Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE)

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Objectives: To evaluate the efficacy and toxicity of paclitaxel and cisplatin alternating with paclitaxel and etoposide doublet regimen (TP/TE), for salvage of patients with high-risk gestational trophoblastic neoplasia (GTN).

Patients and methods: Twenty-four patients with GTN received TP/TE. Sixteen had failed previous chemotherapy including six with cisplatin-based regimens (group A) and eight changed to TP/TE because of prior treatment-induced toxic effects (group B).

Results: In group A, three patients (19%) achieved a complete response (CR) and five (31%) a partial response (PR). All CR and four PR patients remain alive with a median follow-up of 25 months (range 9–48). The eight patients failing TP/TE subsequently died. Thus, the overall survival of the 16 patients in group A was 44% (seven of 16), rising to 70% (seven of 10) if the six patients who had failed prior cisplatin-based chemotherapy were excluded. In group B, four patients were assessable for response (two CR, two PR) and six remain alive (median follow-up 19 months) giving an overall survival of 75%. TP/TE was well tolerated, with only one patient discontinuing therapy because of toxic effects.

Conclusion: TP/TE is an effective, well-tolerated, salvage treatment for relapsed patients who are heavily pretreated for GTN. Further studies of this regimen are warranted.

Key words: chemotherapy, gestational trophoblastic neoplasia

Introduction

Gestational trophoblastic disease (GTD) is a well recognised but rare complication of pregnancy [1–3]. It comprises a spectrum of disorders ranging from the premalignant conditions of complete and partial hydatidiform moles (CHM and PHM, respectively), through to the malignant invasive moles, choriocarcinomas and placental site trophoblastic tumours (PSTT). The latter three conditions are also known as gestational trophoblastic tumours or gestational trophoblastic neoplasia (GTN). The initial treatment of molar pregnancies which represent the commonest form of GTD is usually by uterine evacuation. This is often curative but progression to GTN occurs in 16% of CHM and 0.5% of PHM [4] and in these cases chemotherapy is required. In addition, choriocarcinoma and PSTT can also develop after any type of pregnancy including miscarriages and term deliveries and both usually require chemotherapy [2, 3].

Although the overall survival of patients receiving chemotherapy is high (98%), this is dependent on the risk of developing disease resistant to single-drug therapy determined by the Federation of Gynaecologists and Obstetricians (FIGO) scoring system [5]. Patients scored as low risk (score 0–6) receive methotrexate and folic acid and have a survival rate of ~100%, but a third require second-line chemotherapy, either with single-agent i.v. actinomycin D or with etoposide, methotrexate, actinomycin D alternating with cyclophosphamide and vincristine (EMA/CO) [6]. Patients scored as high risk (score ≥7) receive EMA/CO as first-line therapy and have a survival rate of ~90% [7]. Nevertheless, just >10% of patients fail this therapy. To salvage women failing EMA/CO, we have previously shown that the addition of cisplatin to etoposide (EP) alternating weekly with EMA (1 day only) with or without surgery salvages a further 75% of cases [8]. However, 40% of patients receiving EP/EMA suffer multiple grade 3 or 4 toxic effects which included neutropaenia (68%), thrombocytopenia (40%), anaemia (21%), renal (41%) and other side-effects. Consequently, there is a need to develop a salvage regimen that is less toxic than EP/EMA.

Several isolated case reports suggest that paclitaxel-containing regimens have activity in GTN [9, 10]. Here, we present our experience of the use of paclitaxel and cisplatin...
patients and methods

patients

Twenty-four patients referred to the Charing Cross Hospital Gestational Trophoblastic Disease Centre and treated with TP/TE (Table 1) from 22 December 1999 to 19 March 2007 were reviewed in this study. The patients were classified into two groups: (i) those who had become refractory or relapsed following other chemotherapy regimens and (ii) those who had not tolerated other treatments due to toxic effects (Figure 1). Patient characteristics are summarised in Table 2. All pathology was reviewed centrally. Those with GTN following a molar pregnancy had their diagnosis based on histopathological review of the original mole combined with a plateaued or rising human chorionic gonadotrophin (hCG) according to previously published criteria [6]. However, in most cases, additional tissue was available for a firm pathological diagnosis of choriocarcinoma. All patients with PSTT had histologically verified diagnoses (Table 3).

