to salvage 58 out of 151 (38%) of LR patients from 2000 to 2006 compared to 97 out of 426 (23%) before 2000.

Fourteen patients had discordant risk scores when applying the two scoring systems used in our centre separately to these patients.

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Ten of the 14 patients were considered HR using the SCCSS before 2000. They were treated with the MAE regimen with 100% CR and overall survival. If FIGO 2000 had been used instead of the SCCSS then these 10 patients would have been treated as LR with MTX/FA only. On the other hand, the other 4 patients presented to our centre from 2000 to 2006 and were considered LR using FIGO 2000 and treated with MTX/FA. Only one achieved CR although all were fully salvaged with second line AE. If these patients had been scored using the SCCSS, they would be have been considered HR and treated with MAE.

In our experience, FIGO 2000 has placed some of the patients who would be high risk using SCCSS into the low risk category. This may be explained by lower scores assigned in FIGO 2000 to some of the risk factors βhCG level of $\geq 10^5$ IU/l, number of metastases >8, previous failure of 2 or more drugs and interval to treatment >12 months. These risk factors were assigned a score of 6 in the SCCSS compared to 4 in FIGO 2000. In addition, the elimination of ABO blood group as a risk factor in the latter system may be relevant.

Wang et al. compared the efficacy of the FIGO 2000 staging and risk factor scoring system in comparison to the original World Health Organization (WHO) prognostic scoring system (1983). They reported a 97% correlation between the two systems with only 2 patients classified as middle risk group in the WHO system, allocated to the high-risk group by the FIGO 2000 system [19].

Of note, as well, is that patients with a score of 6 under the new system represent a grey zone between LR and HR. In our experience single agent MTX/FA is often not effective, with 63% of them requiring second line, but successful, chemotherapy with AE. Eighteen of these 19 patients had a βhCG level of $\geq 10^5$ IU/l this representing the most important risk factor in this group. In this group of patients with score 6, a median of 5 courses of MTX/FA were given prior to change to second-line therapy and a median of 10 salvage AE courses were required.

The complete response rates for patients, in this study, with low risk GTN were 61% and 77% when treated before and after 2000 respectively. These results are similar to those reported by others [20–22]. The CR rates for the MEA regimen given to HR patients were 75 and 79.5% when treated before and after 2000 respectively, which is superior to that reported with the MAC (methotrexate, dactinomycin and cyclophosphamide) regimen [6,23,24] and comparable with EMA/CO (etoposide, methotrexate and dactinomycin, alternating with cyclophosphamide and vincristine) [25–27].

AE was the most common salvage regimen for LR patients and cisplatin based regimens were most often given to HR patients. In those patients who failed first line chemotherapy the overall salvage rates with second line regimens were 87.9% and 92.8%, before and after 2000 respectively, in LR patients. HR patients who failed first line therapy had a 75% salvage rate over both time periods. All these figures for salvage are similar to or better than those reported in other series [25,27–30].

In conclusion, acceptable response rates were achieved with first line and second line chemotherapy regimens for patients with GTN. It was observed that, there is an increasing need for second line chemotherapy for low risk patients under the revised FIGO/WHO system. Patients with a risk score of 6 should be considered for an early switch to salvage treatment when there is inadequate response to methotrexate/folinic acid. Consideration should be given to changing the cut-off score for low risk from 6 to 5 or reviewing the scores assigned to various re-treatment risk factors under the revised FIGO/WHO system by increasing the risk score allocated to βhCG level of $>10^5$ IU/L from 4 to 6.

Conflict of interest statement

The authors declare that there are no conflicts of interest in this work.

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