Systemic management of malignant ovarian germ cell tumors in older women: two case reports and a review of the literature

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Abstract

Background Ovarian germ cell tumors (OGCT) account for 2-5% of ovarian malignancies, with an annual incidence of 0.5-1:100,000, typically occurring in young women. Yolk sac tumor (YST) is the second most common type of OGCT and has an aggressive phenotype. The rarity of this pathology in postmenopausal women poses challenges in the diagnosis and treatment.

Patients and Methods We report two clinical cases of YST in postmenopausal women treated at the Royal Marsden and discuss diagnosis and treatment issues of OGCTs in older women. A literature review was also performed, which identified thirty-nine cases, including the two reported in this article.

Results and Conclusion This showed that YSTs in older women are rare and are generally aggressive with poor clinical outcomes. Twelve of the described patients with malignant OGCTs died within 8 months of diagnosis. In conclusion, YST in postmenopausal women can have an aggressive disease course compared with younger patients. More evidence for the tolerability and outcomes of cytoreductive surgical approaches and intensive chemotherapy regimens in older patients is required.

Key words: chemotherapy, ovarian germ cell tumors, postmenopausal, yolk sac tumors

Introduction

Ovarian germ cell tumors (OGCTs) are rare, comprising 2% to 5% of all ovarian malignancies [1]. OGCTs usually occur in young women, with a peak incidence at age 20 years and rare reports when age is over 40 years [2]. In the first 2 decades of life, 60-70% of ovarian tumors are of germ cell origin, 30-65% of which are malignant [3, 4]. A SEER database analysis identified 2514 women with malignant OGCTs between 1978 and 2010. Median age at diagnosis was 22 years (range 0–93 years), with 91% of the patients being under 40 years of age [5]. The annual incidence of OGCTs at all ages is about 0.5-1 in 100,000. Predisposing risk factors are currently poorly understood [5-7].

OGCTs are classified as dysgerminomatous or non-dysgerminomatous. During embryogenesis, germ cells develop in the wall of the yolk sac and migrate to the genital ridge, where they are included in the developing gonad. Differentiation into somatic tissues, germinal epithelium and yolk sac can result in the development of teratoma, dysgerminoma and yolk sac tumor (YST)/endodermal sinus tumor, respectively.

The most common type of malignant OGCT is dysgerminoma (30-50%), which is often considered the female equivalent of testicular seminoma. In the group of non-dysgerminomatous tumors, the most common entities are YSTs, immature teratomas with malignant degeneration and mixed germ-cell tumors [8, 9].

YSTs originating from germ cells is unlikely in postmenopausal women. Four theories describing the pathogenesis of postmenopausal YST have been described: the teratoma theory, retrodifferentiation, the collision theory and the (neo)metaplasia theory [10-12]. Neometaplasia, also called aberrant differentiation, refers to carcinomas having the capability for germ cell differentiation, and the germ cell component is thought to derive from somatic mesodermal cells rather than germ cells [10, 13, 14].

The majority of YSTs in postmenopausal patients are associated with epithelial ovarian carcinoma and appear to have a worse outcome than isolated epithelial ovarian carcinoma. These mixed tumors represent an aggressive variant characterized by rapid growth, advanced stage at diagnosis and relative resistance to chemotherapy. The YST component of mixed tumors is often present in recurrent tumors after

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chemotherapy which suggests that the chemoresistance of this component may play an important role in determining outcome [15, 16].

In this article, we describe two cases of YST in postmenopausal women. These cases have recently been reported by our group with an emphasis on the pathological aspects [17]. In addition, a literature search on PubMed was performed to facilitate a review of the current evidence base for the treatment of these rare tumors in older patients. The search included relevant articles published from January 1976 until November 2015 and was based on combinations of the following free-text key words: yolk sack tumors, ovarian germ cell tumors, postmenopause, alpha-fetoprotein (αFP).

Case Reports

Case 1

A 67-year-old woman presented with a history of abdominal discomfort and a palpable abdominal mass. Magnetic resonance imaging (MRI) showed a pelvic mass inseparable from the left ovary, peritoneal deposits and free fluid in the pelvis. Preoperatively, cancer antigen 125 (CA125) was elevated at 700 U/mL. Alpha-fetoprotein (αFP) levels were not taken at diagnosis because this was not a standard test for women aged >40 years. The patient underwent primary cytoreductive surgery with total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), pelvic lymphadenectomy, appendectomy, and partial omentectomy and peritonectomy and was left with no macroscopic residual disease. Surgical findings included a mass arising from the left ovary with involvement of the rectum and pelvic peritoneum. FIGO stage was IIIc.

