Results of a prospective dose-intensive regimen in 27 patients with small cell carcinoma of the ovary of the hypercalcemic type


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Background: The evaluation of first-line intensive combination therapy in small cell carcinoma of the ovary (SCCO).

Patients and methods: Debulking surgery; four to six cycles of chemotherapy with cisplatin (P) 80 mg/m² day 1, Adriamycin (A) 40 mg/m² day 1, Vepeside (V) 75 mg/m²/day days 1–3, Cyclophosphamide (EP) 300 mg/m²/day days 1–3, every 3 weeks and granulocyte colony-stimulating factor with, in case of a complete remission, high-dose chemotherapy with Carboplatin, Vepeside, Cyclophosphamide and stem-cell support.

Results: Twenty-seven patients (median age 25 years); International Federation of Gynecology and Obstetrics stage: five I, four IIC, 17 IIIC–IV and one unknown. Twenty patients underwent complete surgery. Eight patients progressed under chemotherapy. Among 18 patients in complete response (CR), 10 received high-dose chemotherapy (CT) (three stem-cell collection failures, two protocol violations, two disease progression and one refusal). The main grade 3–4 toxic effects were hematologic. There were eight relapses among the 18 CR, four of which were pelvic alone. Among the 27 patients, 13 died and 10 patients are in CR1, three in CR2. The median follow-up is 37 months (8–166) and the median duration of the 18 CR is 30 months (5–111). Overall survival at 1 and 3 years is 58% [confidence interval (CI) 40% to 75%] and 49% (CI 30% to 67%).

Conclusions: Initial dose-intensive therapy achieves interesting overall survival in SCCO.

Key words: chemotherapy, high-dose therapy, ovarian cancer, small cell carcinoma

introduction

Small cell carcinoma of the ovary (SCCO) is a rare tumor that was first described by Dickersin and Scully in the 1980s [1, 2]. As tumors are highly undifferentiated, the histogenesis remains obscure (epithelial, germinal or mesenchymatous) but most tumors are immunoreactive for epithelial markers and of the epithelial type at ultrastructural examination [3, 4]. This entity is suspected when there is an undifferentiated ovarian carcinoma composed of small cells with scanty neoplasm occurring in a young patient (mean age 24 years) and associated with para-endocrine hypercalcemia (which resolves following tumor removal) in ~60% of the cases [5]. The prognosis is generally very poor with only 33% of the patients with a stage IIA tumor alive and free of disease but no patients with advanced stages in the Young series of 150 patients. Patients died rapidly, usually within 2 years [5]. In different small series published after this large one, some patients who received semi-intensive chemotherapy with or without radiotherapy are still alive. To date, there is no published prospective series of homogeneous therapy.

One way to increase survival is to try to optimize induction and/or consolidation therapy. Among experimental approaches, treatment intensification followed by autologous hematopoietic stem-cell transplantation (AHSCT) is worth developing further. As SCCO was described as a highly aggressive tumor in a very young patient population usually with a high rate of initial responses (but often with rapid disease progression) and given the results of dose-intensive therapy in small-cell lung carcinomas published by our institution, we opted to treat these patients prospectively with intensive combined modality therapy. Treatment consisted in semi-intensive chemotherapy combined with extensive surgery and one cycle of high-dose consolidation chemotherapy (CT) followed by AHSCT in case of a complete response (CR).

patients and methods

From 1992 to 2005, a total of 38 patients were treated at the Institut Gustave-Roussy (IGR) or another collaborative hospital for a SCCO of the
hypercalcemic type. All patients with a diagnosis of SCCO and who had not received any previous chemotherapy regimen were eligible for the study. Twenty-seven were considered eligible for the prospective dose-intensive therapy regimen. Eleven patients were not eligible because they were referred after first-line therapy and/or had already received another regimen (in two cases because of a misdiagnosed dysgerminoma and a juvenile granulosa cell in another case).

The remaining 27 patients were treated with the intensive combined modality approach as first-line therapy, 15 of them at the IGR and 12 outside, after a review of the slides by the same pathologist at our institution. The protocol was approved by the institutions’ local committees and patients gave their oral informed consent.

Disease was staged using the International Federation of Gynecology and Obstetrics (FIGO) staging classification for ovarian carcinomas.

Life tables were computed using the Kaplan and Meier method [6].

treatment
Treatment consisted in the following:

- Non-conservative debulking surgery initially or after three to six cycles of chemotherapy and in the absence of progressive disease. It consisted in a total hysterectomy, bilateral oophorectomy, omentectomy, pelvic and lumbar-aortic lymph node dissection and peritoneal biopsies. The histological diagnosis was made in all cases initially by surgery (at least an oophorectomy) before chemotherapy.

