A phase II multicenter study of oxaliplatin in combination with paclitaxel in poor prognosis patients who failed cisplatin-based chemotherapy for germ-cell tumors

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Background: The aim of this study is to determine feasibility and efficacy of the combination regimen oxaliplatin and paclitaxel in patients with cisplatin (CDDP)-refractory germ-cell tumors (GCT).

Patients and methods: Patients with either a cisplatin absolute-refractory GCT defined as progressive disease (PD) during or within 1 month of CDDP administration or with a poor prognosis relapse, defined as PD between the second and the sixth month after CDDP administration, were treated with a combination of oxaliplatin (130 mg/m²) and paclitaxel (175 mg/m²) administered every 21 days. Primary end point was efficacy.

Results: Twenty-seven patients were included. Patients were pretreated with a median of two lines of cisplatin-based chemotherapy (range 1–5). Sixteen patients were absolute refractory. Five patients had relapsed after high-dose chemotherapy plus stem-cell support. There were no complete responses but there was one marker-positive partial response and nine disease stabilization (34, 6%). After a median follow-up of 65 months, two patients are disease-free survivors. Main toxicity was leucocytopenia grade 3/4 in 30% of the patients.

Conclusion: Combination chemotherapy with oxaliplatin and paclitaxel is feasible with acceptable toxicity and may be effective if combined with additional treatment in patients with CDDP-refractory GCT.

Key words: cisplatin refractory, germ-cell tumors, oxaliplatin, paclitaxel

introduction

Germ-cell tumors (GCT) are highly sensitive to chemotherapy. Cisplatin-based combinations, followed by appropriate surgical resection of residual masses, achieve cure in 80% of patients with disseminated disease. However, the cure rate in patients who relapse despite adequately administered first-line therapy remains within the range of 20%–25% when the reference second-line chemotherapy regimen combining standard-dose cisplatin, ifosfamide and vinblastine is administered [1]. The role of salvage high-dose chemotherapy (HDCT) with stem-cell rescue in this setting is still debated, particularly for patients who experience disease progression within 6 months of cisplatin administration [2, 3]. These patients may be offered phase II treatments with new drugs. Paclitaxel and oxaliplatin are new chemotherapeutic agents with different mechanisms of action. Paclitaxel has been recognized as the most promising new drug for patients with GCT, with single-agent overall response rates (ORRs) attaining 11%–26% [4–7]. With oxaliplatin, a platinum compound which is non-cross-resistant to cisplatin [8], a 19% ORR has been reported in a phase II trial in patients with cisplatin-refractory GCT [9]. The single-agent activity of each drug and increased activity of oxaliplatin when combined [10, 11] were the rationale underlying this phase II study testing the paclitaxel–oxaliplatin (OP) combination in patients with poor prognosis disease following cisplatin-based chemotherapy.

patients and methods

This prospective phase II study involved seven centers, all belonging to the French Federation of Comprehensive Anticancer Centers.

eligibility

Eligible patients had a histologically confirmed metastatic GCT, gonadal or extragonadal, nonseminomatous or seminomatous or with mixed histology, at least one bidimensionally measurable lesion ≥20 mm on computed tomography (CT) scan or significantly elevated tumor markers (TM) exceeding twice the upper limit of normal (ULN) at two consecutive measurements. Disease progression had to have been evidenced by a ≥25%
increase in the product of the perpendicular diameters of measurable tumor masses, new lesions on imaging studies or a confirmed ≥10% rise in previously elevated α-fetoprotein (AFP) or human chorionic gonadotropin (HCG) levels. In case of a growing nonseminomatous germ-cell tumors (NSGCT) without TM elevation, histologic documentation was required to avoid confusing tumor progression with growing mature teratoma. Any numbers of previous regimens were allowed as long as cisplatin had been administered. Patients who progressed during or within 1 month of cisplatin administration were considered as refractory and referred to as refractory (REF), while patients who progressed between the second and the sixth month after completion of a cisplatin-based chemotherapy were considered as having a poor prognosis relapse and referred to as REL.

At least 3 weeks were required to have elapsed following chemotherapy or major surgery. Other eligibility criteria included age ≥18, an Eastern Cooperative Oncology Group performance status, (PS) of zero, one or two, no prior treatment with taxanes or oxaliplatin, no symptomatic higher than grade one peripheral neuropathy, no symptomatic brain or leptomeningeal metastases. Laboratory eligibility criteria included: neutrophil count ≥1.5 × 10⁹/l, platelet count ≥100 × 10⁹/l, total bilirubin ≤1.5 ULN, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤2.5 ULN in the absence of liver metastases or five or less if there were liver metastases and creatinine ≤3 ULN.