Initial pathological examination reported a high-grade clear cell carcinoma affecting the left ovary. On further review at our institution, the histology was in fact considered to be indicative of a YST, with most of the right ovary showing glandular morphology with tubular type glands dispersed in a fibrotic stroma.

Follow-up CT performed one month after the surgery revealed large-volume peritoneal disease, mainly in the lesser omentum, plus serosal liver and splenic involvement, as well as moderate left hydronephrosis secondary to the peritoneal disease. After an uneventful postoperative recovery, the patient received one cycle of adjuvant carboplatin and paclitaxel. MRI scan showed a good response. In light of the revised diagnosis, the patient was switched to the 5-day BEP regimen (cisplatin 20 mg/m^2 intravenously [IV] on days 1–5; etoposide 100 mg/m^2 IV on days 1–5; bleomycin 30,000 IU on days 1, 8 and 15 of a 21-day cycle). Postoperative αFP was 31,014 kU/L and β-human chorionic gonadotrophin (βhCG) was 43 mIU/L.

Despite the good clinical response and dramatic reductions in αFP (15 kU/L) and βhCG (<2 mIU/L) levels after 6 cycles of BEP, levels of αFP began to rise within one month of the end of treatment. CT scan results showed stability of disease. The patient subsequently underwent positron emission tomography (PET) scanning, which documented disease adjacent to the splenic hilum plus several areas of peritoneal disease within the pelvis, measuring 2-3 cm. It was considered that curative second debulking surgery at this stage was unlikely to be successful in view of the rapidity of relapse and platinum-refractory disease. Additional chemotherapy was proposed, with the possibility of reconsidering surgery depending on the patient's response. Weekly paclitaxel and gemcitabine were commenced. After three cycles of chemotherapy, CT scanning showed further disease progression with enlargement of the pre-existing peritoneal lesions and likely new peritoneal and liver serosal disease; the αFP level had increased significantly (from 619 to 6,241 kU/L). Due to the lack of response to treatment and the development of significant peripheral neuropathy, paclitaxel was switched to carboplatin but the patient deteriorated clinically after an additional three cycles. Imaging confirmed small bowel and distal sigmoid obstruction due to the large volume of peritoneal disease. This was not amenable to surgery and the patient passed away 11 days later, within 12 months of the initial diagnosis.

Case 2

A 59-year-old woman was referred to the gynecology clinic with a history of abdominal distension, pain, weight loss and anorexia. Her medical history included heart failure, arterial hypertension and chronic obstructive pulmonary disease (COPD). MRI of the abdomen and pelvis showed a large heterogeneous 20 × 27 × 15 cm mass arising from the pelvis as well as peritoneal nodularity. The CA125 at diagnosis was 266 U/mL. The patient underwent TAH, BSO, omentectomy and appendectomy. Intraoperative findings included ascites with a 40 cm right ovarian cyst that was adherent to small bowel loops and the rectosigmoid area. Postoperative recovery was complicated by septic shock with multiorgan dysfunction and she required a further exploratory laparotomy, haemofiltration and ventilatory support in intensive care. Biopsy showed the presence of a YST with a glandular configuration and areas of neuroendocrine tumor with a range of differentiations.

Postoperative staging was FIGO stage IIC mixed yolk sac and neuroendocrine tumor of the right ovary with a postoperative αFP of 57 kU/L and a postoperative CT showed no residual disease. Over subsequent months, the patient had multiple episodes of sepsis requiring prolonged admission in intensive care. Given the significant morbidity after

surgery, adjuvant chemotherapy was not administered. The αFP level had normalized by one month post-operatively (6 kU/L). One year later, the patient presented with a chest infection and a significantly increased αFP level (<39,000 kU/L). A CT scan revealed peritoneal disease indicative of disease recurrence with a right hydronephrosis secondary to an occlusive mass lying in the right hemi-pelvis. The risk of bleomycin-associated pulmonary complications was considered high given the prior chest infection and limited respiratory reserve. Therefore, chemotherapy with carboplatin plus etoposide (EC; carboplatin AUC4 on day 1, etoposide 100 mg/m^2 IV for 3 days) was given. There was evidence of biochemical and radiological responses after three cycles. However, despite a continued fall in αFP, the end of treatment scan (after 6 chemotherapy cycles) showed early progression, with new solid peritoneal lesions and new distal compression of the right ureter. Further surgery was considered but the patient declined this due to the previous postoperative complications she had experienced. Her clinical condition gradually deteriorated and she passed away 16 months after first-line chemotherapy (21 months after the initial diagnosis).

