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Original Research

The results of treatment with high-dose chemotherapy and peripheral blood stem cell support for gestational trophoblastic neoplasia

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High-dose chemotherapy

Abstract ***Objective:*** The objective of the study was to evaluate the effect of high-dose chemotherapy (HDC) with peripheral blood stem cell support (PBSCS) on survival of patients with gestational trophoblastic neoplasia (GTN) with either refractory choriocarcinomas or a poor-prognosis placental site/epithelioid trophoblastic tumours (PSTT/ETTs).
Methods: Databases of two referral centres for gestational trophoblastic disease were searched, and 32 patients treated with HDC between 1994 and 2015 were identified. Tissue samples were retrieved for genetic evaluation. Cox regression analyses were performed to identify possible predictors of overall survival (OS).
Results: HDC induced a sustained complete response in 7 patients. Overall, 41% (13/32) of the patients remained disease free after HDC with or without additional treatment. Patients who survived had much lower human chorionic gonadotropin (hCG) values (all $\leq$12 IU/L) before and after HDC than those who died of disease. Univariable Cox regression analysis demonstrated that hCG >12 IU/L before or after HDC, International Federation of Gynaecology and Obstetrics (FIGO) stage II-IV and presence of metastases at the time of diagnosis were significantly associated with adverse OS. However, only hCG values before HDC remained significant in a multivariable model ($p < 0.001$). Five of 11 (45%) patients with PSTT/ETT presenting $\geq$48 months after antecedent pregnancy and 6 of 14 (43%) patients with refractory

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choriocarcinoma were in remission. Three treatment-related deaths occurred.
Conclusions: Despite 3 treatment-induced deaths, HDC with PBSCS appears to be active in salvaging selected patients with poor-prognosis PSTT/ETTs and refractory choriocarcinomas. Low hCG values before HDC seems a beneficial predictor of OS and may suggest that HDC acts more like a consolidation therapy.

1. Introduction

The majority of patients with low-risk gestational trophoblastic neoplasia (GTN) are cured with mono-chemotherapy such as methotrexate or dactinomycin. A small number of patients develop resistance, requiring use of another monotherapy or multiagent chemotherapy to achieve remission. Multiagent chemotherapy is the primary treatment for high-risk GTN. However, 20–40% of high-risk patients develop resistance to this therapy or relapse after remission and need salvage chemotherapy [1–3]. When further chemotherapy and salvage surgery fail, high-dose chemotherapy (HDC) with peripheral blood stem cell support (PBSCS) is often considered a method of last resort. Results of HDC in refractory GTN were previously reported in 2005 [4]. Although a response rate of 45% was found, only 2 of 11 patients achieved long-term survival. Explanations for these disappointing results included the small numbers of patients, case selection and the possibility that one round of HDC was insufficient. Indeed, two or more cycles of HDC appears to be better than one in the management of multiple myelomas and germ cell tumours [5,6]. Consequently, the role of HDC in the management of refractory GTN remained uncertain.

Another group of GTN patients that may benefit from HDC are women with poor-prognosis placental site trophoblast tumours (PSTTs) or epithelioid trophoblast tumours (ETTs). PSTT is a rare form of GTN with a 10-year overall survival (OS) of 70% [7]. Patients with stage I disease do not benefit from adjuvant chemotherapy. However, higher stages require either preoperative and/or postoperative chemotherapy to achieve remission. In the study by Schmid *et al.* [7], the key independent predictor of survival was the time interval since antecedent pregnancy. All 13 patients with an interval of ≥48 months eventually died of their disease, regardless of stage and despite surgery and chemotherapy. Although survival of occasional patients with such long intervals has been described by other authors in smaller series, such patients seem highly likely to succumb from their disease [8]. This is in marked contrast to patients presenting within 48 months, where survival rates appear to be around 98% (48/49 patients) [7].

Therefore, we hypothesised that patients with PSTT and/or the related ETT and an interval of ≥48 months since the antecedent pregnancy could benefit from HDC with PBSCS as part of early disease management rather than waiting for relapses. Consequently, we aimed to evaluate the effect of HDC with PBSCS on survival of patients with either drug-resistant choriocarcinoma or poor-prognosis PSTT/ETT and to evaluate the additional benefit of a second cycle of HDC.

