Title Page

Original article

Can the FIGO 2000 scoring system for gestational trophoblastic neoplasia (GTN) be simplified? A new retrospective analysis from a nationwide data-set

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Abstract

Background: Worldwide introduction of the FIGO 2000 scoring system has provided an effective means to stratify patients with gestational trophoblastic neoplasia (GTN) to single- or multi-agent chemotherapy. However, the system is quite elaborate with an extensive set of risk factors. In this study, we re-evaluate all prognostic risk factors involved in the FIGO 2000 scoring system and examine if simplification is feasible.

Patients and methods: Between January 2003 and December 2012, 813 patients diagnosed with GTN were identified at the Trophoblastic Disease Centre in London and scored using the FIGO 2000. Multivariable analysis and stepwise logistic regression were carried out to evaluate if the FIGO 2000 scoring system could be simplified.

Results: Of the eight FIGO risk factors only pre-treatment serum human chorionic gonadotropin (hCG) levels exceeding 10,000 IU/l (OR = 5.0; CI 2.5-10.4) and 100,000 IU/l (OR = 14.3; CI 4.7-44.1), interval exceeding 7 months since antecedent pregnancy (OR = 4.1; CI 1.0-16.2) and tumor size of over 5 cm (OR = 2.2; CI 1.3-3.6) were identified as independently predictive for single-agent resistance. In addition, increased risk was apparent for antecedent term pregnancy (OR = 3.4; CI 0.9-12.7) and the presence of 5 or more metastases (OR = 3.5; CI 0.4-30.4), but patient numbers in these categories were relatively small. Stepwise logistic regression identified a simplified risk scoring model comprising age, pre-treatment serum hCG, number of metastases, antecedent pregnancy and interval but omitting tumor size, previous failed chemotherapy and site of metastases. With this model only 1 of 725 patients was classified differently from the FIGO 2000 system.

Conclusion: Our simplified alternative using only five of the FIGO prognostic factors appears to be an accurate system for discriminating patients requiring single as opposed to multi-agent chemotherapy. Further work is urgently needed to validate these findings.

Key words: Gestational Trophoblastic Neoplasia, classification, staging, FIGO, risk factors

Key message: The current FIGO 2000 scoring system for gestational trophoblastic neoplasia is quite

elaborate with an extensive set of risk factors. We therefore present a re-evaluation of the FIGO 2000 and propose a simplified alternative. Using only five of the FIGO risk factors, this alternative appears to retain accurate discrimination for patients requiring single- as opposed to multi-agent chemotherapy.

Introduction

Gestational trophoblastic disease (GTD) comprises a group of pregnancy related disorders including the premalignant complete and partial hydatidiform moles through to the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1]. The malignant counterparts are often collectively referred to as gestational trophoblastic neoplasia (GTN). Fortunately, with the introduction of effective chemotherapy, GTN has become highly curable with overall survival rates approaching 99% [1-4].

Cure for non-PSTT/ETT forms of GTN can often be achieved with single-agent chemotherapy comprising either methotrexate (with or without folinic acid rescue) or actinomycin D. However some patients require multi-agent chemotherapy most commonly comprising etoposide, methotrexate, actinomycin D alternating weekly with cyclophosphamide and vincristine (EMA/CO) to achieve long-term remission [4]. Over the years, several important predictors of unfavorable prognosis such as serum human chorionic gonadotropin (hCG) levels and site of metastases have been proposed [2, 5, 6] to stratify patients between single or multi-agent therapies. These factors have formed the basis of a number of different clinical scoring systems [5, 7], used to distinguish GTN patients as either having a low- or high-risk of developing resistance to single-agent chemotherapy.

To help facilitate comparison of datasets between international treatment centres, a renewed scoring system was introduced in 2000 [8, 9]. The new FIGO 2000 risk scoring system was based on a combination of anatomic and pathophysiological features of the disease and was developed with the effort of a number of international societies including the International Society for the Study of Trophoblastic Diseases (ISSTD), the International Gynaecologic Cancer Society (IGCS) and International Fedaration of Gynaecology and Obstetrics (FIGO)[9, 10].

The worldwide introduction of the FIGO 2000 has provided an opportunity to reach agreement on

classification and subsequent treatment for patients with GTN. However, the system is quite elaborate and comprises an extensive set of risk factors, several of which relate to tumor bulk and may therefore not be independently prognostic [2, 6, 11]. A greater number of factors involved will likely result in an increased variability in scoring and classification. Especially in a low incidence disease like GTN however, global unification is essential to optimize management.