- Chemotherapy consisted of cisplatin (P) 80 mg/m² i.v. >1 h on day 1, adriamycin (A) 40 mg/m² on day 1, vepeside (V) 75 mg/m²/day >1 h i.v. on days 1–3, cyclophosphamide (EP) 300 mg/m² on days 1–3 (PAVEP) and granulocyte colony-stimulating factor (G-CSF) (filgrastim or lenograstim) 5 µg/kg days 7–12. This PAVEP regimen was given every 3 weeks for four to six cycles. Dose adjustments were made according to hematologic toxicity. Treatment was withheld if the absolute neutrophil count was <1000/mm³ or the platelet count <100 000/mm³. The number of cycles was determined according to the initial stage (four for stage I and six for stages II and III), toxicity and the ability to collect stem cells.

- In case of a complete remission, this initial regimen was followed by one cycle of high-dose consolidation chemotherapy with carboplatin (400 mg/m²/day days 1–4), vepeside (450 mg/m²/day days 1–4) and cyclophosphamide (1600 mg/m²/day days 1–4) (CARBOPEC regimen) followed by AHSCCT. Stem cells were collected after the third or fourth cycle of PAVEP supported by G-CSF (filgrastim or lenograstim), 5 µg/kg/day, from day 6 until apheresis. The concentration of CD34+ cells required for the administration of high-dose therapy was at least 3 × 10⁶ cells/kg of body weight. In case of harvest failure, a new attempt at stem-cell mobilization using a double G-CSF dose >5 days from steady state was proposed to the patient after the next course of PAVEP or alone. Complete remission was assessed by surgery when performed after chemotherapy or by abdominal, pelvic and thoracic computed tomography scan when surgery was performed initially.

results
A total of 27 patients were treated between June 1992 and June 2005 with the intensive combined modality approach, at five centers (15 of 27 patients at the IGR and 12 outside) (Figure 1). Among those 27 patients, five were initially misdiagnosed as having germ-cell tumors in three cases (dysgerminoma in two cases and Yolk sac tumor in one case) and granulosa cell tumor in two cases. The diagnosis of SCCO of the hypercalcemic type was present in all cases, with a large cell component (large cell variant) in 15 cases.

Median age was 25 years (12–40); 16 of the 27 patients were in the second decade of life. Two patients were pregnant (6 months and 8 weeks) at the time of the diagnosis. There was no hypercalcemia. The pregnancy was continued until a natural delivery in the former patient but was discontinued in the latter. Two days after delivery, the patient who gave birth to a normal child at 9 months gestation presented with acute pain caused by hemorrhage linked to tumor rupture. She was then referred to our institution and surgery was completed but she died of her disease 6 months later.

The most common presenting symptoms were abdominal pain (12 of 27), an abdominal mass (9 of 27), hemoperitonitis (one case), urinary frequency (two cases), polyuro-polydypsia due to hypercalcemia (one case) and in two cases tumors were asymptomatic (tumors diagnosed at ultrasound examination during pregnancy).

The median ovarian tumor size in 19 patients for whom it was available was 16 cm (9–21 cm). The serum calcium level was at the upper limit of normal in 4 of 26 cases tested after diagnosis.

According to the FIGO classification, three patients had stage IA disease, two unspecified stage I, four stage IIC, 14 stage IIIIC, three stage IV disease (one pleural, one hepatic and one splenic site) and one whose tumor stage was unknown. The tumor was bilateral in two cases (one stage IIC and one stage IV).

Twenty patients underwent complete debulking surgery (six initial surgery and 14 debulking surgery after three to six cycles of chemotherapy). All patients without complete surgery (7 of 27 patients) died.

The median number of PAVEP cycles administered was 6 (range one to six cycles).

Eight patients progressed on PAVEP therapy, most of the time after an initial partial response, and all have died. One patient died of paraneoplastic malignant hyperthermia, 2 days after the beginning of chemotherapy.

Among the 18 patients in CR after PAVEP therapy and surgery, 10 received high-dose CT and eight did not (three stem-cell collection failures, two progressive disease at the time of high-dose therapy, two protocol violations and one refusal).

Two of the latter patients received total abdominal radiotherapy (20 Gy) and pelvic radiotherapy (45 Gy), respectively.

No toxic death occurred. The main grade 3–4 toxic effects of PAVEP therapy were hematologic. In 21 patients, 104 cycles of PAVEP were assessable. Despite the administration of G-CSF, 19 febrile neutropenia events occurred in 11 patients. Eight patients (38%) required red blood cell transfusions (27 cycles) and 11 (52%) platelet transfusions (21 cycles). Surgical evacuation of an abscess was necessary three times (pelvic, axillary and pleural abscess).

Eight relapses occurred among the 18 patients in CR, three among the 10 patients who received high-dose therapy and five among the eight who did not. The relapse was pelvic alone in four cases. Thirteen patients died and 10 are in CR1, three in CR2 and one is alive with disease. All patients without complete surgery died. Among the 10 patients who received high-dose CT, three relapsed in the pelvic area. Two of them died and one patient is in CR2 after surgery, chemotherapy and radiotherapy (48 months). The other patient who developed a pelvic relapse...
is in CR2 after surgery, chemotherapy and radiotherapy (6 months). Median follow-up is 37 months (8–166) and the median duration of the 18 CR is 30 months (5–111).