2. Material and methods

Databases of two referral centres for GTN (Charing Cross Hospital and Weston Park Hospital) in the United Kingdom were searched to identify patients treated with HDC between 1994 and 2015 for further analysis. Information on age, antecedent pregnancy, course of disease, hCG levels, FIGO scoring and stage, previous treatment schedules, type and number of high-dose schedules employed together with response, toxicity and survival was collected. Missing data were retrieved from the medical files and anonymised. Four regimens of HDC were used (Table 1) with carboplatin, etoposide, cyclophosphamide and paclitaxel (Carbop-EC-T) being the most frequent. Patients who received HDC in the adjuvant setting had stem cell mobilisation immediately after completing chemotherapy, and as soon as their blood counts had recovered, they were admitted for HDC. The average time from completing chemotherapy to HDC (including interval stem cell collection) was 5 weeks. In the adjuvant setting, chemotherapy was given for 12–16 weeks according to tolerability before stem cell mobilisation and HDC. Where hCG was elevated, chemotherapy was given until the hCG normalised or reached its lowest plateau before proceeding to HDC. If pathological material was available, genetic analysis was undertaken to confirm the gestational origin of the tumours. Patients with non-gestational tumours were excluded from the study.

In total, 34 GTN patients were treated with HDC between 1994 and 2015. Genotyping confirmed the gestational nature of the tumour in 25 of 27 cases with no or insufficient tumour tissue available in 7 cases. Five of the genetically confirmed GTNs originated from complete hydatidiform moles (CHMs). Two patients with confirmed non-gestational tumours were excluded.

Table 1
High-dose regimens.

High-dose regimens	Dosage (mg/m^2)	Days
Carbo-EC-T (Charing Cross Hospital)	Paclitaxel 75 mg m^2	−7, −5 and −3
	Etoposide 450 mg m^2	−7, −5 and −3
	Carboplatin with AUC 10	−7, −5 and −3
	Cyclophosphamide 60 mg kg^1 + mesna	−5 and −3
CEM (Weston Park Hospital)	Carboplatin (AUC 15)	−5 to −2
	Etoposide 100 mg m^2 b.d.	−5 to −2
	Melphalan 140 mg m^2	−1
CTE (Weston Park Hospital)	Carboplatin 500 mg m^2 or AUC 7	−8, −7 and −6
	Thiotepa 300 mg m^2	−5, −4 and −3
	Etoposide 250 mg m^2	−5, −4 and −3
High-dose Carbo/Etop (Weston Park Hospital)	Carboplatin 700 mg m^2	−5 to −3
	Etoposide 750 mg m^2	−5 to −3

AUC, area under the curve; Carbo-EC-T, carboplatin, etoposide, cyclophosphamide and paclitaxel; Carbo/Etop, carboplatin and etoposide; CEM, carboplatin, etoposide and melphalan; CTE, carboplatin, thiotepa and etoposide.

However, the 7 cases that could not be genotyped were included because their tumours were pathologically and clinically considered to be gestational. Moreover, excluding them from the subsequent analyses did not lead to different conclusions (data not shown).

Patients were divided into two groups according to their histology: those with choriocarcinoma (group 1) and those with PSTT, ETT or a combination of PSTT with other histologies (group 2). In seven patients who started treatment before 2002, the CXH scoring system was used instead of the FIGO scoring system [9]. All these patients had a CXH score ≥9 and were considered high risk. Complete response (CR) was defined as normalisation (≤4 IU/L) of previously elevated hCG (>4 IU/L) within 4 weeks after HDC sustained for at least 1 month. In non-hCG secreting disease, CR was defined as resolution of measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria. A partial response (PR) was defined as 50% reduction in serum hCG levels within 4 weeks after HDC or >30% reduction in tumour size (RECIST) also sustained for at least 1 month. Progressive disease (PD) was defined as a rising hCG over at least 2 values within 4 weeks after HDC or increase in tumour size >10%. Stable disease (SD) was anything between PR and PD. The serum hCG was measured at least weekly using the Charing Cross radioimmunoassay for Charing Cross patients or by Siemens Immulite for all other patients. Imaging was undertaken before HDC before proceeding to the second round of HDC and repeated again after the second HDC within 4–6 weeks of discharge from hospital. Imaging comprised a minimum of magnetic resonance imaging head and pelvis, contrast computed tomography (CT) chest and abdomen and in some cases [^{18}F]fluorodeoxyglucose positron emission tomography-CT scans.

Toxicity within 1 month after HDC was scored according to common terminology criteria for adverse events (CTCAE)-4 criteria. For patients who underwent 2 courses of HDC, only the highest grade of the reported adverse event(s) was noted. Only non-haematological toxicity was reported because as expected all patients experienced grade IV haematological toxicity. Follow-up after treatment was as previously described [7].