In this study, fifteen years following the introduction of FIGO 2000, we decided to re-evaluate all prognostic factors involved in the FIGO 2000 scoring system to determine whether simplification of this system is feasible.

Materials and methods

Patients

All patients diagnosed with GTN between January 2003 and December 2012 were identified from the electronic database of the Trophoblastic Disease Centre at Charing Cross Hospital in London. Patients with a histopathological diagnosis of PSTT or ETT were excluded, resulting in 813 GTN patients of which 725 were low-risk and 88 were high-risk by FIGO 2000 scoring. Uni- and multi-variable analyses were conducted for 705 of 725 low-risk patients, since this was the total number of cases where their response to single-agent therapy was known. The remaining 20 patients had FIGO score 6 disease and either wanted high-risk treatment or were advised to start high-risk treatment because of a very high pre-treatment serum hCG typically in excess of 400,000 IU/L [12].

Management protocols

Prior to treatment all patients were assigned to low- or high-risk groups in accordance with the FIGO 2000 scoring system for GTN (Supplementary Table 1). Low-risk patients received single-agent methotrexate with folinic acid rescue (50 mg intramuscular MTX on days 1, 3, 5, and 7 and folinic acid 15 mg orally on days 2, 4, 6, and 8). In patients developing resistance or unmanageable toxicity, therapy was changed to either single-agent actinomycin D (ActD) or multi-agent chemotherapy comprising etoposide, methotrexate and actinomycin D alternating weekly with cyclophosphamide and vincristine (EMA/CO). The decision to use ActD as opposed to EMA/CO was based on the serum hCG level at the point of resistance. Patients with an hCG $\leq$ 300 IU/L received ActD whilst those > 300 IU/L were given EMA/CO as previously described [13]. ActD was given as 0.5 mg intravenously on days 1-5 every two weeks [13]. Patients with disease resistant to ActD received EMA/CO chemotherapy subsequently. High-risk patients received multi-agent chemotherapy with EMA/CO as first-line therapy. In patients presenting with very advanced disease, induction low-dose etoposide and cisplatin was given prior to commencing either EMA/CO or EP/EMA (etoposide and cisplatin alternating weekly with etoposide, methotrexate and actinomycin D). Appropriate adaptation for

occult or overt CNS disease was provided as previously described [14, 15]. Disease response and resistance to therapy was assessed by serum hCG measurements undertaken twice weekly until hCG was normal and then weekly until 6 weeks after completion of chemotherapy using the Charing Cross hCG radioimmunoassay as previously described [4].

Statistical analysis

The predictive value of the prognostic factors for chemoresistance to MTX or ActD was assessed in low-risk patients using univariate and multivariable logistic regression.

Thereafter, a backward stepwise (Wald) logistic regression was carried out for all patients to evaluate if simplification of the original FIGO system was feasible. To minimize the number of low-risk patients unnecessary subjected to the more aggressive multi-agent chemotherapy with consequent toxicity, simplified models were only considered if at least 98% of patients had concordant FIGO classification. Guided by the previous results, a small set of modified FIGO models that best resembled classification of the original FIGO 2000 was constructed. Finally, with receiver operating characteristic (ROC) curves, the discriminating power of the alternative models in comparison to the original FIGO classification was evaluated. All statistical analyses were performed with SPSS for windows 22.0.

Results

Patient characteristics of the 813 patients with GTN are shown in Table 1. Twenty-eight percent of low-risk patients eventually needed salvage multi-agent chemotherapy after initial MTX/FA with or without subsequent ActD. One death associated with acute renal failure occurred as a result of complications during multi-agent therapy for widespread disease.

Table 2 shows the results of the univariate and multivariable analysis performed for low-risk patients treated with single-agent chemotherapy. Site of metastases and previous failed chemotherapy were not included in the analysis as all patients with widespread metastases or previous failed chemotherapy were classified as high-risk patients and therefore not treated with single-agent therapy. Tumor size, antecedent term pregnancy, interval and pre-treatment serum hCG were significant predictors for single-agent resistance in univariate analysis. In multivariable analysis, pre-treatment serum hCG levels exceeding 10,000 IU/L (OR = 5.0; CI 2.5-10.4) and 100,000 IU/L (OR = 14.3; CI 4.7-44.1), interval exceeding 7 months since antecedent pregnancy (OR = 4.1; CI 1.0-16.2) and tumor size of over 5 cm (OR = 2.2; CI 1.3-3.6) were all identified as independent predictive factors for resistance to single-agent therapy. An increased risk was apparent for antecedent term pregnancy (OR = 3.4; CI 0.9-12.7) and the presence of 5 or more metastases (OR = 3.5; CI 0.4-30.4). However, numbers in these categories were relatively small.