Discussion

OGCTs in postmenopausal patients are extremely rare, with only 37 prior cases reported in the literature (Table 1). The age at initial presentation ranged from 48 to 86 years [2, 10-13, 16, 18-39], a malignant epithelial component was identified in 23 of the 37 cases [2, 10-12, 22-24, 26, 28, 29, 33, 34, 36, 37, 39-41], OGCTs were associated with endometriosis in seven cases [10-12, 23, 29, 34, 41], and eleven cases involved pure YST histology [16, 18-21, 25, 30-34], with the oldest reported patient with pure YST being 86 years old [16].

Clinical information regarding the diagnosis, natural history, treatment and outcome of OGCTs is mainly based on retrospective case series. Prospective clinical trials in female OGCTs are limited, particularly those including postmenopausal women. The most common presenting symptoms are abdominal pain and a rapidly growing palpable pelvic-abdominal mass. Abdominal pain can present in an acute manner reflecting necrosis, rupture or torsion of the ovary. Dysgerminomas on the other hand constitute a group of slower growing tumors, which can present with non-specific abdominal symptoms. Less common signs include abdominal distension, fever, ascites and vaginal bleeding [1,3, 42, 43]. Staging is according to the FIGO system, as for epithelial ovarian cancers. Approximately 60-70% of cases are diagnosed as stage I or II, 20-30% as stage III and rarely stage IV [9]. Lymph node involvement (pelvic and retroperitoneal) can occur as it does in epithelial ovarian cancer, particularly in dysgerminomas. Bilateral ovarian disease is rare, with the exception of dysgerminomas where it can be found in 10-15% of cases [44].

Making a diagnosis can be challenging because αFP is not routinely tested in postmenopausal women. Tumor markers to be assessed should include αFP, lactate dehydrogenase (LDH), βhCG and CA125, and these are important in diagnosis, surveillance, monitoring response to treatment and potentially prognosis [45-48]. YSTs typically produce αFP, while βhCG production can be found in choriocarcinomas, embryonal carcinomas and polyembryomas; the latter two can also produce αFP. Mixed OGCTs can produce both markers or neither, reflecting the composition of the tumor. Dysgerminomas can produce high levels of LDH or low levels of βhCG, in relation with syncytiotrophoblastic cells. An increase of CA125 is not common.

Treatment

The principles of cytoreductive surgery as applied in epithelial ovarian cancer have been used in OGCTs, although the role of aggressive cytoreduction is not well defined in advanced disease. Two Gynecologic Oncology Group (GOG) studies (GOG-10 and GOG-45) found differences in response to chemotherapy according to the residual disease status; postmenopausal women were underrepresented in both studies. In a study of adjuvant VAC (vincristine, dactinomycin, cyclophosphamide) in eleven patients with minimal residual disease after surgery (defined as ≤3 cm), six (55%) experienced recurrence over a median follow-up period of 24 months. In contrast, 9 of 11 (82%) with residual nodules exceeding 3 cm in diameter recurred over the same time period [49]. In another study, patients with clinically non-measurable disease had a higher likelihood of remaining progression free at 2 years (65% *vs*. 34%) [50]. Second-look surgery may be considered to assess residual disease, although the role of aggressive surgery in this context remains unclear; no benefit was found in patients without a teratoma component, <5 cm of radiological residual disease after chemotherapy and normalization of tumor markers [51, 52].

Chemotherapy

Prior to the introduction of platinum-based combination chemotherapy, the prognosis of OGCT was poor [3]. BEP is now the current standard regimen for both adjuvant and first-line treatment in advanced disease. This option superseded regimens such as VAC and PVB (cisplatin, vinblastine, bleomycin) because it was found to be equally effective with an improved toxicity profile [53-57]. For young women with malignant OGCTs treated after the introduction of cisplatin-based chemotherapy, the 5-year survival

rate approaches 90% [5]. In general, post-operative chemotherapy is indicated in patients with dysgerminoma, with the exception of adequately staged IA patients. The relapse rate is between 10-25%. Importantly, almost all relapses can be cured with chemotherapy [58]. Post-operative chemotherapy is indicated in non-dysgerminomas, with the exception of stage I, grade 1 immature teratomas [3]. Treatment with the BEP or EC regimens is recommended in several clinical guidelines [59-62].