Anonymised patient records were used, and therefore, informed patient consent was not required. We utilised SPSS, version 22, for statistical analyses including non-parametric tests such as Fisher's exact test and Mann–Whitney U test to compare between groups 1 and 2, and Cox regression to identify possible predictors of survival after HDC. Limited by the number of events, the two most relevant variables shown by univariable Cox regression analysis to be significantly associated with survival were entered into a Cox regression model for multivariable analysis. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Description of patients

The characteristics of 32 patients with GTN are presented in Table 2. Histology showed choriocarcinoma in 14 cases (group 1), while among the remaining 18 patients (group 2), 6, 5, 3 and 4 cases had PSTT, ETT, mixed ETT/PSTT or mixed choriocarcinoma/PSTT, respectively.

The majority had an antecedent term pregnancy (22/32), but genetics showed that 5 originated from undiagnosed CHM from pregnancy losses. The interval to the start of treatment was >12 months in 22 patients, including 11 patients with ETT and/or PSTT presenting ≥48 months after delivery (Fig. 1). Most CC patients were originally at high risk (FIGO score ≥7) upon presentation (12/14) although 2 presented with low-risk disease and subsequently failed ≥2 lines of multiagent chemotherapy before needing HDC.

PSTT/ETT tumours secrete a disproportionately low concentration of hCG for the volume of disease present [7]. Indeed, the median hCG level was significantly higher immediately before HDC in patients in group 1 compared with group 2 patients (Table 2: median 353 IU/L vs 11 IU/L; $P = 0.025$).

Almost all patients (30/32) had surgery at some point during their treatment. Twenty-two patients received 1 course of HDC, and 10 of the more recently treated patients received tandem HDC.

3.2. Outcome

Fig. 1 shows that 6 of 14 (43%) group 1 and 7 of 18 (39%) group 2 patients became long-term survivors

Table 2
Patient characteristics.

	Group 1[a], $N = 14$, n (%)	Group 2[b], $N = 18$, n (%)	P
Age, years, mean (range)	35.2 (25–52)	38.6 (23–59)	0.523
Antecedent pregnancy			0.192
Hydatidiform mole	0 (0%)	0 (0%)	
Term	8 (57%)	14 (78%)	
ToP/miscarriage	5 (36%)	2 (11%)	
Unknown	1 (7%)	2 (11%)	
Interval			0.045
<4 months	3 (21%)	1 (6%)	
4–6 months	1 (7%)	0 (0%)	
7–12 months	3 (21%)	1 (6%)	
13–47 months	4 (28%)	5 (28%)	
≥48 months	2 (14%)	11 (61%)	
Unknown	1 (7%)	0 (0%)	
FIGO score at the time of diagnosis			–
<7	2 (14%)	N/A	
7–11	4 (29%)	N/A	
≥12	8 (58%)	N/A	
Stage at the time of diagnosis			0.08
Stage I	1 (7%)	8 (44%)	
Stage II	0 (0%)	1 (6%)	
Stage III	5 (36%)	4 (22%)	
Stage IV	7 (50%)	5 (28%)	
Unknown	1 (7%)	0 (0%)	
Median hCG IU/L (range)			
Before HDC	353 (2–136730)	3.5 (2–1967)	0.025
4 weeks after HDC	11 (1–5864)	5 (2–1363)	0.568
Median lines of prior chemotherapies (range)	3.5 (2–8)	2.5 (1–4)	0.013
Peripheral blood stem cell support			
Median dose of CD34 + cells x10^6/kg (range)[c]	3.6 (2.1–5.8)	3.1 (1.0–5.0)	0.258
Median days to 0.5 × 10^9/l neutrophils (range)[d]	11.5 (9–21)	11 (8–28)	0.290
Median days to 20 × 10^9/l platelets (range)[d]	18.5 (12–59)	18 (10–76)	0.899
HDC schemes			1.000
Carbo-EC-T	9 (65%)	11 (61%)	
Carbo/etop	4 (28%)	4 (22%)	
CEM	1 (7%)	2 (11%)	
CTE	0 (0%)	1 (6%)	
HDC			0.712
1 course	9 (64%)	13 (72%)	
2 courses	5 (36%)	5 (28%)	

Carbo-EC-T, carboplatin, etoposide, cyclophosphamide and paclitaxel; Carbo/Etop, carboplatin and etoposide; CEM, carboplatin, etoposide and melphalan; CTE, carboplatin, thiotepa and etoposide; ETT, epithelioid trophoblastic tumour; HDC, high-dose chemotherapy; PSTT, placental site trophoblastic tumour; ToP, termination of pregnancy.

[a] Choriocarcinoma.

[b] PSTT or ETT or mixed PSTT/ETT or mixed PSTT/choriocarcinoma.

[c] Data based on the first procedure of n = 28.

