Survival and reproductive function of 52 women treated with surgery and bleomycin, etoposide, cisplatin (BEP) chemotherapy for ovarian yolk sac tumor

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Background: Ovarian yolk sac tumor (YST) is a very rare malignancy arising in young women. Chemotherapy has dramatically improved the prognosis. Current treatment consists of surgery followed by bleomycin, etoposide, and cisplatin (BEP) chemotherapy. However, given the rarity of this tumor, ovarian YST-specific survival and outcome after such treatment are not precisely known.

Patients and methods: This report concerns prospectively recorded cases that were either treated at Institut Gustave Roussy (Villejuif, France) or referred there for advice about therapy. From 1990 to 2006, 52 patients underwent surgery followed by BEP chemotherapy. Data on patient characteristics, treatment, survival, and fertility outcome were analyzed to assess treatment efficacy and gonadal toxicity after achieving a complete remission.

Results: Thirty-five patients had stage I/II tumors while 17 patients presented with stage III/IV disease. With a median follow-up of 68 months, the overall 5-year survival and disease-free survival rates were 94% and 90%, respectively. Forty-one women underwent fertility-sparing surgery. Pregnancy was achieved in 12 of 16 (75%) women who attempted conception. Overall, 19 pregnancies have been recorded.

Conclusions: BEP chemotherapy following fertility-sparing surgery is a very effective treatment of ovarian YSTs. Most of the patients who attempt conception after complete remission will have children.

Key words: alpha-fetoprotein, BEP, endodermal sinus tumor, fertility, malignant ovarian germ-cell tumor

Introduction

Ovarian yolk sac tumors (YSTs) account for 20% of malignant ovarian germ-cell tumors (MOGCTs), and are the second most frequent histological subtype, after ovarian dysgerminoma. YSTs occur mostly in adolescent and young women and are rare (incidence rate of 0.048/100 000 women-years in the United States) [1].

YST was first described in 1939 by Schiller, who proposed a mesonephroid origin. About 20 years later, Teilum reclassified the embryological origin and designated them endodermal sinus tumors [2]. Later on, these tumors were named YSTs because of the similarity with the extraembryonal yolk sac and vitelline structures. Serum alpha-fetoprotein (AFP) is a useful marker for the diagnosis and management of YSTs, because it is elevated in all patients with tumors containing an YST component [3].

Most authors agree that YSTs carry the worse prognosis among the group of MOGCTs. Before the era of modern chemotherapy, the actuarial survival rate at 3 years was 13% [4]. The rare series published on YSTs usually include pure YSTs as well as mixed MOGCTs with YST components, mainly because the prognosis is thought to result from the YST component [5]. Cisplatin-based multiagent chemotherapy has dramatically improved the prognosis of MOGCTs. More recently, the bleomycin, etoposide, cisplatin (BEP) combination appeared to be the most active combination regimen, as reported in testicular tumors. Currently, the standard chemotherapy regimen comprises three to four courses of BEP [6]. This approach, however, was developed on the basis of the results following treatment of MOGCT [7, 8]. No series has been published on specific outcomes of ovarian YSTs treated with BEP chemotherapy. Here, we report our experience in 52 patients with ovarian YST.

Patients and Methods

Patient Population

This retrospective study is on the basis of prospectively recorded ovarian YST cases at the Institut Gustave Roussy (Villejuif, France). From 1990 to 2006, a total of 52 female adolescent and adult patients with pure or mixed
YST were either treated at the Institut Gustave Roussey or referred there for advice about therapy after surgery and received BEP chemotherapy. Pediatric cases were excluded because some studies have reported that the physiology of YSTs occurring in children and young women could be different [9]. Information concerning all patients was abstracted from the medical records in accordance with local regulations and with the approval of the local Institutional Review Boards. Information on the tumor status, last physician visit, menstrual history, hormone therapy, and reproductive history was requested from the corresponding physicians in a questionnaire, for patients who were not followed up at the Institut Gustave Roussey. Fertility rates, pregnancy outcomes, and ovarian function results were analyzed.

**tumor classification**
Tumors were staged and classified according to clinical and pathological information. The histological type was defined according to the World Health Organization classification [10]. Tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian cancers [11]. Most of the stage I lesions, however, had not been properly assessed according to FIGO recommendations in patients referred after surgery, especially peritoneal cytology. Stage Ia was therefore defined as a tumor strictly limited to one ovary with an intact capsule and without ascites and stage Ic tumors were strictly limited to one ovary but exhibited capsular rupture or ascites >100 ml.