Using stepwise backwards (Wald) logistic regression, FIGO criteria lacking significant independent value were eliminated, identifying three simplified models. In these models 4 (model 2) or 5 (model 1 and 3) of the original 8 FIGO criteria were sufficient for identical risk classification in 99% of patients (Table 3)**.** The discriminating power of these simplified FIGO scoring systems was compared to the original FIGO 2000 using ROC analysis. In model 1 and 2, six and seven patients respectively were classified differently. In model 3, with the elimination of tumor size, site of metastases and previous failed chemotherapy, classification for one patient changed from low-risk to high-risk. None of these patients had more than 4 metastases or metastases outside the lungs. Supplementary Table 2 shows

the characteristics of all eight cases with a different risk classification when using one of the simplified alternatives in comparison to the FIGO 2000.

Discussion

The FIGO 2000 comprises a weighted prognostic scoring system resulting in a calculated total score and subsequent classification of GTN patients with low-risk and high-risk of resistance to single-agent chemotherapy. Most prognostic factors relate to tumor bulk, it is therefore questionable whether all these factors are required for adequate classification of patients [16]. Furthermore, with the use of interrelated factors the actual weight for certain items could be overrepresented using FIGO 2000.

With use of uni- and multivariable logistic regression, a smaller selection of risk factors could be identified as significant predictors for single-agent resistance [1-4]. In concordance with other studies, both tumor size and pre-treatment serum hCG emerge as important prognostic variables in our analysis [5, 11]. As all patients with GTN likely undergo imaging with pelvic ultrasound, tumor size can be derived quite easily in a non-invasive manner. In some cases, the volume of a trophoblastic tumor however may not represent the proportion of viable cells due to variations in the extent of necrosis and hemorrhage [17]. Serum hCG is a disease-specific tumor marker, associated with burden of disease and is easily measured quantitatively. hCG levels of over 10,000 IU/L and 100,000 IU/L in particular reflect strong relations to treatment failure in low-risk patients. As commercially available assays for quantification of serum hCG concentrations use different sets of antibodies and often a different standard, assay results strongly depend on the type of assay used. Although the effect is probably modest with high hCG levels, problems may occur with monitoring of response and follow-up in the lower range of hCG levels [1, 17, 18].

While antecedent term pregnancy and interval since diagnosis have been associated with poor prognosis in univariate analyses, they however lose their significant prognostic value in some multivariable analyses [2, 6, 19]. For interval, the resulting hazard ratio appears non-linear and results likely depend on the chosen cutoff time. A sensible cutoff point will probably be beyond 12 months since diagnosis, as suggested by Powles et al. [20]. In our study only few patients had an

interval exceeding 7 months, and likewise an increased risk of single-agent resistance was seen. In patients with antecedent term pregnancies, we observed an increased risk of single-agent resistance, but even in this rather large cohort of patients, numbers in this subcategory remain small. Although choriocarcinoma could be considered a surrogate marker for antecedent term pregnancy, the latter term is preferred as histological confirmation is not always available. Problems with correct identification of the antecedent pregnancy and interval subsequently, can particularly occur when a patient has previously experienced an abortion without histological examination.

The effect of advanced age in GTD incidence has been evaluated regularly [21-23]. It's possible effect on the development of GTN and survival however has been under debate[2, 5, 6, 11]. In line with the majority of studies, age was not identified as an independent prognostic factor in the present study. However, treatment often differs with advanced age, since hysterectomy is a reasonable treatment option when fertility preservation is not desired and a reduction of toxicity from chemotherapeutic regimens may be profitable. Furthermore, considering all factors required for staging, age is probably one with the least possible uncertainty [17].

For both site of metastases and number of metastases, measurements are highly dependent on the used imaging technology used. For practical purposes and uniformity, simple investigation tools such as X-ray provide adequate clinical guidance [17]. Only few patients with a high number of metastases (5 or more) exist, possible implications on prognosis therefore remain unclear. Furthermore, there is wide consensus on the effects of widespread metastases on single-agent resistance and survival [2, 5, 6, 11]. In this cohort however, patients with widespread metastases were all characterized by a total FIGO score of over 10. Simultaneous presence of other prognostic factors has obviated the occurrence of misclassification in this group.