Records of previous surgical or chemotherapy treatments, either in other hospitals or at Charing Cross Hospital, were documented and summarised in Table 3. The FIGO prognostic risk score at initial diagnosis for each patient was reviewed [5, 6]. The median FIGO scores were 7 (range from 3 to 19) in group A and 11 (range 4–20) in group B (Table 2). Five patients with PSTT (two in group A and three in group B) were not scored as this system does not provide useful prognostic/therapeutic information for this disease. All low-risk patients received methotrexate and folic acid therapy initially. The high-risk patients previously treated in the UK had received combination therapy with EMA/CO or if ultrahigh risk (e.g. liver mets) with EP/EMA. The latter was also used in patients with metastatic PSTT. Two patients referred from abroad had other initial therapies (Table 3).

Monitoring of hCG to detect drug-resistant disease, relapse and response to therapy was carried out as previously described [6–8].

treatment

The TP/TE schedule is listed in Table 1. TP alternating every 2 weeks with TE to form one cycle of therapy. All patients had their glomerular filtration rate (GFR) formally assessed by 51-chromium EDTA clearance measurements. Only patients with a GFR of >50 ml/min were given the regimen. All patients had given written consent to the treatment.

Before each course of treatment, full blood count and renal function were checked. If the total white blood cell (WBC) <2.0 x 10^9/l, absolute neutrophil count (ANC) <1.0 x 10^9/l or platelets <75 x 10^9/l, treatment was delayed until recovery above these figures. Prophylactic s.c. injections of granulocyte-colony stimulating factor for 3–4 days were used. If the blood creatinine or urea increased to >1.5 x upper limit of normal, the EDTA clearance was repeated and the dose of cisplatin was reduced accordingly: EDTA clearance 50–59 ml/min cisplatin given at 50 mg/m², 40–49 ml/min drop to 40 mg/m² and <40 ml/min substitute cisplatin with carboplatin area under the curve (AUC) of 4.

Patients receiving chemotherapy were assessed by hCG levels twice weekly. A partial hCG response was defined as a fall of hCG by >50% sustained for >1 month. A complete response was defined as normalisation of the hCG level maintained for at least 1 month after stopping chemotherapy. Treatment was discontinued when the hCG was normal for 8 weeks. Other reasons for stopping therapy were drug resistance defined as a plateaued or rising hCG level over three and two consecutive samples, respectively, or because of toxicity.

Following chemotherapy, patients were monitored by hCG levels in blood and urine weekly for 6 weeks and then with decreasing frequency until eventually on six monthly urine measurements as previously published [6–8].

The study was approved by the local institutional review board.
patients switched to TP/TE following toxic effects (group B)

previous therapies. Eight patients were treated with TP/TE due to intolerable toxic effects [neutropaenic sepsis (n = 5), thrombocytopenia (n = 2) or grade 4 mucositis (n = 1)] from their prior treatment (Table 3 and data not shown). Seven patients had one previous regimen of chemotherapy (five with EP/EMA and two with EMA/CO), with one patient having two previous regimens. The latter patient had achieved remission with EMA/CO, but relapsed and then developed toxicity from EP/EMA.

response/survival. A median of 3.5 cycles of TP/TE (range 2–7 cycles) were given. There were four responders (two CR and two PR) and four patients not assessable for response because their hCG was already normal or close to normal at the time of starting TE/TP. Two patients (one PR and one unassessable for response) subsequently relapsed/progressed and despite further therapy including surgery and chemotherapy were not salvaged. One of these patients had a 20-year interval between her last pregnancy and the onset of choriocarcinoma, a known poor prognostic factor [13]. Therefore, six of eight patients who switched to TP/TE following toxic effects remain alive to give an overall survival of 75%, with a median follow-up of 19 months (range 6–34 months).