**response criteria**
The definition of response was that used in the case of testicular tumors [12]. Patients were classified as having achieved either a complete response (CR) or an incomplete response (IR). A CR to chemotherapy was defined as the disappearance of all clinical, radiographic, and biochemical evidence of disease or when all resected masses contained necrotic debris, fibrosis, or mature teratoma. A CR to chemotherapy plus surgery was defined when serum tumor markers had normalized and all residual disease had been removed, but viable MOGCT was found at any resected sites. Any degree of response that was lower than a CR was considered as an IR.

**treatment and follow-up**
In the case of early-stage disease, surgical guidelines in our institution recommended salpingo oophorectomy with peritoneal staging procedures (routine peritoneal cytology, multiple peritoneal biopsies, and omentectomy). In the case of advanced disease, unilateral salpingo-oophorectomy, omentectomy, and resection of macroscopic lesions on the peritoneum with a fertility-sparing intent was attempted whenever possible. Residual disease was documented carefully in terms of size and extent during initial surgery. Most of the patients who were referred after surgery were treated using a single ovarian procedure without staging surgery. In such cases, surgical restaging was considered after initial chemotherapy. The presence and size of residual disease were determined on the basis of the analysis of surgical reports and postoperative imaging studies.

All patients received BEP chemotherapy. Two different regimens were used.

- **A** Bleomycin (10–15 mg, days 1–3), etoposide (100 mg/m², days 1–3), and cisplatin (100 mg/m², day 1) every 4 weeks, for a planned total of three to six cycles [7].
- **B** Bleomycin (30 mg, days 1, 8, and 15), etoposide (100 mg/m², days 1–5), and cisplatin (20 mg/m², days 1–5) every 3 weeks for a planned total of three to four cycles [8].

From 1990 to 1995, the choice between regimens (A) and (B) was at the discretion of the attending physician. Regimen (B) was used from 1996 onwards.

Routine primary prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not advised. Pulmonary and renal functions were closely monitored in all patients. Bleomycin was stopped when there was a drop in the diffusing capacity of the lungs for carbon monoxide (DLCO).

Secondary surgery after completing chemotherapy was not routinely recommended. Patient follow-up included a clinical examination, blood marker measurements, and imaging at least every 3 months during the first year following chemotherapy and at gradually increasing intervals thereafter. A 2-year interval from the end of chemotherapy was strongly advised before allowing pregnancy.

**statistical analysis**
Overall survival (OS) was the primary end point for this retrospective analysis, and it was defined as the time from the date of the diagnosis to the date of death or date of the last news. Outcome analyses were carried out for event-free survival (EFS). Time to an event was defined as the time from the diagnosis until the first occurrence of disease progression, IR, relapse, second malignancy, or death or until the last reported contact if no event occurred meanwhile. The diagnosis of mature teratoma during secondary surgery was not considered an event. OS and EFS were estimated using the Kaplan–Meier method [13].

**results**

**patient characteristics**
Patient characteristics are summarized in Table 1. The median follow-up for the 52 women was 68 months (5–156). Table 2 lists pathological findings.

Thirty-four patients received BEP in an adjuvant setting and 13 for an incomplete resection or advanced disease. Five women who were surgically staged Ia during initial surgery did not receive adjuvant chemotherapy. All of them relapsed and were treated with the BEP regimen as first-line chemotherapy.

**treatment and toxicity**
Table 3 details initial treatments. All but one patient underwent surgery at diagnosis. Due to unresectable disease which extended to the peritoneal cavity, only one patient had percutaneous biopsies initially. However, after four cycles of BEP, she underwent unilateral salpingo oophorectomy.

Radical (from 1990 to 2000) and fertility-sparing (from 1991 to 2006) surgeries were carried out in 11 of 52 (21%) and 41 of 52 (79%) women, respectively. Overall, 17 of 52 (32%) patients underwent a repeated surgical procedure after chemotherapy for the following reasons:

- A systematic procedure (5 of 17 patients).
- Inadequate initial surgery (3 of 17 patients).
- The presence of residual masses on imaging carried out at the end of chemotherapy (9 of 17 patients). All of them had a normal serum AFP level.