A clinical history and physical examination with CT scan imaging of the brain, abdomen, pelvis and thorax were carried out within 14 days before inclusion. Blood tests including serum hCG, AFP, lactate dehydrogenase, creatinine, ALT, AST and bilirubin determinations were carried out within 7 days before inclusion. All patients gave their written informed consent, and the study was approved by an Ethics Committee in accordance with national standards of good clinical practice. An independent steering committee was constituted.

treatment
Patients received paclitaxel, (175 mg/m²) in a 3-h i.v. infusion followed by oxaliplatin, (130 mg/m²) in a 2-h i.v. infusion on day 1 every 21 days. Treatment delays (of up to 2 weeks) were allowed. Treatment with granulocyte colony-stimulating factor was planned for patients with febrile neutropenia or grade 4 neutropenia ≥7 days, until recovery with a neutrophil count ≥3 × 10⁹/l. Dose reductions were specified for patients with grade 4 neutropenia or thrombocytopenia, infection or any grades 3–4 toxicity other than nausea and vomiting.

safety and responses
Physical examinations and TM determinations were repeated at 3-week intervals. Imaging studies to define the extent of disease were carried out at 6-week intervals, and, if a response was established, imaging was repeated after 4 weeks to confirm it.

The primary end point was drug activity on the basis of a reduction in tumor size and a tumor marker decrease (TMD). The reduction in tumor size was evaluated according to World Health Organization criteria. A complete response (CR) was defined as the disappearance of all clinical, radiographic and biochemical evidence of disease. Partial responses were defined as a >50% decrease in bidimensional tumor measurements with normalization of previously elevated markers (PR m⁻²). TM normalization and decreases ≥90% and ≥50% were also recorded. The response rate (RR) was calculated with the CR and PR m⁻². Secondary end points included tolerance, time to progression and overall survival.

Adverse events were classified according to National Cancer Institute—Common Toxicity Criteria (version 2).

statistical methods
A two-step design according to a modified Gehan method was used. Fourteen assessable patients were to be entered at the first step. If no response was observed, the probability of missing a RR ≥20% would have been ≤0.05, and the study would have been terminated. If at least one response was observed in the first 14 patients; 11 further patients were to be recruited for a more accurate evaluation of the improvement rate.

results

patient characteristics
The study was activated in June 2000 and was terminated on 30 December 2002. Twenty-seven patients were included. One patient was never treated. The 26 treated patients were assessable for toxicity and for response. Twenty-three patients had elevated TM at the time of inclusion in the trial and were also assessable for TMD.

Baseline patient characteristics are summarized in Table 1. Sixteen patients were refractory (REF) and 10 had an early relapse after cisplatin-based chemotherapy (REL). Five patients had received previous HDCT. Four patients had a mediastinal primary. Twenty-three patients had elevated TM: (n = 12) for elevated serum AFP (mean 874, median 182, range 22–2199 ng/ml) and (n = 14) for elevated serum hCG (mean 3478, median 247, range 27–21 000 mUI/ml). Twenty patients had previously undergone surgery for metastases, which consisted in a retroperitoneal lymphadenectomy in 15 (which had required

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Patient characteristics (n = 27)</th>
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<tbody>
<tr>
<td>Patients included (n)</td>
<td>27</td>
</tr>
<tr>
<td>Ineligible patient</td>
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<tr>
<td>Median age, years (range)</td>
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<tr>
<td>ECOG PS 0/1/2</td>
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<tr>
<td>Sex ratio males/females</td>
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<td>Histology</td>
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<td>NSGCT</td>
<td>19</td>
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<tr>
<td>Seminoma</td>
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<td>6</td>
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<td>Primary site</td>
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<tr>
<td>Number of metastatic sites</td>
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<tr>
<td>Two sites</td>
<td>9</td>
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<tr>
<td>Five lines</td>
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<tr>
<td>Refractory/relapse</td>
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</table>

ECOG, Eastern Cooperative Oncology Group; NSGCT, nonseminomatous germ-cell tumors.
a nephrectomy in three of them), thoracic surgery in seven and surgery for brain metastases in one patient.