In the US National Comprehensive Cancer Network (NCCN) guidelines, adjuvant chemotherapy is recommended for any stage embryonal tumor or YST and stage I, grade 2/3 or stage II-IV dysgerminomas. This is recommended to be BEP for 3 cycles for good risk and 4 cycles for poor risk patients or EC for 3 cycles for stage IB-III dysgerminomas for whom minimizing toxicity is critical. In young patients with stage IA/IB dysgerminoma, stage IA/grade 1 immature teratoma, stage IA embryonal tumors or stage IA YSTs, observation or chemotherapy may be considered [62].

In the European Society of Medical Oncology (ESMO) guidelines, BEP is recommended for 3 cycles in completely resected disease and for 4-5 cycles (with bleomycin omitted to reduce lung toxicity) for patients with macroscopic residual disease. The recommended strategy for stage IA dysgerminomas and stage IA, grade 1 immature teratoma is observation. The need for adjuvant treatment in the setting of stage IA, grade 2-3 and stages IB-IC is controversial. ESMO guidelines also discuss the role of targeted agents, with tyrosine kinase inhibitors (e.g. imatinib and sunitinib) and anti-angiogenic agents (e.g. bevacizumab) stated to be of interest [61].

Use of adjuvant EC (etoposide, carboplatin) in dysgerminoma as a means to reduce toxicity (GOG-116) showed that the regimen was generally well tolerated [63]. Grade ≥3 thrombocytopenia and ≥3 neutropenia were reported, along with one case of grade 3 neutropenic fever. No other grade 3 or 4 toxicities occurred and there were no reported recurrences during a median follow-up of 7.8 years. The study was closed before completing target accrual after the results of two large randomized studies in metastatic testicular cancer concluding that the substitution of carboplatin for cisplatin resulted in inferior efficacy [64, 65]. However, the GOG-116 study authors concluded that EC can be regarded an alternative treatment option for selected patients in whom minimizing toxicity is deemed important.

In stage I malignant OGCT patients, a strategy of close clinical, radiological and serological surveillance after surgery can be considered, as suggested in the guidelines. However, it is important to recognize that the basis for this recommendation is largely from studies of younger patients [66-71].

In advanced disease, risk stratification using the testicular tumors' IGCCCG (International Germ Cell Cancer Collaboration Group) system might identify patients who could benefit from more intensive first-line chemotherapy. In a retrospective study including post-menopausal patients, the IGCCCG classification was significantly correlated with progression-free survival (PFS) and overall survival (OS) [72].

In recurrent disease, BEP should be considered in patients previously not treated with platinum-based chemotherapy. Salvage regimens described include TIP (cisplatin, ifosfamide, paclitaxel), VAC, PVB, VIP (vindesine, ifosfamide, cisplatin), VeIP (vinblastine, ifosfamide, cisplatin) and other platinum-based regimens more commonly used in epithelial ovarian cancer (e.g. carboplatin plus paclitaxel) [50]. High-dose chemotherapy in association with autologous stem cell transplantation may be an option in fit patients, although these regimens are associated with important acute and late toxicities [73]. Data on salvage surgery for chemotherapy-refractory disease are scarce and particularly so in older patients who may have less tolerance of high-intensity regimens. In a study of secondary surgical debulking in 20 patients with OGCTs treated between 1975 and 1992, a survival advantage could be found in patients with immature teratoma. It should be noted, however, that not all patients had been treated with cisplatin-based chemotherapy, given the timespan of this study [74]. Secondary cytoreductive therapy may be beneficial in selected patients, particularly those with immature teratoma and a growing teratoma syndrome [61].