[d] Data based on the first procedure of n = 30.

following HDC with or without additional therapies. Combining the groups, in 23 patients with assessable disease, HDC induced a CR in 7, PR in 8 and SD in 6 (Fig. 2). All PRs and 4 with SD eventually died. Six of the CR patients relapsed with two being salvaged with further therapy/surgery and the rest succumbing from their disease (4). PD evidenced by a rising hCG during HDC occurred in 2 women, both dying ≤4 months after treatment. Response to HDC was not assessable in 9 patients because of normal hCG levels and no measurable disease pre-treatment and post-treatment (Fig. 2). These women received adjuvant HDC because they were considered to be at risk of recurrence and/or to have a poor prognosis after multiple relapses and included: 3 CC failing multiple prior chemotherapy lines, 5 PSTT/ETT patients with an interval ≥48 months and 1 multiply relapsed PSTT patient. Eight of these non-assessable patients are in remission, 7 without further therapy, but the woman with multiply relapsed PSTT died from HDC-induced complications. Additional treatment after HDC was administered to 16 patients (50%). This resulted in a CR in 4, either by surgery alone in 2 or using combined systemic therapy, surgery and radiotherapy in 2 patients (Table 3).

Therefore, following HDC, 13 patients (41%) survived overall, of which 9 (28%) were cured without

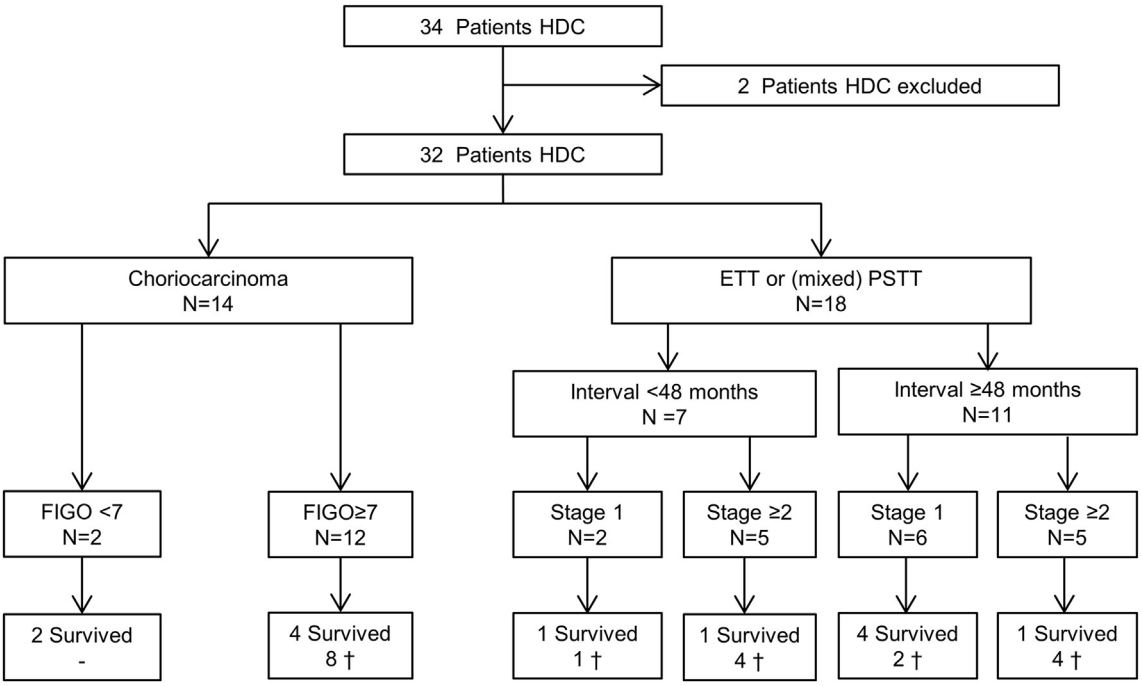

Fig. 1. Outcome after HDC in drug-resistant choriocarcinomas and poor-prognosis placental site/epithelioid trophoblastic tumours. †Deaths; ETT, epithelioid trophoblastic tumour; HDC, high-dose chemotherapy; PSTT, placental site trophoblastic tumour.

further salvage therapy (Fig. 2). The survival of patients receiving 2 courses of HDC was higher than those treated with 1 course (60% vs 32%; 6/10 vs 7/22) although this did not reach statistical significance (Table 4). The clinical characteristics of the 13 survivors are further described in Table 3. Median follow-up time was 55 months (range 13–153 months).

3.3. Toxicities and deaths

Serious non-haematological toxicity (grade III–V) associated with HDC was reported in 23 patients (Table 5). There were 3 treatment-related deaths within 30 days of completion of the first ($N = 2$) or second course of HDC ($N = 1$). Two of these deaths were from sepsis and 1 from multiorgan failure. The most frequent low grade non-haematologic adverse events after HDC were gastrointestinal toxicities, hypomagnesaemia and mucositis. Neurological side effects such as peripheral neuropathy and impaired hearing were more common after a second course of HDC. Hypokalaemia was the most common high-grade toxicity (Table 5). One patient with a perforated small bowel underwent a small bowel resection 4 weeks after HDC. Another patient refused a second course of HDC due to extreme fatigue and malaise.