Overall survival of the entire population at 1, 2 and 3 years is, respectively, 58% [confidence interval (CI) 40% to 75%], 49% (CI 30% to 67%) and 49% (CI 30% to 67%) (Figure 2). The median follow-up is 33 months (14–77 months) for the five patients with stage I disease who are all alive (CI 26% to 67%). The survival rate for the other 21 patients is 46% at 1 year and 33% at 2 and 3 years (CI 16% to 56%) with a median follow-up of 38 months (19–165 months).

**Discussion**

SCCO are rare tumors usually affecting young women and children. They grow very aggressively and the majority of patients present with advanced stages above stage IA and die rapidly (within 6 months). Potential prognostic factors excepted the disease stage (stage IA versus others) are age >30 years, a normal pre-operative calcium level, a tumor size <10 cm, the absence of large cells, surgical resection including bilateral oophorectomy and post-operative radiotherapy for some cases [7].

Reports on large series in the literature are few and far between. In the latest series published [8], 10 of 17 patients had stage I disease. Six of 10 patients had conservative surgery but most of them received pelvic irradiation with or without abdominal irradiation. Only one patient with stage III disease is alive without recurrence.

Unfortunately, most of the time, these tumors present at advanced stages (>stage IA), the tumor size exceeds 10 cm and...
they occur in the second decade of life. Nevertheless, they are particularly chemosensitive at the outset but can rapidly escape therapy probably as a result of drug resistance. To optimize the practical use of anticancer chemotherapy in these young patients, we attempted an aggressive strategy with extensive surgery to lower the tumor burden on the one hand and dose-intensive chemotherapy to circumvent cell mutations on the other hand.

Our institution has developed, in a cooperative group setting, intensive chemotherapy for small-cell lung cancer (SCLC) and demonstrated that multidrug therapy and dose intensity are important prognostic factors in these diseases [9, 10]. Compared with the EP regimen, the PAVEP regimen yielded higher response rates and better survival rates in patients with extensive SCLC without affecting the quality of life of the patients during chemotherapy [9]. Because of similar histologic features and a comparable clinical evolution, we decided to administer this active drug combination in SCLC to patients with SCCO. We report on a series of 27 patients with SCCO prospectively treated with the same intensive therapy program.

The only report in the literature on long-term responses and overall survival in SCCO is associated with semi-intensive chemotherapy combining vinblastine, cisplatin, cyclophosphamide, bleomycin, Adriamycin and etoposide (the VPCBAE regimen) [11, 12]. Six patients were reportedly treated with this combination: two had stage IA, one stage IIC, two stage IIIA and one stage IIIC. Four have relapsed and died between 11 and 18 months after the diagnosis, but two were alive at 29 months (stage I) and 66 months (stage IIIC), respectively. However, four to six patients relapsed even after a good initial response, when assessable. The other reports are essentially descriptive and few of them report on the results of more conventional chemotherapy regimens with platinum-based combinations. Most of the series report on different disease management programs [1, 5, 8, 13]. There is no report on long-term survival with these therapies. There are no published data on the impact of surgery in SCCO. Most of data on epithelial ovarian tumors suggest a statistically significant positive correlation between the percentage of maximum cytoreduction and log median survival [14]. One argument in favor of maximum cytoreduction is that this would facilitate the effects of post-operative chemotherapy. We therefore had strong grounds to consider that aggressive surgical cytoreduction of these particularly aggressive tumors might contribute to enhanced survival. That is why maximum debulking surgery was recommended.

We therefore focused on increasing the dose intensity of consolidation therapy by using high doses of active drugs with stem-cell support whenever possible. First, we must emphasize that this strategy is feasible with manageable toxicity, as long as therapy is adequately monitored by well-trained oncologists. Secondly, results in terms of overall survival are impressive for this particular tumor and even for advanced disease (at least 21 patients had a stage above I). Only 10 patients have completed the planned program but seven are still in CR1 after HDCT versus 3 of 6 patients in CR after the initial procedure who cannot receive HDCT for technical reasons (the two cases with progressive disease have been excluded). Recently, Leyraz et al. [15] reported on the lack of efficacy of very high-dose induction chemotherapy in SCLC but there are no published data on the effect of high-dose CT. The results of a national study in SCLC (the CLEOPATRE study) are awaited.

Currently, there are two ways to improve the survival of this population. The first is to try to reduce the number of relapses after a CR. The four pelvic relapses after CR (with two deaths among four relapsing patients) in this series argue in favor of pelvic radiotherapy in patients in CR after high-dose chemotherapy or after first-line chemotherapy and surgery if high-dose chemotherapy proved unfeasible due to failure of stem-cell collection. Because of these pelvic relapses and the two cases of bilateral disease in 27 patients, we do not recommend conservative surgery as suggested by a few authors based on case reports with a short follow-up (2 and 2.5 years) [16, 17].

The second way is to improve response to initial chemotherapy. Arriagada et al. [10, 18] showed that treating SCLC with higher doses of cyclophosphamide and cisplatin in the first course prolonged overall survival, which has persisted with a median follow-up of 11 years. We also propose to increase doses of cisplatin by 20% during the first cycle (100 mg/m²).

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references