Toxicity of chemotherapy and tolerability in older patients

Survival rates decrease by age across almost all solid-organ malignancies [75]. The reasons for this are multiple and likely to include late presentation, higher stage at diagnosis and potential undertreatment due to concern over the impact of medical comorbidities on patients' ability to tolerate systemic chemotherapy and aggressive surgical approaches [76]. There remains a paucity of data supporting the treatment of older, more comorbid patients with ovarian malignancies, due largely to the under-representation of older women in clinical trials [77]. Nevertheless, the evidence base is certainly improving with increasing effort being directed towards prediction of systemic therapy toxicity in epithelial ovarian cancer and other solid organ malignancies, as well as evolving regimens that may be better tolerated in an older, more comorbid population. The literature supporting the treatment of rare tumors such as GOCT in older women is particularly sparse and much of what is currently known is extrapolated from toxicity data derived from male GCT studies. Several studies have shown that platinum-based doublet chemotherapy can be well tolerated in a selected

Table 1. Demographics of 37 postmenopausal patients with ovarian germ cell tumors. Adapted from Boussios et al. [17]

Author (ref)	Cases	Age at diagnosis, ys	Stage	Histology	Surgery	Chemotherapy	Outcome
Arai et al. [2]	1	71	I	Mixed: MC cystadenocarcinoma-YST	TAH, BSO	EP	DOD at 6Mo
Kamoi et al. [10]	1	54	IC	Mixed: YST + EM	Tumor debulking	Ca (ip) followed by PeEP × 5	DF at 21Mo
Lopez et al. [11]	1	51	IC	Mixed: EM-YST, MC cystadenoma	TAH, BSO, omentectomy	BEP × 3	DOD at 10Mo
Rutgers et al. [12]	1	50	IA	Mixed: YST + EM	TAH, BSO, omentectomy, peritoneal washings	MOC × 5 preoperatively and VP × 1 postoperatively	DOD at 8Mo
Abe et al. [13]	1	52	IC	Mixed: YST + EM	TAH, BSO, omentectomy, pelvic and para-aortic lymphadenectomy	BEP × 3 followed by TCa × 3	DF at 20Mo
Brown et al. [18]	1	57	III	Pure: YST	TAH, BSO, omentectomy	None	DOD at 3Mo
Ferracini et al. [20]	1	63	N/A	Pure: YST	TAH, tumor debulking	None	DOD 2D postoperatively
Cisło et al. [19]	1	50	IC	Pure: YST	TAH, BSO	MOC	DOD at 22Mo
Mazur et al. [27]	1	82	IA	Mixed: MC cystadenofibroma-YST	TAH, BSO, omentectomy	None	DF at 24Mo
Kinoshita et al. [25]	1	62	IA	Pure: YST	TAH, BSO, omentectomy	VPeP × 5	N/A
Pliskow et al. [32]	1	54	N/A	Pure: YST	TAH, BSO, omentectomy	BEP × 3	DF at 24Mo
Kammerer-Doak et al. [24]	1	53	N/A	Mixed: YST + embryonal carcinoma	TAH, BSO, omentectomy, appendectomy, pelvic and para-aortic LN Bx	BEP × 3	DF at 60Mo
Takizawa et al. [36]	1	69	III	Mixed: YST + papillary serous carcinoma	BSO, partial omentectomy	P × 2 (ip) followed by CAP × 6. Second line CaE × 2 due to biochemical recurrence	DOD at 24Mo
Nogales et al. [29]	4	64 71 71 73	IA IA III III	Mixed: YST + EM Mixed: YST + EM + EAF Mixed: YST + EM Mixed: YST + carcinosarcoma	TAH, BSO TAH, BSO TAH, BSO LSO, omentectomy, appendectomy, and uterine Bx	MOC × 3 P-based × 6 P-based × 1 None	DOD at 14Mo DF at 12Mo DOD at 3Mo DOD at 5Mo
Horiuchi et al. [23]	1	53	IA	IA Mixed: YST + EM	TAH, BSO, omentectomy, pelvic LN Bx	VPeMC × 6	DOD at 6Mo
Oh et al. [30]	1	75	IIIC	Pure: YST	TAH, BSO, sigmoid colectomy, omentectomy, pelvic LN Bx	EP-based × 3	DOD at 4Mo
Filiz et al. [21]	1	76	II	Pure: YST	TAH, BSO, omentectomy, pelvic and para-aortic LN Bx	BEP × 4	DOD at 6Mo
García-Galvis et al. [22]	1	69	IV	Mixed: YST + carcinosarcoma	Tumor debulking and omentectomy	None	DOD 10D postoperatively

