A phase II trial of high-dose chemotherapy (HDCT) supported by hematopoietic stem-cell transplantation (HSCT) in germ-cell tumors (GCTs) patients failing cisplatin-based chemotherapy: the Multicentric TAXIF II study

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Received 30 December 2013; revised 20 February 2014; accepted 27 May 2014

Background: High-dose chemotherapy (HDCT) is an effective salvage treatment of germ-cell tumors (GCTs) patients. In the first salvage setting, 30%–70% of patients may achieve durable remissions. Even when HDCT is administered as subsequent salvage treatment, up to 20% of patients may still be definitively cured. However, patients with refractory/relapsed disease still have a very poor long-term prognosis, requiring earlier intervention of HDCT.

Patients and methods: This phase II trial was addressed to nonrefractory patients failing Cisplatin-based chemotherapy. Inclusion criteria included seminomatous GCT in relapse after two lines of chemotherapy, nonseminomatous GCT in relapse after first or second lines, partial remission after first line, primary mediastinal GCT in first relapse. Patients received two cycles combining Epirubicin and Paclitaxel (Epi-Tax), followed by three consecutive HDCT, one using a Paclitaxel/Thiotepa (Thio-Tax) association and two using the 5-day Ifosfamide–Carboplatin–Etoposide regimen. The main objective was to determine the complete response rate.

Results: Forty-five patients were included between September 2004 and December 2007: 44 received the first HDCT cycle, 39 two HDCT cycles, 29 could receive the whole protocol. Sixteen patients did not receive the entire protocol, including eight (17.7%) for toxic side-effects. Two patients (4.4%) died of toxicities, and 17 (37.7%) of disease progression. With a median follow-up time of 26 months (range, 4–51), the final overall response rate was 48.8% (including a complete response rate of 15.5% and a partial response/negative serum markers rate of 26.6%) in an intent-to-treat analysis. The median progression-free survival (PFS) and overall survival (OS) times were 22 months [95% confidence interval (CI) 2–not reached] and 32 months (95% CI 4–49), respectively. The 2-year PFS was a plateau setup at 50% (95% CI 32–67) and the 2-year OS was 66% (95% CI 44–81).

Conclusion: The TAXIF II protocol was effective in nonrefractory GCT patients failing Cisplatin-based chemotherapy. The toxic death rate remained acceptable in the field of HDCT regimens.

Trial registration number: NCT00231582.

Key words: germ-cell tumors, high-dose chemotherapy, hematopoietic stem-cell transplantation, TAXIF II trial, nonrefractory patients

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introduction

First-line standard pharmacological treatment of metastatic germ-cell tumors (GCTs) remains a Cisplatin-based combination named Bleomycin, Etoposide and Cisplatin (BEP). Despite its considerable high cure rate, there are still 10%-20% of patients who failed to achieve long-term free-disease survival [1, 2]. Those patients are candidates to receive initial salvage therapy with either the Vinblastine–Ifosfamide–Cisplatin (VeIP) or Etoposide in place of Vinblastine (VIP) standard chemotherapy regimen or a combination of Ifosfamide and platinum salts associated to Paclitaxel (TIP) [3–5].

In addition, salvage high-dose chemotherapy (HDCT) has been used since the late 1980s [6] but its success was initially limited by high levels of treatment-related mortality. In this setting, the collection of stem cells from peripheral blood led to improvements in efficacy with reduced toxicity. However, reports comparing high-dose (HD) versus conventional-dose chemotherapy (CT) in previously treated patients are limited and based on studies with small number of patients, heterogeneous inclusion criteria and a diversity of treatment options [1, 7]. Therefore, no standard treatment of patients who are refractory to chemotherapy of any line or who failed second-line treatments has been completely established to date [8–10].

Since patients with incomplete response after first-line chemotherapy or patients having an extragonadal primary tumor rarely achieve a complete response (CR) with conventional chemotherapy, they should be included in studies evaluating the potential role of intensive approaches [11, 12].

