Combining gemcitabine, cisplatin, and ifosfamide (GIP) is active in patients with relapsed metastatic germ-cell tumors (GCT): a prospective multicenter GETUG phase II trial


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Background: The standard treatment of patients with metastatic germ-cell tumor (GCT) relapsing after first-line chemotherapy is based on a cisplatin and ifosfamide-containing three-drug regimen, which usually yields a complete response (CR) rate <50%. As gemcitabine consistently displayed activity in patients with advanced GCT and as synergy with cisplatin was reported, we integrated this drug into the salvage triplet regimen and assessed its activity in this phase II study.

Patients and methods: The GIP regimen consisted in gemcitabine 1000 mg/m² day 1 and 5, ifosfamide 1200 mg/m²/day day 1–5, cisplatin 20 mg/m²/day day 1–5, and granulocyte colony-stimulating factor 263 μg/day day 7–15, repeated every 3 weeks for four cycles. Eligibility criteria were that patients had favorable prognostic factors to conventional-dose salvage chemotherapy including a testis primary tumor and a previous CR to first-line chemotherapy for metastatic disease. The primary end point was the CR rate and a two-stage Simon design was used.

Results: Thirty-seven patients were accrued and 29 (78%) achieved a favorable response, including a CR in 20 (54%) and a partial response with normalization of tumor markers (PRm−) in 9 (24%). With a median follow-up of 53 months (13–81), the 2-year overall survival rate is 73% (57%–84%) and the continuous progression-free survival rate is 51% (35%–66%). Myelosuppression was the main toxicity including febrile neutropenia in 8 (22%) patients and 18 (50%) cases required platelet infusion. No grade 3 and 4 peripheral neurotoxicity or renal toxicity occurred. Two patients died of treatment-related toxicity, one of them with cancer progression.

Conclusion: In a multicenter context, four cycles of the GIP regimen achieved a high CR rate in patients with relapsed testicular GCT. The GIP regimen avoided severe neurotoxicity and yielded a high survival rate.

Clinical trial number: NCT00127049.

Key words: germ-cell tumor, chemotherapy, salvage, gemcitabine

introduction

Approximately 80% of patients with metastatic germ-cell tumors (GCTs) achieve a continuous complete response (CR) after cisplatin-based chemotherapy followed, if needed, by resection of residual masses [1, 2]. The cure rate decreases dramatically for patients who do not achieve a CR and for those who relapse after a CR, with only about 30%–40% achieving a continuous CR [3]. Standard systemic therapy for these patients is usually a triplet chemotherapy regimen combining cisplatin, ifosfamide, and a third drug (vinblastine, etoposide, or paclitaxel) [1]. The role of high-dose chemotherapy plus stem-cell transplantation is controversial in this setting. Although retrospective analysis of large datasets suggested a potential gain in survival [4, 5], no survival nor even progression-free survival benefit was evidenced in the only phase III trial conducted which tested high-dose chemotherapy versus standard-dose chemotherapy in 280 patients [6]. Furthermore, whereas in another phase III trial of 230 patients, sequential high-dose chemotherapy was associated with a better outcome than single
high-dose chemotherapy, this benefit seems to be related to excess toxicity-related deaths in the single high-dose arm, rather than to improved anticancer efficacy in the sequential arm [7]. Although no predictive factor for better efficacy of high-dose over standard-dose chemotherapy is available to assist treatment decision making, prognostically relevant parameters have been identified. In the early 2000s when the present study was designed, data available from the Memorial Sloan Kettering Hospital group [8, 9] suggested that patients with a testis primary cancer, previous chemotherapy limited to one line, and those who had achieved a previous CR were predicted to experience a better outcome. Taking these data into account a decade ago, the French Study Group of Genito-Urinary Tumors (GETUG) recommended that patients with relapsing disseminated GCT after chemotherapy for nonstage I disease and an anticipated favorable outcome be treated with standard-dose chemotherapy, while others would be considered for high-dose chemotherapy. Trials [10], including this one, were designed and conducted in both subgroups, to test this new approach. The present study was a phase II trial focused on patients with a relapsed metastatic GCT and an anticipated favorable outcome. It evaluated the use of gemcitabine in the cisplatin–ifosfamide-based triplet regimen (GIP) in combination with granulocyte colony-stimulating factor (G-CSF). The rationale for using gemcitabine was the reported efficacy of this drug either as a single agent [11, 12] or in combination [13–17] in patients with highly pretreated GCTs, and its synergy with cisplatin in various neoplasms [18]. The GIP regimen has previously been used and reported in patients with other malignancies including lung cancer [19–22] and bladder cancer [23]. In this article, we report the results of this phase II trial.