An assessment of toxicity of the BEP regimens (grade 3/4) was available in 37 of 52 (71%) patients. Myelosuppression was measured.
the most frequent toxicity, with 29 of 52 (54%) patients experiencing grade 3/4 hematological toxicity. Neutropenic fever occurred in 7 of 52 (13%) patients. Red blood cell and platelet transfusions were necessary in five and three patients, respectively. One patient died of infectious peritonitis during neutropenia, 13 days after the first cycle of BEP. She had presented with stage IIIc disease and had undergone extensive surgery (bilateral salpingo oophorectomy, total abdominal hysterectomy, partial colectomy, and pelvic node dissection), 12 days before the beginning of chemotherapy.

Non-hematological toxicity was moderate. Seven patients experienced lung toxicity. In this context, the DLCO decreased in 6 of 52 patients (17%) but they recovered a normal lung capacity after treatment completion. One woman was diagnosed as having bronchiolitis obliterans organizing pneumonia (BOOP) without any change in pulmonary function. No significant otoxicity, neurotoxicity, or nephrotoxicity were recorded.

Five-year estimated OS and EFS rates were 94% and 90%, respectively (Figure 1A). OS was better for stages I–II compared with stages III–IV (Figure 1B) disease.

A single patient, staged Ia after surgery, did not receive adjuvant chemotherapy. Six months later, a peritoneal recurrence was treated with BEP chemotherapy but bleomycin was not administered on the 15th day (hematological toxicity). An IR was achieved (absence of serum AFP normalization). Eventually, a CR was obtained with salvage chemotherapy combining cisplatin, vinorelbine, paclitaxel, and gemcitabine. Twelve months after the end of chemotherapy, she remained disease free.

Overall, 3 of 52 patients relapsed after BEP chemotherapy. All the relapses occurred in patients treated with regimen (B). One patient with stage IV pleural disease experienced a drop in the DLCO after the first BEP cycle. Bleomycin was therefore
discontinued. Then, only cisplatin and etoposide (EP) were administered and progression of peritoneal disease occurred after the fourth chemotherapy cycle. She died in spite of salvage chemotherapy with cisplatin, ifosfamide, and vinblastine.

Two patients relapsed following BEP therapy at 2 and 7 months after achieving a CR. The first patient was 5 months pregnant at diagnosis of the recurrence. She underwent unilateral salpingo oophorectomy for a stage Ic lesion. Due to abnormally elevated AFP, she received a first cycle of chemotherapy combining cisplatin, bleomycin, and vinblastine, 2 weeks before delivery. Forty days later, she was treated with BEP, but she experienced massive pulmonary embolism. Bleomycin was discontinued due to respiratory failure, and subsequent therapy consisted of three EP cycles, which failed to prevent the patient’s death as a result of peritoneal tumor progression, 5 months after the initial relapse. The second patient initially presented with a stage IIIC tumor was treated with conservative surgery, followed by four BEP cycles. After relapse, an IR (persistently elevated serum AFP) was obtained with two consecutive lines of chemotherapy (cisplatin, ifosfamide, vinblastine, followed by adriamycin, paclitaxel) consolidated with high-dose chemotherapy (ifosfamide, carboplatin, etoposide) plus autologous stem-cell transplantation (HDC–ASCT). Then, positron emission tomography revealed limited peritoneal uptake. Eventually, she achieved a CR after surgical resection of an 8-mm tumor nodule and she is currently alive and free of recurrence (8 years after the end of treatment).

No relapses occurred >12 months following the end of treatment.

fertility outcome and long-term chemotherapy-related toxicity

All patients had regular menstrual cycles before the diagnosis of the ovarian YST. Table 4 shows fertility outcome. Surgery-related menopause was an obvious consequence of radical surgery in 11 of 52 (21%) patients. Regular menstruations after achieving a complete remission was observed in 39 of 40 (97%) patients treated with conservative surgery. Intermittent biological ovarian endocrine dysfunction was diagnosed in one patient. She was the one treated for a relapse with two consecutive lines of chemotherapy followed by HDC–ASCT and surgery.

The duration of postchemotherapy amenorrhea was analyzed exclusively in patients (n = 26) in complete remission who had undergone conservative surgery but were not treated with estroprogestative drugs during and after chemotherapy. Data were available for 15 of 26 patients. The median time to full recovery of regular menses was 5 (1–8) months after BEP chemotherapy.