We have previously shown the feasibility and efficacy of a HD regimen combining two mobilization CT cycles and three intensive cycles of chemotherapy in patients with refractory/relapsed poor prognosis disease [13]. The multicentric TAXIF I trial allowed us to develop a concept of three consecutive HDCT regimens delivered in a short period of time. The encouraging TAXIF I results and the suitable response rate observed with the two taxane-based mobilization cycles prompted us to develop a new triple HDCT study with a modified therapeutic program. In this article, we report the results of the completed TAXIF II trial in which relapsing patients previously treated with Cisplatin (CDDP)-based chemotherapy and who did not progress within 4 weeks after completing their last chemotherapy cycle received the first HD course using Paclitaxel instead of Cyclophosphamide, and Thiotepa (Thio-Tax) at higher dose than that used in our previous protocol.

methods

patients selection and characteristics

Inclusion criteria for the study were GCTs patients previously treated with CDDP-based chemotherapy, who did not progress within 4 weeks after completing their last CDDP-based regimen. Patients included in the study were 18 years old or older with a life expectancy of at least 3 months. Eligibility requirements included histological diagnostic of a GCT without cytological evidence, and measurable elevation of tumor markers (alpha-fetoprotein [AFP] > UNL and/or human chorionic gonadotrophin [hCG] > 2IU/l). Seminomatous or nonseminomatous GCTs were included with gonadal, extragonadal, retroperitoneal or primary mediastinal primary location. For seminomas, patients with recurrence after two initial regimens of chemotherapy were included. For nonseminomatous GCTs, patients with incomplete responses, extragonadal tumors at the first recurrence and failure after two initial regimens of chemotherapy were included. Other inclusion criteria were absence of renal insufficiency, negative HIV status, normal hematopoietic, renal, hepatic, pulmonary tests and a cardiac ejection fraction ≥50%. The presence of primary and uncontrolled central nervous system (CNS) metastasis excluded patients from the study.

Each patient underwent regular evaluations that included measurements of serum marker levels, imaging workup, standard hematologic, renal, liver tests, pulmonary function testing and ventricular ejection fraction measurement. The study protocol was approved by the Ethic Committee of the Hospital Saint-Antoine in Paris. All patients provided written informed consent before enrollment.

chemotherapy

Patients were scheduled to receive five cycles of chemotherapy; two courses of front-line mobilization CT followed by three HDCT supported by peripheral blood stem-cell transplantation (Figure 1). The induction/mobilization CT consisted in a combination of Epirubicin (100 mg/m²) and Paclitaxel (250 mg/m²) in a 3-h infusion, administered both on days 1 and 15 (Epi-Tax 1 and Epi-Tax 2). The first HDCT regimen (Thio-Tax) consisted in an association of Thiopeta (720 mg/m²; 6-h infusion, 240 mg/m²/day) and Paclitaxel, 360 mg/m² (continuous infusion, 120 mg/m²/day for 3 days). The second and the third courses [Ifosfamide–Carboplatin–Etoposide (ICE)-1 and 2] consisted in a combination of Etoposide (150 mg/m² twice a day, in a 2-h infusion, for 5 days—total dose of 1500 mg/m²), Ifosfamide (2400 mg/m²/day in a 3-h infusion, for 5 days—total dose of 12 000 mg/m²) and Carboplatin (area under the curve (AUC) 4/day, in a 6-h infusion, for 5 days—total dose of AUC 20). Ifosfamide was deleted for ICE-2 in case of encephalopathy during ICE-1. PBSC harvest and infusion, sodium mercaptosulfonate administration and supportive cares were used according to the TAXIF I protocol [13, supplementary Appendix I, available at Annals of Oncology online].

evaluation of toxicity, response to therapy and survival

The study was designed in two steps according to the Gehan method [14, supplementary Appendix II, available at Annals of Oncology online]. In the first phase, 14 patients were included. Given that more than one CR was observed, the study subsequently continued to include a total of 45 patients.

Primary end points were the clinical CR rates for resistant, nonrefractory patients whatever the line of therapy and after two lines of CDDP-containing regimen for relapsing patients. Secondary end points were overall (complete plus partial) response rate (ORR), overall survival (OS) and progression-free survival (PFS) rates, toxicities and toxic death rate.

The statistical analysis was done in terms of intent to treat. Toxicity and response to therapy were evaluated according to the ECOG/WHO criteria [15, 16]. The durations of PFS and OS were calculated according to the Kaplan–Meier method, from the date of inclusion to the date of progression or the most recent evaluation and from the date of inclusion to the date of death or the most recent evaluation if still living, respectively [17].