**patients and methods**

**eligibility**

Thirty-seven patients were entered in this prospective phase II trial.

Eligibility criteria were as follows: patients older than 16 years, histologically proven disseminated (nonstage I) GCT, or the diagnosis of NSGCT based on very elevated serum human chorionic gonadotropin hormone (hCG) and/or alfa fetoprotein (AFP), relapsed disease classified as good prognosis according to the MSKCC classification criteria [a testicular primary site, prior treatment limited to one program (or six or fewer cycles of cisplatin), either a CR or a partial response (PR) with normal serum AFP and hCG], relapse documented by rising AFP and/or hCG or by a biopsy, no previous carcinoma, excepted basal-cell carcinoma of the skin, adequate renal function: measured or calculated creatinine clearance >60 ml/min, absence of residual nephrotoxicity. A dose reduction was to be discussed with the lead investigator for subsequent cycles only in case of persistent severe renal (creatinine clearance <60 ml/min), neurological, auditory, or hematological toxicity.

Febrile neutropenia was typically treated with empirical broad-spectrum antibiotics on an inpatient basis. Packed red blood cell transfusions were used in case of severe anemia (hemoglobin levels <8 g/dl) and platelet transfusions were used by institution policy, typically in case of severe thrombocytopenia (<10 000–20 000/μl) or if associated with hemorrhage.

A complete blood test and tumor marker (hCG, AFP, LDH) determination were carried out before each cycle. After completion of chemotherapy, a CT scan of the chest, abdomen, and pelvis was repeated and surgical resection of any residuum was recommended if tumor markers had normalized. Patients with progressive disease (PD) were candidates for either salvage surgery or high-dose chemotherapy plus a stem-cell transplant.

**evaluation and biostatistics analysis**

Patients with normal tumor markers and no clinical or radiologic evidence of disease were classified as having achieved a CR to chemotherapy (cCR). Patients with normal tumor markers and completely resected residual masses containing only necrosis or teratoma were classified as having achieved a pathologic CR (pCR). Patients with normal tumor markers and completely resected masses containing viable cancer were classified as having achieved a surgical CR (sCR). Patients with a PR and normalized tumor markers were classified as ‘PR tumor marker negative’ (PRm−). PD was defined as rising tumor markers confirmed at least twice or the appearance of new lesions, except when pathologic evidence of a growing teratoma syndrome [24, 25] was provided. A CR was considered to have occurred if any of the following was achieved: cCR, pCR, sCR. A favorable response was defined when either a CR or a PRm− was achieved. The primary end point was the CR rate and a two-stage Simon design was used, with 80% power to detect at least 24 CR. The number of patients to be accrued on to the trial was 37 and the hypothesis was to be recycled every 3 weeks provided the following conditions were met: physical condition compatible with chemotherapy, neutrophil count >1000/mm³ or >500/mm³ if they were increasing, platelet count >100 000/mm³, absence of residual nephrotoxicity. Survival times were calculated from the date of chemotherapy initiation to the date of progression or death (progression-free survival) and the date of death (overall survival). Survival curves were estimated using the Kaplan–Meier method. Toxicity was assessed using NCI-CTC criteria.

**results**

From September 2004 to February 2009, 37 patients were accrued. Their baseline characteristics are summarized in Table 1. Two patients had no available histology before treatment and centers were from the French Groupe d’Etude des Tumeurs Uro-Genitales (GETUG). All patients filled out a signed written consent form.