We however have to keep in mind that the present FIGO score, whilst only designed for stratifying

patients between low- and high-risk treatments is also used to identify patients at greatest risk of early death within 4 weeks of commencing therapy and late death from multi-drug resistant disease. These ultra-high risk patients, present with widespread metastatic disease, reflected by a very high FIGO score (>12), are at significant risk for pulmonary, intra-peritoneal or intracranial hemorrhage and may benefit from low dose induction chemotherapy. Furthermore, those with liver metastases with or without brain metastases are at increased risk of late death [15] Removal of criteria that reflect these factors in a simplified system would hinder identification of these patient groups [14]. Consequently, the new system will need to be carefully evaluated with sufficient patient numbers in the high and ultra-high risk groups.

Consensus exists on the concept of re-staging in case of relapse with full re-assessment of spread of disease and previous chemotherapy response. Failure to respond to single-agent therapy already justifies the start of a different single-agent regimen or multi-agent therapy depending on hCG value. Confusion may however exist on the definition of failed chemotherapy. It would therefore be helpful to provide a clear definition on failed chemotherapy with the revised FIGO 2000 (i.e. rise of serum hCG after two chemotherapy cycles.

It appears that only a small proportion of FIGO 2000 prognostic factors is needed to differentiate patients with low- versus high-risk of single-agent resistance. This could lead to a relatively straightforward system with a small subset of easily retrievable factors, ideally reducing variability in scoring and improving agreement between centers. A simplified model with age, pre-treatment serum hCG levels, number of metastases, antecedent pregnancy and interval alone resulted in an identical risk classification as the original FIGO 2000 in all but 1 of the 194 low-risk patients that needed to switch to high-risk therapy. Tumor size, previous failed chemotherapy and site of metastases did not provide much added value.

After fifteen years of experience with the worldwide accepted FIGO 2000, the present study provides

a useful overview of its design and performance in a large nationwide cohort. Although the number of patients with resistance to single-agent therapy in the low-risk group made us inquisitive on possible improvements in the performance of FIGO 2000, exploration of possible improvement in classification is challenging when only the prognostic factors currently employed in the FIGO 2000 are considered. Doppler ultrasonography, used to measure uterine vascularity through pulsatility index has been suggested as an independent prognostic factor for resistance to single-agent chemotherapy [24]. Further improvement by including novel variables such as Doppler pelvic ultrasonography should be considered. A renewed evaluation, preferably through international research collaboration would be needed to further validate these findings and refine FIGO 2000 into a straightforward classification system we could all embrace.

Conclusion

The total FIGO score is determined by a summation of scores for eight prognostic factors. The majority of factors relate to tumor bulk and are not independently prognostic for single-agent resistance. Our simplified alternative using only five of the FIGO prognostic factors remains an accurate system for discriminating patients requiring single as opposed to multi-agent chemotherapy. This simplified alternative would ideally reduce variability in scoring and improve agreement between centres. However, further validation is required to ascertain how this system performs in distinguishing ultra-high risk and high-risk patients.

Acknowledgments

MJS wishes to thank the UK and NHS England Dept of Health for their continued support of the national Gestational trophoblastic disease service and to acknowledge funding from the Imperial Biomedical Research Centre/National Institute for Health Research and Cancer Research UK/NIHR Imperial Experimental Cancer Medicine Centre as well as the Cancer Treatment and Research Trust.

Funding

None declared.

Disclosure

The authors have declared no conflicts of interest.

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Table 1 Patient characteristics [a]