Patients were evaluated after the two Epi-Tax cycles. The TAXIF II treatment was continued for those patients who had stable disease or if they were considered as responders. Final evaluation was planned at the end of the whole procedure, i.e. HDCT and if carried out, surgery of any residual disease accessible to surgery. In case of progression at any time of the HD procedure, patients were to be withdrawn. Responses were classified into complete chemotherapeutic response, complete surgical response with excision of inactive lesions, including mature teratoma (pCR) and complete surgical response with excision of active malignant lesions (sCR). Favorable
responses were considered to be either CR or PRmq− (partial response with negative tumor markers) [18]. Patients who attained a CR did not receive further therapy. Patients who achieved a PR (PRmq+), those whose tumors progressed, and the complete responders who relapsed were given, if possible, various regimens of CT. Patients who died of therapy and those who were, for any reason withdrawn from therapy at any time of the treatment, were considered as treatment failure. Finally, an independent data monitoring committee (IDMC) was setup to allow us, in case of toxic deaths, to continue the study.

**results**

**characteristics of the patients**

This phase II study was carried out in eight institutions, between September 2004 and January 2010. Forty-five patients were included between September 2004 and December 2007. Twenty-nine (64.4%) patients presented nonseminomatous and 16 (35.6%) seminoma GCTs. At inclusion, 37 patients had history of metastasis; 97% of them had received two prior lines of therapy. Forty-one (91.1%) patients presented with relapse at a metastatic site. Four patients underwent therapy while they had elevated serum markers as the only indicator of their disease. Thirty-seven patients (82.2%) underwent surgery before initial chemotherapy. Baseline characteristics of the patients are showed in Table 1 and supplementary Table SI, available at Annals of Oncology online.

**administration of chemotherapy**

Delivery and median dose intensity of chemotherapy are shown in supplementary Table SII, available at Annals of Oncology online. For both Epi-Tax cycles, the median doses of Epirubicin and Paclitaxel were 190 and 474 mg/m². The median interval times were 14 days (range, 12–21) between first and second courses, 20 days (range, 19–42) between second and third courses, 39 days (range, 28–69) between third and fourth courses and 42 days (range, 39–56) between fourth and fifth courses. Thio-Tax administration was associated with a median hospitalization time of 22 days (range, 7–64). Both cycles of ICE were associated with a median hospitalization time of 24 days (range, 21–39) and 23 days (range, 21–43), respectively.

Among the 45 patients included, 30 (66.7%) received the five planned cycles of CT but only 29 completed the protocol. Reasons for treatment discontinuation of patients enrolled in the study are shown in Figure 2.

**hematopoietic and nonhematopoietic toxicities**

The 45 patients were assessable for toxicity (supplementary Table SIII, available at Annals of Oncology online). The IDMC allowed us to continue accrual of patients after a life-threatening grade IV adverse event was observed.

In a population heavily pretreated with Cisplatin-based chemotherapy, only one patient failed to be harvested. The median duration time of grade IV neutropenia was 11 (range, 6–18), 13 (range, 9–16) and 13 (range, 10–28) days, for the three HD cycles, respectively.

No cardiac adverse events were observed during the Epi-Tax sequence. Enterocolitis with occlusive symptoms was observed in two patients during ICE-1 therapy and one patient during ICE-2 therapy. Grade III/IV peripheral neuropathies, enhanced by previous administration of Paclitaxel were observed during both ICE-1 and ICE-2 regimens for 18 and 3 patients, respectively. However, no long-term disabling peripheral neuropathy

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**Figure 1.** Chemotherapy protocol. Doses are given in mg/m², except for Carboplatin.
was deployed in long-term survivors. Two patients suffered from grade III transient hearing impairment. Grade IV infection was observed in three patients during Thio-Tax therapy and for two patients in ICE-2. Fungal infections were observed in Thio-Tax, ICE-1 and ICE-2 in 5 (21.7%), 4 (17.4%) and 2 (11.1%) patients, respectively. One case of Herpes Zoster infection was observed. Reasons of grade III/IV liver toxicity observed in one-third of the patients were probably multifactorial, mainly due to sepsis episodes and administration of Carboplatin at HD.