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<th>Table 4. Reproductive outcome after complete remission (n = 49)</th>
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<td>Primary infertility before yolk sac tumor</td>
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<td>Potentially fertile</td>
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<td>Not attempting conception</td>
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<td>Age &gt; 35 years</td>
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<td>Previous children</td>
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<td>Tubal sterilization</td>
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<td>Multiple uterine myomas</td>
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<td>Partner’s azoospermia</td>
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<td>Patients achieving pregnancy</td>
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*n = 1 with additional endocrine dysfunction.
Fertility outcome was investigated in the 40 potentially fertile patients. During the follow-up period, 19 pregnancies were recorded in 12 of 16 (75%) women who attempted conception. Eventually, 15 children free of any malformations or developmental problems were born to 11 patients.

At present, the follow-up period is insufficient to ascertain whether patients treated for ovarian YSTs will experience a premature menopause as compared with healthy women. No recurrence has developed in patients who became pregnant.

Despite the extended follow-up, only minimal long-term chemotherapy-related toxicity was observed. Persistent lung toxicity (BOOP) and hypertension which occurred 10 years from the end of treatment were diagnosed in one and two patients, respectively.

discussion

Given the very low number of patients, current treatment is an adaptation of that used for ovarian and testicular malignant germ-cell tumors [7, 8, 14]. Here, we report a study on survival and outcome in 52 patients with ovarian YSTs who underwent surgery plus BEP chemotherapy. To our knowledge, this is the first study that specifically addresses these questions in the context of ovarian YSTs. Patient characteristics in our series are closely comparable to those previously published [4, 15–17]. Five-year OS and event-free survival were, respectively, 94% and 90%. These results are much better compared with previous reports with surgery plus cisplatin-based regimens [16, 17]. Moreover, we show that a high cure rate is achievable even in patients presenting with advanced disease, even though the prognosis is worse than for early-stage tumors. Compared with other regimens, BEP appears to be the best active first-line option for primary, metastatic, or recurrent disease. Although all the relapses occurred in patients treated with regimen (B), it is not possible to draw any conclusion about a potential difference between these two regimens because of the very low number (5 of 52) of patients treated with regimen (A). As is the case in nonseminomatous testicular tumors, bleomycin seems to be mandatory for the treatment of ovarian YSTs. Indeed, relapses have been observed in 2 of 3 (67%) patients in whom bleomycin was discontinued after the first cycle. On the whole, these results are comparable to those obtained for nonseminomatous testicular cancer [18, 19].

Chemotherapy-related toxicity was in keeping with our expectations. Nevertheless, one patient died of neutropenia-related peritoneal infectious disease. A retrospective analysis showed that she had an abdominal abscess before beginning chemotherapy. If this case is excluded, acute toxicity was acceptable and severe toxicity was infrequent, although grade 3/4 myelosuppression was observed in the majority of patients. Currently, the administration of G-CSF would help us manage such toxicity. We did not observe any severe pulmonary toxicity, ototoxicity, or nephrotoxicity, which is consistent with the results of Williams and Gershenson BEP trials for MOGCTs [7, 8]. Long-term toxicity was limited and mainly consisted in hypertension, as already described in testicular cancer survivors [20].

As most of the patients are young and nulligravida, fertility preservation is advocated as a secondary objective in women treated for MOGCTs. In this regard, conservative surgery followed by chemotherapy compared with radical surgery has been reported to be equally effective for patients with stage I tumors [4]. However, in the context of advanced disease or a histological variant other than immature teratoma, extensive surgery could have continued to be the most valuable therapeutic option. The advent of very effective chemotherapy (notably BEP regimen) for MOGCTs once again raised the question of whether fertility-sparing surgery should be carried out in every patient. Several authors have shown that conservative surgery could be safely carried out in advanced stages if effective chemotherapy is administered [21–25].