**treatment administered**
A total of 87 cycles were administered. The median number of OP cycles administered was 4 (range 1–7).

**adverse events**
Overall, the OP combination was well tolerated. Grades 2–4 adverse events are summarized in Table 2. No patient died as a result of treatment. No patient discontinued therapy because of toxicity. Adverse events which affected most patients included grade 1 or 2 fatigue, nausea and/or vomiting, anorexia and grade 1 or 2 sensory neuropathy.

**RRs and survival data**
No CR or PR m– was achieved in the first 14 patients, but one PR was confirmed on imaging in a patient who had been refractory upfront and had been treated with two cycles of HDCT before the study. His/her hCG level was at 13 500 mIU/ml upon inclusion in the study but had dropped to 46 mIU/ml at the time of imaging evaluation. This PR m+ was considered good enough to proceed to the second step of the study.

The RR based on CR and PR m– was 0% [95% CI (confidence interval) 0% to 13%]. One patient achieved a PR m+ and nine patients had stable disease (SD) (34.6%) (95% CI 25% to 44%). Ten of 23 patients with initially abnormal markers had a TMD ≥50% (43%) (95% CI 23% to 63%) and six of them had a TMD ≥90% (26%) (95% CI 15% to 37%).

The median overall time to progression (TTP) was 1.4 months (CI 95% 0–14.8). The median TTP for patients who had a TMD ≥50% was 4.2 months (CI 95% 2.5–5.7). The median overall survival time was 8.8 months (CI 95% 5–12). Further therapies may have been facilitated by the protocol: four patients (14.8%) received further HDCT but none achieved a CR or a PR m– after HDCT. Eight patients underwent surgery. Two patients who had SD after the study treatment are long-term survivors. One patient had a stage IIC bulky seminoma with initially normal TM. In this case, progressive disease (PD) was pathologically documented after cisplatin-based chemotherapy. After four cycles of OP, disease stabilized. The second patient had a refractory NSGCT after two previous lines of chemotherapy with hCG at 164 mIU/ml, received two cycles of OP, exhibited a transient rise in hCG which subsequently normalized and imaging confirmed SD. Both patients received ‘consolidation’ HDCT. Disease stabilization on imaging with normal TM was still observed on imaging after HDCT. They both underwent surgery for residual masses. The histological diagnosis was fibrosis and necrosis in the first patient and mature teratoma in the second patient. The patient who had a PR m+ after the study treatment and another patient who had initially elevated AFP and reached SD with TM normalization refused further treatment, including surgery of residual masses. They both remained progression free for 6 months but eventually died of disease.

Univariate analysis found no significant prognostic factor among the following variables: TM status, PS or tumor sites.

**discussion**
The rationale behind this phase II trial of OP combination in poor prognosis patients previously treated with cisplatin for a GCT was on the basis of the results of phase II trials of each drug used alone in similar patients and the assumption that better results would be obtained if the drugs were administered in combination rather than as single agents. There are four phase II trials of single-agent paclitaxel in a similar setting. In the first trial, paclitaxel was administered at a dose of 250 mg/m² in 15 patients, 11 of whom had previously received three lines of chemotherapy. The authors reported a 13.3% RR. However, this RR corresponded to one SD with a TMD ≥50% for 10 weeks and one PR of 9 weeks duration confirmed on imaging [4]. In a subsequent trial, paclitaxel was also administered at a dose of 250 mg/m² but in order to be eligible, patients had to have received only one line of conventional cisplatin-based chemotherapy: the reported RR was 26% in 31 patients, with three CR, only one of which was durable and one PR m– in a seminoma patient [5]. In the third study, paclitaxel was given at a dose of 225 mg/m². Eligible patients had to have PD either after two lines of chemotherapy or after HDCT or refractory disease. Among the 24 treated patients, one CR and five PR m–, converted into a surgical CR after resection of residual masses, were achieved which translated into a 25% RR. It was concluded that paclitaxel demonstrated significant antitumor activity in these patients. However, despite the use of all types of additional treatment considered indicated on an individual basis, there were only four long-term progression-free survivors among these 24 patients (17%) [6]. In the last study, paclitaxel was administered at a dose of 175–200 mg/m². Eligible patients were either refractory or had received one line of chemotherapy with a combination of etoposide, ifosfamide, vinblastine, bleomycin and cisplatin, which was the investigational treatment for poor risk patients previously treated with cisplatin for a GCT. It was considered that paclitaxel had minimal antitumor activity in these patients [7].