Author (ref)	Cases	Age at diagnosis, ys	Stage	Histology	Surgery	Chemotherapy	Outcome
Zaloudek C. [37]	1	59	III	Mixed: CCAC – YST	TAH, BSO, omentectomy and tumor debulking	N/A	N/A
Roth et al. [34]	4	67	IIIC	Mixed: YST + LGSC	Partial omentectomy and tumor debulking	P-based adjuvant	DOD 10D postoperatively
		48	IA	Mixed: EM + CCAC + YST	TAH, BSO	P-based adjuvant	DF at 24Mo
		49	IIIA	Mixed: CCAC + YST	TAH, BSO, omentectomy	P-based adjuvant	DOD at 15Mo
		60	IC	Pure: YST	TAH, BSO, omentectomy, appendectomy and LN Bx	TCa	DF at 14Mo
Hembah-Hilekaan et al. [38]	1	58	III	Pure: dysgerminoma	Infra-colic omentectomy with tumor debulking	BEP × 2	DOD at 1Mo
Giuliani et al. [39]	1	73	IA	Mixed: YST + EM	BSO and omentectomy	TCa × 6	DF at 22Mo
Lange et al. [16]	1	86	IIIC	Pure: YST	TAH, BSO, omentectomy, peritoneal stripping	BEP × 4	N/A
Meguro et al. [28]	1	58	I	Mixed: AFP producing a denocarcinoma with adenofibroma showing germ cell differentiation	TAH, BSO, omentectomy	TCa × 6	DF at 12Mo
Sukumaran et al. [35]	1	52	III	Mixed: YST-serous cystadenoma	Surgical resection of the tumor	N/A	N/A
Roma et al. [33]	2	61	N/A	Mixed: papillary serous with minor components of EM and YST	TAH, BSO and staging Bx	(ip) × 6	Rec at 7Mo
		70	N/A	Pure: YST	TAH, BSO and staging Bx	6 cycles	Rec at 7Mo
Koi et al. [26]	1	56	IIIC	Mixed: YST + EM	TAH, BSO, pelvic lymphadenectomy, appendectomy and partial omentectomy, and peritonectomy	BEP × 2. Second line chemotherapy TCa × 6	DF at 48Mo
Parker et al. [31]	1	60	III	Pure: YST resection of the terminal ileum	Tumor debulking hemi-colectomy, by POMeB–MCE and caecum, ileostomy	BEP × 2 followed postoperatively	Rec 17D
Chen et al. [40]	1	61	IC	Mixed: papillary serous with components of CCAC and YST	TAH, BSO, omentectomy, appendectomy, pelvic lymphadenectomy and para-aortic lymphadenectomy	TCa × 6	DF at 6Mo
Yu et al. [41]	1	55	N/A	Mixed: YST + embryonal carcinoma + mature teratoma + CCAC	THA, BSO, omentectomy, right infundibulopelvic ligament resection and bilateral paracolic sulci peritoneal Bx	BEP × 7	N/A

A: adriamycin; B: bleomycin; Bx: biopsy; BSO: bilateral salpingo-oophorectomy; C: cyclophosphamide; Ca: carboplatin; CCAC: clear cell adenocarcinoma; D: days; DF: disease-free; DOD: died of disease; E: etoposide; EAF: endometrioid adenofibroma; EM: endometrioid carcinoma; FU: follow-up; ip: intraperitoneal; LGSC: low-grade serous carcinoma; LN: lymph nodes; LSO: left salpingo-oophorectomy; M: dactinomycin; MC: mucinous; Me: methotrexate; Mo: months; N/A: not available; O: vincristine; P: cisplatin; Pe: pepleomycin; Rec: recurrence; T: taxane; TAH: total abdominal hysterectomy; V: vinblastine; ys: years; YST: yolk sac tumor.

older population. However, completion rates of the planned full course of chemotherapy remain lower in older patients [78-80]. Less is known about the tolerability of the relatively higher intensity BEP regimen in the older population. Common reported toxicities are alopecia, fatigue, nausea and myelosuppression. Cisplatin neurotoxicity may manifest as hearing impairment or peripheral neuropathy. Cisplatin-containing regimens also carry a risk of nephrotoxicity and cardiovascular risk, which may potentially be more significant in an older, less fit group [81]. Bleomycin-associated pulmonary fibrosis is an uncommon, but severe, side effect that warrants careful respiratory assessment before therapy. Risk factors for bleomycin toxicity include increasing age (particularly >40 years), high cumulative dose (>400 mg), renal impairment, smoking history, supplemental oxygen therapy and existing lung disease [82, 83].