toxicity of TP/TE. The TP/TE regimen was generally well tolerated (Table 5). The commonest toxicity seen was transient neutropenia (National Cancer Institute—Common Toxicity Criteria grades 3–4, WBC <2 × 10⁹/l or ANC <1 × 10⁹/l), which occurred in 10 (42%) patients. However, there were no
neutropaenic sepsis episodes. Moreover, no dose reductions or delays were required. Mild nausea (grade 1) was recorded in three (13%) patients and controlled with additional antiemetics. One patient developed grade 2 renal toxicity (GFR decline from 63 ml/min to 37 ml/min), and the cisplatin was substituted with carboplatin at AUC 4. Peripheral neuropathy was seen in five (21%) patients, which was mild and transient in four cases. However, one of these patients developed grade 3 neuropathy and was the only individual in this series who had to stop TP/TE.

**discussion**

GTN is a relatively rare tumour which should be managed in specialist centres. In such centres, the overall survival is high at >98%. However, 14% of high-risk patients who received EMA/CO chemotherapy, as well as 1% of low-risk patients, who initially had methotrexate followed by EMA/CO, will require further treatment [6, 7]. Various salvage chemotherapy regimens have been used including EP/EMA [8, 14, 15]. The response rates for this regimen are high with 75% of EMA/CO failures (excluding PSTTs) achieving long-term survival with or without additional surgery. However, toxicity was a major problem. Thus, there is a need to develop other regimens which are less toxic but equally efficacious.

In this study, we investigated the potential value of the TP/TE regimen which has previously been used for germ cell tumours [11]. Recently, this regimen has also been reported in case studies to be beneficial in two pretreated patients with GTN [12]. In our current series, 24 patients were treated with this salvage therapy of whom 16 had received it because their disease was either refractory or had relapsed to previous therapies. The survival in this group was not surprisingly low at 45% because most patients had received...