Gershenson was the first to show that the majority of women cured with these treatments recovered normal menstruations and that patients attempting conceptions frequently succeeded [26]. Furthermore, pregnancies are possible after fertility-sparing surgery followed by chemotherapy even in patients presenting with advanced disease [23, 25, 27]. The question, however, has not been solved in the specific context of ovarian YSTs. In line with the paradigm shift in the surgical treatment of MOGCTs, none of the women in our series have undergone radical surgery since the year 2000. Here, we report that even for the patients with the poorest prognosis, a high curability rate can be achieved with BEP chemotherapy following conservative surgery. In agreement with the results of previous studies, most of the women recovered normal menses after chemotherapy. The median duration of amenorrhea after chemotherapy (5 months) was similar to that previously reported [25, 27, 28]. Out of 16 women having attempted conception, 11 became mothers. Pregnancies were observed in patients with both limited and advanced stages. We did not observe any fetal malformation which was not the case in the Zanetta study [24], but this discrepancy may be explained by the reduced number of pregnancies recorded in our study.

The trend towards lower iatrogenic toxicity raises the issue of close surveillance instead of adjuvant chemotherapy for stage Ia ovarian YSTs after surgery. This approach may be of interest in MOGCTs, although further studies are warranted [6]. In the specific context of ovarian YSTs, the largest published series (71 women) showed that relapses occurred in the great majority (22 of 27) of resected stage I tumors when chemotherapy was not administered [4]. In a recent study, relapses occurred in 2 of 6 patients after conservative surgery and close surveillance of stage Ia ovarian YSTs [29]. However, in another study, all three patients with a mixed stage Ia YST did not relapse after surgery alone [22]. In our series, five patients treated for a stage Ia YST relapsed after surgery alone. Although they all achieved a persistent CR after chemotherapy, watchful waiting after surgery for stage Ia disease should be carefully evaluated before it is adopted in routine clinical practice.

Progressive or recurrent ovarian YST after treatment with BEP chemotherapy is associated with a poor prognosis. As there are no existing guidelines in this setting, we can again adapt chemotherapy regimens according to those administered to patients with relapsed testicular cancer. Several treatment options including combination of vinblastine, ifosfamide, cisplatinum, or paclitaxel, ifosfamide, cisplatinum, or...
HDC–ASCT could be used to treat recurrent ovarian YST [12, 28, 30]. Antiangiogenic therapy may be of great interest, as YSTs are highly vascularized tumors [31]. It should also be emphasized that secondary cytoreductive surgery could play a crucial role when tumors are limited and resistant to chemotherapy. Indeed, one patient achieved a persistent CR after several chemotherapy regimens followed by surgical resection.

In summary, we recommend fertility-sparing surgery for all patients with ovarian YSTs whatever the stage of the disease is. Initial evaluation of female adolescents and young women with a suspected ovarian tumor should include CA125 as well as germ-cell tumor markers [AFP, beta-human chorionic gonadotropin (hCG), and hCG]. This attitude will help to distinguish epithelial and nonepithelial tumors before surgery which will be optimized accordingly. The aim of the surgery is to remove the primary ovarian tumor without excessive morbidity. Watchful waiting after surgery for stage la YST requires further investigation. Thus, three to four cycles of BEP chemotherapy should be administered while carefully monitoring the rate of decline of serum AFP. In the event of positive serum AFP after four cycles of BEP, one should assume that the response is incomplete and salvage chemotherapy should therefore be initiated. Bleomycin is mandatory despite the occurrence of hematological toxicity. Secondary surgery is not routinely proposed, unless residual masses are diagnosed after the end of chemotherapy in the presence of a normal serum AFP level. This attitude is highly recommended in mixed tumors in order to prevent growing teratoma syndrome [32]. During the follow-up, determination of initially elevated markers should be repeated before each cycle of chemotherapy, 1 month after the end of the treatment and then every 3 months during the first 2 years after the end of the treatment. We recommend imaging every 3 months for follow-up during the first year. Apart from identifying relapses, this attitude could help to detect early growing teratoma syndrome, as well as functional ovarian cysts. With the aim of reducing irradiation exposure and obtaining accurate ovarian imaging, ultrasound and computed tomography scan may be used alternatively.

Following these strategies, most patients will be cured and the vast majority will still be able to give birth.

**contributions of authors**

T de La MR, AR, and CL were involved in the conception and design of the study. T de La MR and CL wrote the manuscript.

PP, PD, PM, CH-M, PK, SC, FT, and CL provided study material. T de La MR and CL collected the data. T de La MR, AR, and CL analyzed and interpreted the data. All authors validated the report.

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