**therapy-related deaths**

Two patients (4.4%) died of therapy-related complications, one from persistent sepsis after the ICE-1 cycle and one from multi-organ failure, including sepsis, liver failure and grade IV renal toxicity following the ICE-2 cycle. As planned, this last multi-visceral toxicity was reported to the IDMC who subsequently allowed us to enroll further patients in the study.

**response to therapy**

In the intention-to-treat population, the overall response rate to both Epi-Tax cycles was 50% [95% confidence interval (CI) 35.4–64.6], including a 4.5% CR rate. A final overall response rate of 48.8% (95% CI 34.3–63.3) was achieved for 22 patients. Seven patients (15.5%, 95% CI 5–26) achieved a CR and 12 a PRmq= (26.6%, 95% CI 20–33.2). So far, a total number of 19 patients (42.2%, 95% CI 27.9–56.5) attained a favorable response rate considered to be either CR or PRmq=. Three patients (6.6%, 95% CI 0–13.8) achieved a PRmq+/PR rate.

Twenty patients (15 in PR, 2 with stable disease, 2 considered in progression but with normal tumor markers level, 1 not clearly evaluated) underwent surgery after their last HDCT cycle. Twelve (60%) had marker normalization before intervention. Surgical excision of metastases was carried out at various sites [lymph node dissection (14), lungs (9), liver (3) and brain (1)]. For 19 assessable patients (1 had neither biopsy nor resection), lesions demonstrating positive histology included 10 inactive samples, including pure teratoma (52.6%) and 9 (47.4%) viable GCT samples. Fifteen patients (83.3%) demonstrated a complete macroscopic resection; 6 of them achieved a sCR and 9 a pCR.

Progression or relapse was observed in 19 patients [median delay of onset, 8 months (range, 4–30 months)]. Relapse at the primary site occurred in two patients, while 85% suffered from metastatic relapse. Of the 19 patients with progression or relapse, 18 (94.7%) received subsequent treatment of either surgery (22.2%) or chemotherapy (94.4%).

**survival**

The median follow-up time was 26 months (range, 4–51 months). For each patient, the follow-up period started when the patient entry in the study. The follow-up period ended up when either (i) the patient died, (ii) the last follow-up visit took place or (iii) the closure date of the study (January 2010) was reached. Periods of follow-up are distributed as it follows: 9 patients (20%): <12 months, 12 patients (26.7%): 12–24 months, 22 patients (48.9%): 24–36 months, 2 patients (4.4%): ≥48 months.

Disease progression accounted for 17 deaths. The median PFS was 22 months (95% CI 2–not reached) and the median OS was 32 months (95% CI 4–4). The 2-year PFS was a plateau setup at 50% (95% CI 32–67). The 2-year OS was 66% (95% CI 44–81). No differences were observed between intermediate and

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**Table 1. Characteristics of the patients at the time of inclusion**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>32 (18–51)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (95.5)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>General status, WHO [unknown 1], n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32 (72.7)</td>
</tr>
<tr>
<td>1</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Median follow-up, months (range)</td>
<td>26 (4–51)</td>
</tr>
<tr>
<td>Known primitive site, n (%)</td>
<td></td>
</tr>
<tr>
<td>Testicular</td>
<td>39 (88.6)</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Histology of primitive site, n (%)</td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>Nonseminomatous/mixed tumors</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td>Pure teratomas</td>
<td>28 (62.2)</td>
</tr>
<tr>
<td>Chemotherapy before TAXIF II*, n (%)</td>
<td></td>
</tr>
<tr>
<td>1 regimen</td>
<td>45 (100)</td>
</tr>
<tr>
<td>BEP</td>
<td>36 (80.0)</td>
</tr>
<tr>
<td>EP</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>2 regimens</td>
<td>32 (73.3)</td>
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<tr>
<td>VIP</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>VeIP</td>
<td>24 (56.3)</td>
</tr>
<tr>
<td>≥3 regimens</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Beyer Model [7], n (%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Score ½</td>
<td>35 (77.7)</td>
</tr>
<tr>
<td>Score ≥3</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>Germ-Cell Tumor Risk Classification at diagnosis [11], n (%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>Intermediate prognosis</td>
<td>13 (30.2)</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>21 (48.8)</td>
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<tr>
<td>Metastatic sites at initial diagnosis, n (%)</td>
<td></td>
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<tr>
<td>Lymph nodes</td>
<td>44 (97.7)</td>
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<tr>
<td>Pulmonary</td>
<td>30 (66.6)</td>
</tr>
<tr>
<td>Liver/bone/brain</td>
<td>15 [10/2/3] (33.3)</td>
</tr>
</tbody>
</table>

*The median cumulative dose of Cisplatin received by the patients was 706, 717, 719 and 700 mg for their first, second, third and fourth lines chemotherapy regimen, respectively. A single patient received radiotherapy in conjunction with chemotherapy before inclusion in the study.