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**Table 3.** Patient characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Histology</th>
<th>Sites of disease</th>
<th>FIGO score</th>
<th>No of previous regimens</th>
<th>Previous chemotherapy</th>
<th>Response or toxicity of last therapy</th>
<th>No of cycles of TP/TE</th>
<th>Response to TP/TE</th>
<th>Further chemotherapy</th>
<th>Further surgery</th>
<th>Alive (follow-up, months)</th>
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</tr>
<tr>
<td>28 CC</td>
<td>Lung</td>
<td>3</td>
<td>2</td>
<td>MTX, EMA/CO</td>
<td>PR</td>
<td>11 CR N</td>
<td></td>
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<td>2</td>
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<td>1</td>
<td>EMA/CO</td>
<td>PR</td>
<td>3 PR Y</td>
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<td></td>
<td>Hysterectomy</td>
<td>Y (48)</td>
<td></td>
</tr>
<tr>
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<td>Lung</td>
<td>4</td>
<td>2</td>
<td>EMA/CO, EMA/EP</td>
<td>PR</td>
<td>4 PD Y</td>
<td></td>
<td></td>
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<td>MTX, AD, EMA/CO, EMA/EP</td>
<td>CR</td>
<td>4 PR Y</td>
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<tr>
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<td>PR</td>
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<td>2</td>
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<td>PR</td>
<td>3 PD Y</td>
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<td>N</td>
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<td>MTX, AD, EMA/CO, BEP</td>
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<td>2 PD Y</td>
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<td></td>
<td>Thoracotomy</td>
<td>N</td>
<td></td>
</tr>
<tr>
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<td>Lung</td>
<td>7</td>
<td>2</td>
<td>EMA/CO, EP/EMA</td>
<td>PD</td>
<td>3 PD Y</td>
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<td></td>
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<td></td>
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<tr>
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<td>1</td>
<td>EP/EMA</td>
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<td>2 PD N</td>
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<td>EMA/CO</td>
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<td>EMA/CO</td>
<td>PR</td>
<td>1 PR/tox Y</td>
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<tr>
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<td>PR</td>
<td>2 PD Y</td>
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<td>Lung</td>
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<td>1</td>
<td>EMA/CO</td>
<td>CR</td>
<td>7 PR N</td>
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<td>Hysterectomy</td>
<td>Y (9)</td>
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<tr>
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<td>2</td>
<td>1</td>
<td>MTX, EMA/CO</td>
<td>PR</td>
<td>5 PR N</td>
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<td></td>
<td>Hysterectomy</td>
<td>Y (12)</td>
<td></td>
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<tr>
<td>45 CC</td>
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<td>7</td>
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<td>EMA/CO</td>
<td>CR</td>
<td>5 CR N</td>
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<tr>
<td>Group B</td>
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<tr>
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<td>Lung</td>
<td>NA</td>
<td>1</td>
<td>EP/EMA</td>
<td>Mucositis 6</td>
<td>NA N Hysterectomy Y (34)</td>
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<td>60 CC</td>
<td>Lung</td>
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<td>1</td>
<td>EMA/CO</td>
<td>Neutropenia 4</td>
<td>CR N</td>
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</tr>
<tr>
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<td>Brain/lung/pelvis</td>
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<td>1</td>
<td>EMA/CO</td>
<td>Neutropenia 8</td>
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<tr>
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<td>NA</td>
<td>1</td>
<td>EP/EMA</td>
<td>Neutropenia 4</td>
<td>PR Y Hysterectomy N</td>
<td></td>
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<tr>
<td>40 PSTT</td>
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<td>1</td>
<td>EMA/CO</td>
<td>Neutropenia 2</td>
<td>NA N</td>
<td></td>
<td></td>
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<tr>
<td>24 CC</td>
<td>Lung/brain/pelvic</td>
<td>16</td>
<td>1</td>
<td>EP/EMA</td>
<td>Neutropenia 2</td>
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<td></td>
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<tr>
<td>29 CC</td>
<td>Lung</td>
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<td>2</td>
<td>EMA/CO, EP/EMA</td>
<td>Low platelets 2</td>
<td>PR Y Neurosurgery Y (6)</td>
<td></td>
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<td>29 CC</td>
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<td>1</td>
<td>EP/EMA</td>
<td>Low platelets 3</td>
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</table>

FIGO, Federation of Gynaecologists and Obstetricians; TP/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide; PSTT, placental site trophoblastic tumours; PR, partial response; CR, complete response; PD, progressive disease; BEP, bleomycin, etoposide, cisplatin; MTX, methotrexate; AD, actinomycin D; VBP, vincristine, bleomycin, cisplatin; HD, high-dose chemotherapy; I/FU, ifosfamide, 5-fluorouracil; TG, paclitaxel, gemcitabine; EMA/EC, etoposide, methotrexate, actinomycin D; alternating with etoposide, carboplatin; GC, gemcitabine, carboplatin; CECy, cisplatin/etoposide/cyclophosphamide; DA, docetaxel/adriamycin.
etoposide/etoposide, methotrexate, actinomycin D; TP/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide.

CR, complete response; PR, partial response; FIGO, Federation of Gynaecologists and Obstetricians; PSTT, placental site trophoblastic tumours; EP/EMA, etoposide/etoposide, methotrexate, actinomycin D; TP/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders CR + PR (n = 8)</th>
<th>Nonresponders (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>33 (28–47)</td>
<td>31 (24–61)</td>
</tr>
<tr>
<td>Median FIGO prognostic score</td>
<td>7 (3–13)</td>
<td>7 (4–19)</td>
</tr>
<tr>
<td>Patients with PSTT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Median number of previous regimens</td>
<td>1.5 (1–9)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Number of patients received EP/EMA</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Patients who achieved remission with previous regimens but relapsed</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mean number of TP/TE cycles</td>
<td>5 (1–11)</td>
<td>2.5 (2–5)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; FIGO, Federation of Gynaecologists and Obstetricians; PSTT, placental site trophoblastic tumours; EP/EMA, etoposide/etoposide, methotrexate, actinomycin D; TP/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide.