Oxaliplatin was first used in combination with cisplatin as ‘biplatin treatment’ in GCT patients who had failed cisplatin-based conventional chemotherapy. This combination was
reported to have yielded a 54% RR in 13 patients [12]. There is only one phase II trial of oxaliplatin in refractory/relapsed GCTs: an overall RR of 13% with a dose of 60 mg/m² on day 1, 8 and 15 of a 28-day cycle and 19% with a dose of 130 mg/m² on day 1 were reported, but altogether four responses were ultimately achieved in 32 patients with only one PR m—of 7 months duration in a patient who eventually died of the disease [9]. At the Institut Gustave Roussy, eight patients with cisplatin-refractory (n = 6) or relapsed (n = 2) NSGCT also received single-agent oxaliplatin at a dose of 130 mg/m² every 21 days from 1997 to 1999 as part of a compassionate program. These patients had received a median of 2 (range 1–4) previous regimens: among these eight patients, two achieved a PR m—, and one had a TM decrease ≥50% but long-term survival was not reported [13]. In another phase II study, oxaliplatin combined with irinotecan was reported to have yielded three long-term responses among relapsed or refractory patients [14], while no objective responses or any clinical benefit was achieved in similar patients treated with irinotecan alone [15].

Thus, although the RRs obtained with paclitaxel and oxaliplatin as single agents in similar patients are not clearly established, these results were considered good enough by other researchers to launch a variety of trials using one or the other drug in different combinations.

Indeed, paclitaxel-containing combinations were proven to be active against GCT. Indeed, paclitaxel-containing combinations were proven to be active against GCT. It was used in first-line treatment of poor-risk and intermediate-risk GCT according to the International Germ Cell Consensus Cancer Group (IGCCC) in the T BEP combination [16]. It was also used in first-line salvage treatment of GCT in the paclitaxel, ifosfamide and cisplatin combination. In the initial series, the ORR reported was 77% in 30 patients with good prognostic factors [17]. In a subsequent study in 26 patients fulfilling ‘good-risk’ criteria described by the Memorial Hospital, failure-free survival was 73% compared with 41% for the 17 ‘poor-risk’ patients [18]. In a third study in 46 patients also fulfilling good-risk criteria, a 63% durable CR rate was obtained [19].

Paclitaxel was also included in HDCT regimens as treatment for GCT. As first-line treatment, a favorable outcome was reported in 77% of 52 patients with poor prognosis features according to the IGCCC [20]. In the salvage setting, a paclitaxel-containing regimen followed by sequential HDCT achieved a 51% ORR in patients with poor prognostic factors [21].

In all studies, paclitaxel was associated with cisplatin or HD carboplatin and with other drugs like ifosfamide or etoposide which are known to be active against GCT.

We chose to associate oxaliplatin with paclitaxel because patients were selected due to poor sensitivity [11]. In vivo data are now available since a phase II trial using the same combination as in our study obtained an ORR of 81% in 79 of 98 patients with relapsed ovarian cancer. However, these patients were sensitive to cisplatin [22].

This study had been designed before the results of the two phase II studies of single-agent gemcitabine in GCT, which reported a 15% and 19% ORR [23, 24]. Gemcitabine was later used in combinations: in one series with paclitaxel, a 12.5% durable CR rate was obtained in 32 patients who had relapsed after HDCT [25], and in another series with oxaliplatin, a 13% sustained CR rate was achieved in 35 patients, most of whom had received HDCT before [26] and finally the gemcitabine paclitaxel oxaliplatin combination yielded a 15% CR rate in 73 patients who had relapsed within 3 months of cisplatin administration [27].

In comparison, the results of this trial may seem disappointing. However, the two long-term disease-free survivors after additional HDCT should not be minimized in such a poor prognosis subset of patients. Although it is impossible to guess whether secondary ‘consolidation’ HDCT contributed to the final favorable result, they may have benefited from the OP combination. The patient with a PR m+ and the patient with SD and normalized AFP who refused further treatment both had 6 months without further progression which can only be attributed to the study treatment.

**Conclusion**

Combination chemotherapy with OP is feasible and shows some efficacy even in heavily pretreated patients with cisplatin-refractory GCT. Both drugs warrant being included in clinical trials of salvage regimens in such patients.

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**References**