**treatment**

Chemotherapy consisted in four cycles of the GIP regimen plus G-CSF support, given once every 3 weeks. This regimen was administered on an inpatient basis and consisted in gemcitabine 1000 mg/m²/day, day 1 and 5, ifosfamide 1200 mg/m²/day, day 1–5, and cisplatin 20 mg/m²/day, day 1–5, with G-CSF (lenograstime) at a dose of 263 μg/day from day 7–14 of each cycle. Standard antiemetics and hydration protocols were given. Intravenous mesna 500 mg/m² was administered at h0, h3, h7, and h11 on each day of ifosfamide therapy. A weekly blood cell count was carried out. Treatment was to be recycled every 3 weeks provided the following conditions were met: physical condition compatible with chemotherapy, neutrophil count >1000/mm³ or >500/mm³ if they were increasing, platelet count >100 000/mm³, absence of residual nephrotoxicity. A dose reduction was to be discussed with the lead investigator for subsequent cycles only in case of persistent severe renal (creatinine clearance <60 ml/min), neurological, auditory, or hematological toxicity.

The staging procedure comprised a computed tomography (CT) scan of the thorax, abdomen, and pelvis. A CT scan or an MRI of the brain was also to be carried out. A bone scan was also carried out in case of bone-related symptoms. Serum tumor marker levels (AFP, hCG, lactate dehydrogenase (LDH)) were determined before chemotherapy.

The trial was approved by the Institutional Review Board and by the ‘Comité de Protection des Personnes’ [CPP] (Ethics Committee). The sponsor was the Institut Gustave Roussy, Villejuif, France, and participating
were treated based on clinical presentation and elevated tumor markers. One patient with a primary retroperitoneal GCT was included by mistake. All patients received at least one cycle of chemotherapy: four cycles (\(n=32\) patients; 86%), two cycles (\(n=3\); 8%), and one cycle (\(n=2\); 5%). The median total dose of cisplatin received was stable across cycles (190 mg, range 142–225 mg), while the median total doses of the other two drugs were only very slightly reduced: from 3820 mg (range 1711–4420 mg) at cycle 1 to 3800 mg (0–4420 mg) at cycle 4 for gemcitabine, and from 11 500 mg (range 9120–13 375 mg) at cycle 1 to 11 190 mg (range 6000–13 250 mg) for ifosfamide.

**Table 1.** Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n(%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>37 (20–48)</td>
</tr>
<tr>
<td>Primary tumor site, (n(%))</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>36 (97)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Histology, (n(%))</td>
<td></td>
</tr>
<tr>
<td>Pure seminoma</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Nonseminoma type</td>
<td>26 (74)</td>
</tr>
<tr>
<td>IGCCCG when first-line chemotherapy was given, (n(%))</td>
<td></td>
</tr>
<tr>
<td>Good risk</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Poor risk</td>
<td>9 (26)</td>
</tr>
<tr>
<td>First-line chemotherapy regimen, (n(%))</td>
<td></td>
</tr>
<tr>
<td>BEP</td>
<td>29 (78)</td>
</tr>
<tr>
<td>EP</td>
<td>3 (8)</td>
</tr>
<tr>
<td>CISCA/VB</td>
<td>1 (3)</td>
</tr>
<tr>
<td>T-BEP</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dose-dense GETUG 13 regimen</td>
<td>1 (3)</td>
</tr>
<tr>
<td>BEP + CARBOPEC</td>
<td>1 (3)</td>
</tr>
<tr>
<td>BEP-VIP</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Metastatic sites, (n(%))</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal lymph nodes</td>
<td>26 (76)</td>
</tr>
<tr>
<td>Lung</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Mediastinal lymph nodes</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Cervical lymph nodes</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Other site</td>
<td>7 (21)</td>
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<tr>
<td>Elevated tumor marker only</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Tumor markers (median, range)</td>
<td></td>
</tr>
<tr>
<td>hCG (UI/l)</td>
<td>4 (0–161 300)</td>
</tr>
<tr>
<td>AFP (ng/ml)</td>
<td>5 (1–4807)</td>
</tr>
<tr>
<td>LDH (UI/l)</td>
<td>235 (82–1303)</td>
</tr>
</tbody>
</table>