The 10 patients who received tandem HDC had a median interval of 58 days (range 30–146 days) between the first and the second course of HDC. Four of them died 2, 7, 19 and 13 months after the second HDC from disease progression, with an interval between HDC courses of 38, 53, 75 and 95 days, respectively.

The median duration of stay in hospital from start of HDC (day 1) was 24.5 days with a range of 12 and 62 days

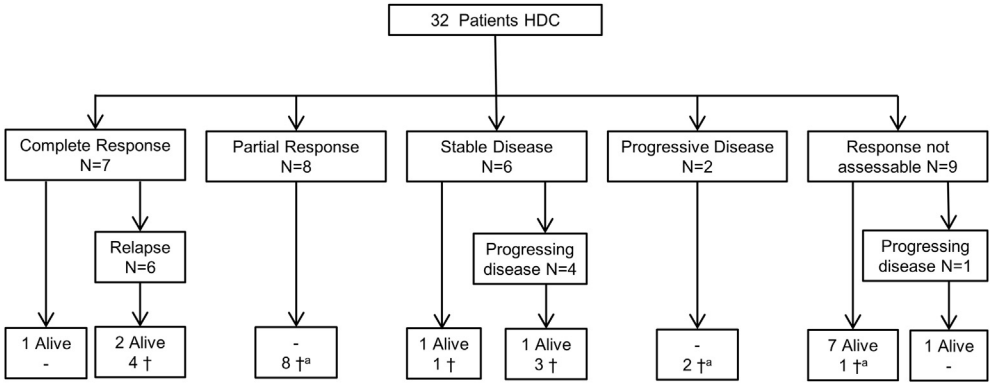

Fig. 2. Response to HDC and outcome; [a]of whom, 1 patient died within 4 weeks after HDC. †Deaths; HDC, high-dose chemotherapy.

Table 3
Clinical characteristics of survivors.

		Age	G	P	Antecedent pregnancy	Interval in months	Stage	Histology	Metastases at the time of diagnosis	Before HDC				HDC	After HDC			
										Initial therapy	Subsequent therapy	Further therapy	hCG before HDC	Number of high dose	hCG 4 wks after HDC	Relapse/ progression	Additional therapy	FU
Assessable disease	1	38	3	2	Miscarriage	13–48	3	CC	Lungs	BEP + thoracotomy	EMA/CO + IT MTX	EP/EMA, TE/TP	12	1	<2	Y	Resection lung metastases	153
	2	23	2	1	Term	<4	1	CC/PSTT	No	MTX	EMA/CO	TE/TP, EP + IT MTX	2	1	<2	Y	TAH, thoracotomy, alimta/cispl, carbo/gem, EP, stereotactic RT cerebellum	95
	3	40	8	6	Term	13–48	3	ETT	Lung	EP/EMA + hysterectomy	TE/TP + IV MTX	TE/TP, radiosurgery thoracotomy	7	1	<2	N	N	55
	4	37	4	3	Miscarriage	<4	4	CC	Lung, liver, leptomeningeal	EP/EMA + IT MTX	TE/TP	X	2	2	<1	Y	Lobectomy	13
	5	34	3	3	Term	<4	?	CC	?	MTX	EMA/CO	TE/TP, hysterectomy	5	2	7	N	N	17
Non-assessable disease	6	45	3	3	Term	≥48	1	PSTT/ETT	No	Hysterectomy	EP/EMA	X	2	2	3	N	N	52
	7	39	2	2	Term	≥48	3	CC	Lungs	TAH + thoracotomy	EMA	EMA/CO, EP, TE/TP, EP high dose, EMA/CO + IT MTX, GEM/cispl, Alimta/cispl	6	1	3	N	N	100
	8	42	9	9	Term	≥48	3	PSTT	Lung	EMA + hysterectomy	EP/EMA	TE/TP, CP, pneumonectomy	4	1	9	N	N	74
	9	39	2	2	Term	13–48	4	CC	Brain, lungs, liver, thyroid	EP/EMA + IT MTX	TE/TP	X	3	2	<2	Y	Resection lung metastasis, EP, GEM-TIP, pembro	36
	10	40	3	3	Term	≥48	1	PSTT/ETT	No	Hysterectomy	EP/EMA	X	2	2	2	N	N	15
	11	39	2	1	Miscarriage	4–6	1	CC	No	MTX	Etop/ActD	EP/EMA, TP/TE, hysterectomy	2	2	<1	N	N	37
	12	59	6	6	Term	≥48	1	CC/PSTT	No	Laparotomy + biopsy	EP/EMA	TE/TP	2	1	<2	N	N	56
	13	43	2	2	Term	≥48	1	PSTT	No	TAH	TE/TP	X	7	1	4	N	N	88