BEP, Bleomycin, Etoposide and Cisplatin; EP, Etoposide and Cisplatin; VIP, Etoposide, Ifosfamide and Cisplatin; VeIP, Vinblastine, Ifosfamide and Cisplatin; WHO, World Health Organization.
poor prognosis groups. PFS and OS rates are shown in Figures 3 and 4.

**discussion**

GCTs patients who relapse after initial chemotherapy can still be cured with subsequent-line regimens. Although the initial salvage approach remains controversial, HDCT is generally the only curative option after two or more regimens. However, the standard HDCT treatment remains to be defined [18–21].

In that sense, we developed this TAXIF II trial to provide guidance for further clinical trials and to outline the status of HDCT in the management of GCTs patients. The results reported here show superior outcomes compared with our previous trial [13]. Supplementary Table SIV, available at *Annals of Oncology* online summarizes activity and toxicity profiles of TAXIF II compared with other HDCT regimens.
The mobilization step was identical to the TAXIF I regimen, a combination of Epirubicin and Paclitaxel. Although Epirubicin is not the most common choice for salvage chemotherapy in GCTs, numerous trials have evaluated the role of anthracyclines in testicular cancer [22–24]. In addition, our robust experience on the use of Epirubicin as a part of the induction cycle of CT (Epi-Tax) has allowed us to efficiently collect hematopoietic stem cells with a good tolerance. Thus, this approach was used to get a rapid control of disease and to harvest PBSC for multiple courses of HDCT. The harvesting has only failed in one patient.

Regarding the HDCT cycles, two main modifications were applied to the current TAXIF II protocol. First, since the administration of Paclitaxel at higher doses than those conventionally used was previously considered feasible and well tolerated [25, 26], Paclitaxel (instead of Cyclophosphamide), at a total dose of 360 mg/m² was combined with Thiotepa (720 mg/m²) during the first HD cycle. The use of Thiotepa was based on the rational developed for dose-intensification therapy. Alkylating agents are the only agents that exhibit a very steep curve of dose–response in preclinical models [27] and thiotepa is considered less toxic than other molecules of this class [28], with the possibility to increase drug up to 20-fold [29]. Other groups have also shown the feasibility and safety of Thiotepa administration as a treatment of relapsed or refractory GCTs patients [30–32]. Importantly, these two anticancer agents show different mechanisms of action, thus avoiding cross-resistance [33, 34].

In addition, given that dose-limiting toxicity of alkylating agents is primarily hematologic [34], the depletion of one of the alkylating drugs should lead to reduced hematologic toxicities. In agreement, in the TAXIF II trial, no grade IV episodes of hemorrhage were observed, and cerebral bleeding was not responsible for therapy-related deaths. The integration of Paclitaxel in HDCT should however be redesigned considering the fact that since the mid-2000s, TIP (Cisplatin, Ifosfamide and Paclitaxel) has almost become universally adopted as standard salvage chemotherapy [2].

Second, the two subsequent courses of HDCT followed a modified ICE protocol, in which the total Ifosfamide dose was enhanced to 12 000 mg/m² and the daily dose of Carboplatin was determined accordingly to its daily clearance value.

Several factors seem to be critical to improve results in terms of toxicity and efficacy of HDCT as salvage therapy. The number of cycles, the time of administration as well as the inter-cycle intervals are among the important prognostic variables. The number of courses of HDCT has improved the results in terms of toxicity and efficacy [12, 35–37]. For instance, Rick et al. [31] using a front-line CT with TIP followed by one cycle of HDCT containing Carboplatin, Etoposide and Thiotepa, first reported a long-term (with a median follow-up of 36 months) remission rate of 26% in relapsed or refractory patients. Following this work, the feasibility and efficacy of several HDCT cycles were explored and established [18, 38, 39]. In this setting, the administration of three rather than two HD cycles has proven to be a strong alternative, as highlighted by the TI-CE protocol (Paclitaxel [T] plus Ifosfamide [I] followed by HD Carboplatin [C] plus Etoposide [E] with stem-cell support) which reported a 5-year DFS of 47% and OS of 52% (median follow-up, 61 months) [40].