Data regarding tolerability of the BEP regimen in older patients come mostly from studies in testicular cancer. A retrospective study of 4235 patients, 236 of them aged ≥50 years-old, was reported by Feldman et al. Regimens used included EP (etoposide, cisplatin) in 78% of patients, BEP in 14%, EC (etoposide, carboplatin) in 6% and VIP in 2%. In 60% of patients, complications led to treatment discontinuation, change in regimen or significant delay. In the case of BEP, 72% of patients changed to alternate regimens, predominantly due to worsening pulmonary function and thromboembolic complications; the rate of neutropenic fever per cycle was 24% in patients treated with this regimen [84]. In another study by Thomsen et al., 135 patients aged ≥40 years with disseminated germ-cell cancer treated with BEP were compared with a control group of younger patients. Accumulated doses were found to be similar. More patients in the older group had episodes of grade 4 leukopenia. No differences in renal dysfunction or pulmonary toxicity were found between the 2 groups. Overall survival was lower in the older group, and this inferior prognosis was suggested to be related to adverse tumor biology and increased comorbidity, although there were no more treatment-related deaths in older compared with younger patients [85]. Wheater et al. presented a retrospective review of the treatment of testicular germ-cell cancers in patients aged ≥60 years. Fifteen patients were reviewed; five were treated with BEP, five with EP, two with single-agent carboplatin, one with EC, one with cyclophosphamide and etoposide, and one with chlorambucil and doxorubicin. Grade 3 toxicities reported were anemia, thrombocytopenia, febrile neutropenia, sensory neuropathy, vomiting, deep vein thrombosis and gastrointestinal bleeding. There were no treatment-related deaths [86].

Prognosis

The prognosis of OGCT in postmenopausal women is poor, even for patients with early-stage disease. Potential reasons for this worse prognosis compared with younger patients include differences in tumor biology, which may be related to the pathogenetic mechanisms of germ-cell tumors in the elderly, and use of less aggressive treatment due to the presence of co-morbidities. In a retrospective study of 2541 patients with malignant OGCT, age >40 years at diagnosis and the presence of metastases were associated with specific mortality [5]. In other studies, however, age was not a significant prognostic factor [15, 48, 87]. Because of its rarity, prognostic factors for YST remain unclear. Specifically for this pathology, stage, chemotherapy with cisplatin combinations, residual disease, the presence of ascites, baseline αFP and αFP decline after surgery have been described as prognostic factors [15, 48, 88, 89].

In the previously-reported cases, 16/31 patients with available staging were diagnosed with stage I disease [2, 10-13, 19, 23, 25, 27-29, 34, 39, 40] but only six of these had a reported survival of more than 20 months [10, 13, 19, 27, 34, 39]. Seven of the 24 reported patients who presented with ovarian YST associated with epithelial ovarian tumors [2, 12, 22, 23, 29, 34] and 4/11 patients with YST without an identifiable epithelial component [18, 20, 21, 30] experienced an initial biochemical response to treatment but subsequently died of disease within 8 months of the initial diagnosis. Both of the patients described in the current paper died of their disease at 12 and 21 months after diagnosis, which is in accordance with other similar cases reported in the literature. At present, it is unclear why relapsed malignant OGCT seems to behave so differently from relapsed testicular germ cell tumor, and additional research is warranted.

In conclusion, YSTs are rare tumors and even more so in older patients. The standard of care involves aggressive surgical approaches and high-intensity chemotherapy regimens. Older patients with more co-morbidities may be at increased risk of toxicity from such an approach and careful evaluation and counseling is key. Further studies evaluating the use of alternative regimens, avoiding the need for bleomycin in patients with risk factors for pulmonary toxicity, are required.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