BEP, bleomycin, etoposide and cisplatin; CC, choriocarcinoma; CP, cyclophosphamide; EP, etoposide and cisplatin; EP/EMA, etoposide, cisplatin/etoposide, methotrexate and dactinomycin; EMA/CO, etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine; Etop/ActD, etoposide and dactinomycin; ETT, epithelioid trophoblastic tumour; FU, follow-up; GEM/cispl, gemcitabine and cisplatin; HDC, high-dose chemotherapy; IT, intrathecal; IV, intravenous; MTX, methotrexate; Pembro, pembrolizumab; PSTT, placental site trophoblastic tumour; RT, radiotherapy; TAH, total abdominal hysterectomy; TE/TP, paclitaxel + etoposide/paclitaxel + cisplatin; TIP, paclitaxel + ifosfamide + cisplatin; X, no further therapy; Y, yes; N, no.

Table 4
One course versus tandem high-dose chemotherapy: patient characteristics and outcome.

	1 course HDC, $N = 22$, n (%)	2 courses HDC, $N = 10$, n (%)	P value
Median age, years (range)	38.5 (23–59)	38 (24–45)	0.760
Antecedent pregnancy			0.143
Term	16 (72%)	6 (60%)	
ToP/miscarriage	3 (14%)	4 (40%)	
Unknown	3 (14%)	0 (0%)	
Interval			0.135
<4	1 (5%)	3 (30%)	
4–6	0 (0%)	1 (10%)	
6–12	4 (18%)	0 (0%)	
13–47	7 (32%)	2 (20%)	
≥48	9 (40%)	4 (40%)	
Unknown	1 (5%)	0 (0%)	
Stage			0.03
Stage I	4 (18%)	5 (50%)	
Stage II	1 (5%)	0 (0%)	
Stage III	9 (41%)	0 (0%)	
Stage IV	8 (36%)	4 (40%)	
Unknown	0 (0%)	1 (10%)	
Median pre-treatment hCG (range)	9.5 (2–15076)	3 (2–31969)	0.182
Histology			0.712
Group 1[a]	9 (41%)	5 (50%)	
Group 2[b]	13 (59%)	5 (50%)	
Survival	7 (32%)	6 (60%)	0.244

P value is from Mann-Witney U test for comparison of medians and from Fisher's exact tests for comparisons of the categorical values.
HDC, high-dose chemotherapy; ETT, epithelioid trophoblastic tumour; PSTT, placental site trophoblastic tumour; ToP, termination of pregnancy.
[a] Choriocarcinoma.
[b] PSTT or ETT or mixed PSTT/ETT or mixed PSTT/choriocarcinoma.

after the first course and 19 days (range 17–30) after the second course. Readmission following discharge up to 4 weeks after HDC occurred in 4 patients.

Overall, 19 patients died, 3 from HDC, 15 of disease and 1 of haemorrhagic complications after resection of a lower lobe lung lesion 8 months after HDC.

Table 5
High-Grade non-haematologic toxicity of HDC.

Grade III–V non-haematologic toxicity of HDC in 23 patients	
Toxicity	No. of patients (%)
Hypokalaemia	8 (35)
Blood disorder[a]	5 (22)
Gastrointestinal[b]	4 (17)
Acute kidney injury	4 (17)
Mucositis	4 (17)
Treatment-related deaths	3 (13)
Febrile neutropenia	3 (13)
Hypomagnesaemia	3 (13)
Impaired hearing	1 (4)
Infection[c]	1 (4)
Sepsis	1 (4)
Respiratory distress	1 (4)
Hypernatraemia	1 (4)
Glucose intolerance	1 (4)

HDC, high-dose chemotherapy.
[a] Abnormal liver function tests.
[b] 1 (or more) of the following symptoms: nausea ($N = 3$), diarrhoea ($N = 1$), vomiting ($N = 1$), abdominal pain ($N = 1$), perforation small bowel ($N = 1$), enteritis ($N = 1$).
[c] Bronchial infection.

3.4. Predictors of survival after HDC

Univariable Cox regression analyses were performed to identify possible predictors of survival after HDC (Table 6). Factors with a significant adverse correlation with survival were original FIGO stage ≥ II ($P = 0.047$), hCG values >12 IU/L before and 4 weeks after HDC (both $p < 0.001$), rising hCG values before HDC ($P = 0.006$) and the presence of metastases at the time of diagnosis ($p = 0.047$). All 13 patients with hCG >12 IU/L before or after HDC died of disease. Patients with hCG concentrations ≤12 pre-HDC had a median OS of 9 months (range 0–13). The median OS of patients with higher hCG values was 6 months (range 0–19) ($p = 0.001$).