**Figure 1.** Progression-free survival (A) and overall survival (B).

**response**

During the first step of this phase II trial, 13 of 23 patients achieved a CR and patient accrual was therefore continued as previously decided. After completion of the total planned accrual of 37 patients, 20 [54% [95% confidence interval (CI) 37% to 71%]] had achieved a CR, consisting in a cCR (\(n=12\)), a pCR (\(n=4\)), or a sCR (\(n=4\)). Additionally, 10 patients had achieved a partial response, including 9 (24%) with normalized serum tumor markers. Altogether, 29 patients (78%) achieved a favorable response.

Overall, 11 patients (30%) were operated on for postchemotherapy residual masses: complete necrosis was found in 7 and viable cancer (nonteratoma) in 4 (among these 11 operated, 8 patients achieved a CR, and 3 achieved a PR with still residuals after surgery). None of these patients had teratoma only on the operated masses.

**survival**

The median follow-up is 53 months (13–81 months) and 18 progression or death events have occurred. PFS and OS curves are shown in Figure 1. The 2-year OS rate is 73% (95% CI 57% to 84%) and the continuous PFS rate is 51% (95% CI 35% to 66%). Of 18 patients who experienced cancer progression, 7 (39%) subsequently received high-dose chemotherapy with a stem-cell transplant.

**toxicity**

Toxicity data are detailed in Table 2 (worse side-effects across treatment). Hematological toxicity was the main adverse event (Table 2). Overall, 50% and 72% of the patients received platelet...
transfusion and red cell transfusions respectively. Of note, no patient developed grade 3 and 4 neurotoxicity. Two patients died of treatment-related toxicity, associated in one with cancer progression.

discussion

As patients with advanced GCT failing first-line chemotherapy are rare, large trials devoted to this issue are few and far between with only two reported phase III trials: one testing a standard-dose triplet chemotherapy regimen versus high-dose chemotherapy, reporting no survival or even a difference in PFS [6], and the other one testing single versus sequential high-dose chemotherapy and reporting a better outcome with the latter approach, mostly due to excess toxicity-related deaths in the single high-dose chemotherapy arm [7]. Since the role of high-dose chemotherapy with a stem-cell transplant is not currently underpinned by level 1 evidence in relapsing GCT, most guidelines and most groups recommend a cisplatin–ifosfamide–based triplet regimen in this setting [1, 2]. Replacing either vinblastine or etoposide by paclitaxel in this triplet was advocated during the last decade [26], although no direct comparison is available or etoposide by paclitaxel in this triplet was advocated during the last decade [26], although no direct comparison is available. Although it is difficult to conduct an indirect comparison in the absence of phase III data, the replacement of paclitaxel by gemcitabine in the salvage triplet seems to result in similar anticancer activity, a lower risk of neutropenic fever (22% versus 48%), and also a lower risk of severe neurotoxicity (0% versus 7% grade 3 and 4). Additionally, following cisplatin-based chemotherapy to treat the first primary GCT, patients who developed metastatic disease in the setting of a second gonadal primary GCT were eligible in the original TIP phase II trial [26]. As we consider that these patients are currently receiving a first-line chemotherapy regimen for their second GCT and not a salvage regimen, they were not eligible for this trial because their likelihood of achieving cure is much closer to that of patients receiving a first-line chemotherapy regimen [31]. Also, patients with a noncisplatin-based regimen were eligible for the TIP trial, whereas they were not for the present study, an important difference being that cancers relapsing after a non-standard treatment are easier to cure with salvage therapy than those relapsing after standard treatments since the latter are considered more chemo-resistant [32].

Due to its promising activity and its modest neurotoxicity profile, the GIP + G-CSF regimen may prove to be an appealing option for patients relapsing after first-line chemotherapy and requiring standard-dose chemotherapy, specifically because patients may be more often treated with regimens associated with neurotoxicity during first-line therapy [29, 33].

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disclosure

The authors have declared no conflicts of interest.

references