Patient characteristic	**Low risk patients (*N*=725)**		**High risk patients (*N*=88)**	
	Mean (sd)	min-max	Mean (sd)	min-max
Age (years)	32.2 (8.0)	14-56	34.7 (9.2)	15-62
Pre-treatment ^{10}log serum hCG (IU/l)	3.8 (1.1)	1-7	4.9 (1.1)	2-7
Interval (months)	1.8 (2.1)	0-35	10.5 (33.2)	0-242
Duration of treatment (months) [b]	1.9 (2.2)	0-15	2.8 (1.6)	0-10
FIGOscore	2.7 (1.6)	0-6	10.3 (3.9)	7-23
Antecedent pregnancy	Number	Percentage	Number	Percentage
Hydatidiform Mole	696	96.0 %	36	40.9 %
Miscarriage	17	2.3 %	4	4.5 %
Term	12	1.7 %	48	54.5 %
Tumor size (cm)				
<3cm	304	41.9 %	11	13.7 %
3-5cm	240	33.1 %	13	16.3 %
>5cm	152	21.0 %	56	70.0 %
Site of metastases				
Vagina	4	0.6 %	4	5.0 %
Lung	56	7.7 %	46	57.5 %
Liver	-	-	6	7.5 %
Brain	-	-	12	15.0 %
Other	-	-	5	6.3 %
Number of metastases				
None	662	91.4 %	23	28.7 %
1-4	58	8.0 %	23	28.7 %
5-8	4	0.6 %	7	8.8 %
>8	-	-	27	33.8 %

[a] For some patients scoring on one or more of the FIGO criteria was unavailable

[b] Duration of treatment is defined in months until normalization in serum hCG levels was reached

Table 2 Univariate and multivariable analysis of prognostic factors for single-agent resistance

Variable	Rate of single-agent resistance (%)	Odds Ratio (95% CI)[a]	Odds Ratio (95% CI)[a]
		Univariate	Multivariable
Age (years)			
<40	159/572 (27.8%)		
≥40	34/133 (25.6%)	0.9 (0.6-1.4)	0.9 (0.6-1.5)
Antecedent pregnancy			
Hydatidiform Mole	183/677 (27.0%)		
Miscarriage	4/17 (23.5%)	0.8 (0.3-2.6)	0.6 (0.1-2.4)
Term	6/11 (54.5%)	3.2 (1.0-10.7) [b]	3.4 (0.9-12.7)
Interval (months)			
<4	179/617 (29.0%)		
4-6	9/73 (12.3%)	0.3 (0.2-0.7) [b]	1.1 (0.5-2.7)
7-12	5/14 (35.7%)	1.4 (0.4-4.1)	4.1 (1.0-16.2) [b]
>12	0/1 (0%)	-	-
Pre-treatment serum hCG (IU/l)			
<1000	19/167 (11.4%)		
1000-10.000	28/187 (15%)	1.4 (0.7-2.6)	1.6 (0.8-3.5)
10.000-100.000	127/324 (39.2%)	5.0 (3.0-8.5) [b]	5.0 (2.5-10.4) [b]
>100.000	19/27 (70.4%)	18.5 (7.1-48.0) [b]	14.3 (4.7-44.1)[b]
Tumor size (cm)			
<3cm	55/302 (18.2%)		
3-5cm	61/232 (26.3%)	1.6 (1.1-2.4) [b]	0.9 (0.6-1.4)
≥5cm	71/142 (50.0%)	4.5 (2.9-7.0) [b]	2.2 (1.3-3.6) [b]
Number of metastases			
None	172/644 (26.7%)		
1-4	19/56 (33.9%)	1.4 (0.8-2.5)	1.4 (0.7-2.6)
5-8	2/4 (50.0%)	2.7 (0.4-19.6)	3.5 (0.4-30.4)
>8	0/0 (0%)	-	-

[a] *CI: Confidence Interval*
[b] *p<0.05*

Table 3 Alternative scoring systems and their performance with FIGO 2000 compared

Model	AUC[a]	True Positive[b]	True Negative[b]	False Positive[b]	False Negative[b]	Sensitivity	Specitivity	Identical classification
Original FIGO 2000	1.000	694	73	0	0	1.00	1.00	100%
Model 1 Age Antecedent pregnancy Pre-treatment serum hCG Tumor size Number of metastases	0.999	693	70	2 [1,2 c]	4 [5,6,7,8 c]	0.99	0.97	99.1%
Model 2 Age Antecedent pregnancy Pre-treatment serum hCG Number of metastases	0.998	720	71	4 [1,2,3,4 c]	3 [5,7,8 c]	1.00	0.95	99.2%
Model 3 Age Antecedent pregnancy Interval Pre-treatment serum hCG Number of metastases	1.000	722	73	1 [4 b]	0	1.00	0.99	99.9%

Allowing for the fact that the FIGO 2000 was already used in this particular data, the AUC, sensitivity and specificity for the original FIGO 2000 were consequently calculated at 1.0.

Risk classification according to the FIGO 2000 was considered 'gold standard'

For every alternative scoring system the number of discordant patients and corresponding casenumbers are highlighted