A multivariable Cox regression analysis was performed using only FIGO stage and the hCG values before HDC as these were the most relevant significant factors from the univariable analysis. The only significant independent predictor of overall survival was an hCG value ≤12 IU/L before HDC.

4. Discussion

The role of HDC for gestational CC failing standard chemotherapies and poor-prognosis PSTT/ETT is uncertain. Prior reports are hampered by single selected cases or small series and give a mixed picture of benefit (Table 7) [4,10–21]. Thus, only 2 of 11 patients in the

Table 6
Univariable and multivariable Cox regression analyses of OS.

	Univariable Cox regression				Multivariable Cox regression		
	No. of patients	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age	32	0.964	[0.912–1.020]	0.201			
Antecedent pregnancy							
Term	22	Ref	–	–			
ToP/miscarriage	7	0.372	[0.103; 1.347]	0.132			
Unknown	3	0.323	[0.071; 1.472]	0.144			
Interval since antecedent pregnancy							
<48 months versus ≥ 48 months	18 vs 13	1.169	[0.452; 3.023]	0.747			
FIGO stage							
Stage 1 versus stage II-IV	9 vs 22	3.521	[1.019; 12.163]	**0.047**	0.812	0.311; 2.123	0.672
Metastases at the time of diagnosis							
Yes versus no	22 vs 9	0.284	[0.082; 0.981]	**0.047**			
Metastases at the time of HDC							
Yes versus no	18 vs 14	0.466	[0.175; 1.237]	0.125			
Histology							
Group 1 versus group 2	14 vs 18	0.868	[0.348; 2.166]	0.761			
Number of chemotherapy lines before HDC	32	0.959	[0.712; 1.291]	0.781			
Surgery before HDC							
Yes versus no	24 vs 8	0.898	[0.322; 2.505]	0.836			
hCG values before HDC					0.141	0.049; 0.402	**<0.001**
≤12 versus >12 IU/L	18 vs 14	0.143	[0.051; 0.405]	**<0.001**			
Rising versus low plateau/normal/falling	13 vs 19	0.276	[0.109; 0.697]	**0.006**			
hCG values 4 weeks after HDC							
≤12 versus >12 IU/L	23 vs 9	0.155	[0.058; 0.409]	**<0.001**			
Number of HDC courses							
1 course versus 2 courses	22 vs 10	0.483	[0.160; 1.458]	0.196			
Additional therapy after HDC							
Yes versus no	16 vs 16	0.537	[0.209; 1.379]	0.196			

Carbo-EC-T, carboplatin, etoposide, cyclophosphamide and paclitaxel; Carbo/Etop, carboplatin and etoposide; CEM, carboplatin, etoposide and melphalan; CI, confidence interval; CTE, carboplatin, thiotepa and etoposide; HDC, high-dose chemotherapy; OS, overall survival; ToP, termination of pregnancy.

Table 7
High-dose chemotherapy for gestational trophoblastic neoplasia in literature.

Year	n	GTD	High-dose chemotherapy (number of courses)	Response (FU)	Reference
1991	1	CC with lung and brain metastases	EC (1) + whole brain RT	Complete (15 months)	[9]
1995	5	Refractory GTN	ICE (1 or 2)	2 complete (68 months, 2 months), 1 died of disease, 2 unknown	[10]
1995	1	CC	CEM (1)	Complete (3 years)	[11]
1996	1	Non-gestational CC with brain metastases	carboplatin, etoposide, ranimustine (1) + surgery, radiotherapy	complete (24 months)	[12]
1997	1	Refractory GTN	ICE (4)	Complete (12 months)	[13]
1997	1	Non-gestational ovarian CC with lung metastases	ICE (1) + surgery	Complete (17 months)	[14]
1998	1	PSTT	CEM (1)	Complete (4 months)	[15]
1999	1	Metastastic PSTT	Carbo/Etop (1)	Temporary, died from disease	[16]
2002	1	Recurrent post-term CC and ETT	Carb-EC (1)	Complete (23 months)	[17]
2004	2	1 CC, 1 mola + PTD	ICE (1)	1 complete (3.5 yr), 1 death (due to complications)	[18]
2005	11	11 refractory or relapsing GTN (including 6 CC, 1 PSTT, 1 mixed CC/PSTT)	Carbo-EC-T, Carb-EM, ICE (1)	2 complete (4 months, 12 months), 3 partial, 6 progressive	[4]
2013	1	Refractory post-term GTN	ICE (4)	Complete (28 months)	[19]
2016	1	CC	ICE (4)	Died of disease	[20]
2018	32	14 CC, 6 PSTT, 5 ETT, 4 mixed CC/PSTT and 3 mixed ETT/PSTT	Carbo-EC-T (1 or 2), Carbo/Etop (1 or 2), CEM (1), CTE (1)	13 survived (13–153 months), 19 deaths	