Table 5. Toxicity profile for paclitaxel/cisplatin alternating with paclitaxel/etoposide

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number of patient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (grade 1)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Anaemia (grades 1–2)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Neutropaenia (grade 3–4)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>No episodes febrile neutropaenia or sepsis</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Thrombocytopaenia (grades 3–4)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Neutropaenia (grade 1 apart from 1 with grade 3)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Renal toxicity (grade 2)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Lethargy (grade 1)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Myalgia (grade 1)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

two or more prior therapies and six had already failed a platinum-based treatment (five EP/EMA and one BEP chemotherapy). However, if we analysed survival in those patients not previously receiving platinum-based therapy but who had failed EMA/CO, then the outcome was much better at 70% (seven of 10 patients). This is rather similar to the previously reported survival rate of 75% (nine of 12) achieved with EP/EMA following EMA/CO failures [8].

Moreover, survival with TE/TP was also good (75%) in the eight patients needing to change treatment because of toxicity to their previous therapy which included EP/EMA in six cases. Of course the higher CR and survival rates in this group may simply reflect chance because of small patient numbers. However, since seven of the eight patients in this group had only one prior treatment regimen, it is more likely that they did well because they were more chemosensitive.

Crucially, unlike EP/EMA, the toxicity profile of TP/TE appears less problematic, despite the fact that the patients given TP/TE were mostly more heavily pretreated. Thus, grade 3 or 4 neutropaenia and thrombocytopaenia occurred in 42% and 13% of patients receiving TP/TE, compared with 68% and 40% for EP/EMA [8], respectively. Moreover, none of the patients receiving TP/TE experienced neutropaenic sepsis and none required dose delays. In contrast, 88% of EP/EMA patients required dose delays, some because of neutropaenic sepsis [8]. Nevertheless, myalgia (grade 1) occurred in one and neuropathy in 21% of patients receiving TP/TE. However, this regimen was discontinued in only one patient due to grade 2 neuropathy. Furthermore, there were no dose reductions with TP/TE and only one patient required substitution of cisplatin with carboplatin because of renal impairment.

The relatively less toxic profile, coupled with the benefits of TP/TE when administered in more chemonaive patients suggest that TP/TE should be considered as an alternative to EP/EMA, in patients who may not tolerate the latter. However, with regard to TP/TE, at least two questions remain unanswered. One is the long-term survival of these patients as follow-up in this series is still comparatively short. The other question is the effect of TP/TE on fertility. Animal studies and case reports have suggested that patients can become pregnant following paclitaxel [16, 17], but further data are required.

The management of patients with metastatic PSTT has yet to be optimised. This is due to the rarity of the disease and its variable chemosensitivity. At our centre these patients routinely receive EP/EMA. However, our results here of TP/TE given to four cases of metastatic PSTT after other chemotherapy suggest it has activity against this condition. Indeed, one patient has become a long-term survivor (Table 3). Nevertheless, whether TP/TE will be as efficacious as EP/EMA for metastatic PSTT [8] remains to be established.

What about patients who fail or relapse following TP/TE? Various other treatments have been described in the past for salvage chemotherapy, including gemcitabine and HDC with stem-cell rescue [18–20]. Here, not surprisingly most patients who relapsed following TP/TE after multiple prior chemotherapy regimens do badly (group A). The outlook is particularly grim for those progressing on TP/TE, despite HDC. The lack of efficacy of HDC in this series is consistent with our observations in the past [21]. However, patients who responded to TP/TE appeared to have a better response to further treatment. In view of the newer agents now available, and the young age of these patients, we recommend that further therapy, including biological agents, should continue to be explored and evaluated in this poor-risk group.

In summary, TP/TE is an effective salvage treatment and should be evaluated further in patients failing EMA/CO and/or EP/EMA. Furthermore, its relative lack of toxicity would...
indicate that it should be considered as an alternative to EP/EMA for second-line treatment of GTN.

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references