Our results corroborate these findings, after three cycles of HDCT in our TAXIF II trial, the 2-year PFS was 50% and 2-year OS was 66%. In term of efficacy, the final ORR was 48.8% and the median PFS and OS were 22 and 32 months, respectively. Considering that 95% of the TAXIF II population had received two lines of CT, our results seems to be favorable compared with studies using HDCT as second salvage therapy and which reported a projected 17% OS rate at 5 years [19]. However, cross-trial comparisons with either TAXIF I or TI-CE may be interpreted with caution since inclusion criteria among studies were different. Although in TAXIF II patients had already failed one salvage regimen, absolutely refractory patients were excluded, in contrast to the other studies.

Furthermore, as reported here, earlier intervention after a maximum of two conventional regimens appears to limit toxicity and could improve outcomes. However, contrasting results have been reported by others [21] who considered that HDCT may be efficient even when applied as third-line or later therapy or in refractory patients.
conclusion
Although the optimal strategy in this setting has yet to be determined, overall, salvage treatment with TAXIF II was feasible and tolerable. It is important to note that this kind of intensification chemotherapy to treat GCTs has to be carried out with acceptable toxicity and morbidity only in selected referral centers.

Even if the conclusions of the 'European Consensus Conference on diagnosis and treatment of germ-cell cancer' [2] pointed out the use of a HDCT regimen including Carboplatin and Etoposide without additional agents such as Ifosfamide, Cyclophosphamide or Thiotepa, it is important to dispose of an alternative salvage regimen containing drugs that had not been used previously. The choice of the regimen will then rely on the expertise of the clinicians working in the referral center. Thus, the TAXIF II program could be used as an alternative option for salvage treatment (after failure of one or two lines of CT) for GCTs poor prognosis patients presenting a recurrent nonrefractory disease.

However, for refractory patients or those who have become refractory to Cisplatin, salvage treatment strategies clearly must be explored. In that sense, the molecular mechanisms supporting Cisplatin insensitivity have provided the rational to design the TAXIF III trial. Based in our own experience over the previous TAXIF trials and supported by the first report published by Voigt et al. [41], we have initiated the TAXIF III program in which patients with refractory disease will be re-sensitized with the Epi-Tax combination and then will be treated by two subsequent HDCT regimens combining the ICE regimen and Bevacizumab. This approach allowed Nieto et al. [42] to reach a 67% event-free survival rate in 21 highly refractory patients. We expect this new approach will increase response and survival rates for poor prognosis patients.

acknowledgements
We thank Christian Kempf, Xavier Huther, Gaëlle Chenuc, Alexia Letierce and Mathieu Robain, 3ES-Cegedim Strategic Data, Boulogne, France, for their help in statistical Analysis, the Clinical Research Unit, Hôpitaux Universitaires de l’Est Parisien (Tabassone Simon and her team, St Antoine Hospital), the Department of Clinical Research and Development (Isabelle Brindel, St Louis Hospital), the GETUG Staff of the Fédération Nationale des Centres de Lutte contre le Cancer (known as UNICANCER), 101 rue de Tolbiac, 75013 Paris, for their help in the realization of this study, Dominique Pouzoulet, Head Nurse, Department of Medical Oncology and Cellular Therapy, Cellular Therapy Unit, Tenon Hospital, and finally, all the nurses of the Bone Marrow Transplant Units for their expert and compassionate care of our patients.

funding
This work was sponsored by Assistance Publique—Hôpitaux de Paris and supported by:

- Bristol-Myers-Squibb Lab, 3, Rue Joseph Monier, 92500 Rueil-Malmaison, France—for the supply of Paclitaxel for the 45 patients (no grant numbers).
- Baxter Lab, 6, Avenue Louis Pasteur, 78310 Maurepas, France—with a grant of 10 000 Euros (no grant numbers).

disclosure
The authors have declared no conflicts of interest.

references