Carb-EC, carboplatin, etoposide and cyclophosphamide; Carbo-EC-T: carboplatin, etoposide, cyclophosphamide and paclitaxel; Carb-EM, carboplatin, etoposide and melphalan; Carbo/Etop, carboplatin and etoposide; CEM, cyclophosphamide, etoposide and melphalan; CTE, carboplatin, thiotepa and etoposide; CC, choriocarcinoma; EC, etoposide and cyclophosphamide; ETT, epithelioid trophoblastic tumour; FU, follow-up; GTN, gestational trophoblastic neoplasia; ICE, ifosfamide, carboplatin and etoposide; PSTT, placental site trophoblastic tumour; PTD, persistent trophoblastic disease; RT, radiotherapy.

largest series [4] achieved a CR and became long-term survivors, but on adding all reported cases together, 48% (13/27) achieved CR and/or remission. Here, we add to our prior 11 cases to report the world's largest series of 32 women. While this is a retrospective analysis with missing data and case selection bias, no case ascertainment or reporting bias exists as this represents the national GTN population within a centralised service. A CR occurred in 30% of patients with assessable disease, and overall, 41% remain disease free after HDC either with or without additional treatments.

So why do the present results look better than our first report? There are several explanations including chance, differences in the populations studied, improved case selection and the introduction of tandem transplants. It is likely that the improvement is due to a combination of factors. Thus, in this series, we have now included patients with ETT or mixed PSTT/ETT presenting after an interval of ≥48 months since the antecedent pregnancy. Treatment protocols were modified when these women were shown to have a poor prognosis [7]. In the present study, 45% (5/11) of these patients survived after HDC since 2005, which is considerably better than in the study by Schmid *et al.* [7] in which all patients died of disease. Of course, this group is still small, and further evaluation is necessary, but it does suggest that HDC may need to be given earlier in the treatment of poor-prognosis PSTT/ETT. The effect of HDC is less clear in patients with non-assessable disease. These patients received HDC in an adjuvant setting because they were considered to be at risk of recurrence and/or to have a poor prognosis after multiple relapses. Most of these patients were long-term responders to HDC and were especially patients with poor-prognosis PSTT/ETT. The better outcomes after HDC compared with that expected from prior experience in similar patients are suggestive of response/benefit from this therapy [7,22,23].

While two courses of HDC seem more beneficial for survival, this may be explained by tumour stage, clinical performance status and tolerability of the first course of treatment. Given the limited number of patients undergoing tandem HDC, we cannot currently give guidance regarding the optimal interval between courses of this toxic therapy. If HDC is not effective, there is still a 25% chance that further salvage chemotherapy may be useful.

HDC is very intensive with a high morbidity, and not all patients will benefit from this treatment. Therefore, appropriate selection of patients for HDC is important. In general, women with GTN refractory to standard chemotherapy regimens are relatively young and of good performance status, making them suitable for such intensive treatment.

So which GTN patients might benefit the most? Our results indicate several univariable-defined good prognostic factors including hCG ≤12 IU/L, low FIGO stage and not having a rising hCG before HDC are important in optimising patient selection for HDC. In multivariable analysis, only an hCG ≤12 IU/L before HDC remained a favourable significant factor. Even in regression analysis without the 9 patients who received HDC in an adjuvant setting, this factor was significantly associated with OS. However, this should be interpreted with caution as our case numbers remain small. The fact that only patients with very low hCG concentrations (≤12 IU/L) seem to benefit from HDC may suggest that HDC acts more as a consolidation therapy and is much less effective in reducing bulky chemoresistant disease. Moreover, although all patients with hCG concentrations >12 IU/L died, it cannot yet be concluded that HDC should not be administered in this group of patients. Instead, these data could help in counselling and management of patient expectations.

5. Conclusions

In summary, our data show that HDC can be beneficial for some patients with GTN who have failed existing therapies or as an adjuvant treatment for poor-prognosis PSTT/ETT expected to otherwise relapse and die. The chance of success must be balanced against the risk of life-threatening complications and the emergence of new less toxic salvage therapies for GTN such as pembrolizumab [24]. Emerging data with the later agent suggests that this should be used before consideration of HDC.

Conflict of interest statement

None declared.

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