References

1. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynaecol 2012; 26:347-55.
2. Arai T, Kitayama Y, Koda K. Ovarian mucinous cystadenocarcinoma with yolk sac tumor in a 71-year-old woman. Int J Gynecol Pathol 1999;18:277-80.
3. Bailey J, Church D. Management of germ cell tumours of the ovary. Reviews in Gynaecological Practice 2005;5:201-6.
4. Quirk JT, Natarajan N, Mettlin CJ. Age-specific ovarian cancer incidence rate patterns in the United States. Gynecol Oncol 2005;99:248-50.
5. Solheim O, Gershenson DM, Trope CG, et al. Prognostic factors in malignant ovarian germ cell tumours (The Surveillance, Epidemiology and End Results experience 1978-2010). Eur J Cancer 2014;50:1942-50.
6. Giambartolomei C, Mueller CM, Greene MH, et al. A mini-review of familial ovarian germ cell tumors: an additional manifestation of the familial testicular germ cell tumor syndrome. Cancer Epidemiol 2009;33:31-6.
7. Albrektsen G, Heuch I, Kvale G. Full-term pregnancies and incidence of ovarian cancer of stromal and germ cell origin: a Norwegian prospective study. Br J Cancer 1997;75:767-70.
8. Gershenson DM, Del Junco G, Copeland LJ, et al. Mixed germ cell tumors of the ovary. Obstet Gynecol 1984; 64:200-6.
9. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev 2008;34:427-41.
10. Kamoi S, Ohaki Y, Mori O, et al. A case of ovarian endometrioid adenocarcinoma with yolk sac tumor component in a postmenopausal woman. APMIS 2002;110:508-14.
11. Lopez JM, Malpica A, Deavers MT, et al. Ovarian yolk sac tumor associated with endometrioid carcinoma and mucinous cystadenoma of the ovary. Ann Diagn Pathol 2003;7:300-5.
12. Rutgers JL, Young RH, Scully RE. Ovarian yolk sac tumor arising from an endometrioid carcinoma. Hum Pathol 1987;18:1296-9.
13. Abe A, Furumoto H, Yoshida K, et al. A case of ovarian endometrioid adenocarcinoma with a yolk sac tumor component. Int J Gynecol Cancer 2008;18:168-72.
14. Garcia RL, Ghali *Vs*. Gastric choriocarcinoma and yolk sac tumor in a man: observations about its possible origin. Hum Pathol 1985;16:955-8.
15. Nawa A, Obata N, Kikkawa F, et al. Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol 2001;184:1182-8.
16. Lange S, Livasy C, Tait DL. Endodermal sinus tumor of the ovary in an 86 year old woman. Gynecol Oncol Case Rep 2012;2:65-6.
17. Boussios S, Attygalle A, Hazell S, et al. Malignant ovarian germ cell tumors in postmenopausal patients: the Royal Marsden experience and literature review. Anticancer Res 2015;35:6713-22.
18. Brown JR, Green JD. Yolk sac carcinoma. South Med J 1976;69:728-31.
19. Cislo M, Wawrzkiewicz M, Rzucidlo Z, et al. [Endodermal sinus tumor--a contribution to the clinical aspects of ovarian tumors]. Zentralbl Allg Pathol 1984;129:17-9.
20. Ferracini R, Gardini G, Lanzanova G, et al. Endodermal sinus tumor in a 63 year old female. Pathologica 1979; 71:885-7.
21. Filiz G, Ozuysal S, Bilgin T. Ovarian endodermal sinus tumor in a 76-year-old woman. J Obstet Gynaecol Res 2003;29:309-11.
22. Garcia-Galvis OF, Cabrera-Ozoria C, Fernandez JA, et al. Malignant Mullerian mixed tumor of the ovary associated with yolk sac tumor, neuroepithelial and trophoblastic differentiation (teratoid carcinosarcoma). Int J Gynecol Pathol 2008;27:515-20.
23. Horiuchi A, Osada R, Nakayama K, et al. Ovarian yolk sac tumor with endometrioid carcinoma arising from endometriosis in a postmenopausal woman, with special reference to expression of alpha-fetoprotein, sex steroid receptors, and p53. Gynecol Oncol 1998;70:295-9.
24. Kammerer-Doak D, Baurick K, Black W, et al. Endodermal sinus tumor and embryonal carcinoma of the ovary in a 53-year-old woman. Gynecol Oncol 1996;63:133-7.
25. Kinoshita K. A 62-year-old woman with endodermal sinus tumor of the ovary. Am J Obstet Gynecol 1990;162:760-2.
26. Koi C, Kurita T, Kagami S, et al. A case of ovarian yolk sac tumor associated with endometrioid adenocarcinoma. Gynecol Oncol Case Rep 2014;9:11-4.
27. Mazur MT, Talbot WH, Jr., Talerman A. Endodermal sinus tumor and mucinous cystadenofibroma of the ovary. Occurrence in an 82-year-old woman. Cancer 1988;62:2011-5.
28. Meguro S, Yasuda M. alpha-Fetoprotein-producing ovarian tumor in a postmenopausal woman with germ cell differentiation. Ann Diagn Pathol 2013;17:140-4.
29. Nogales FF, Bergeron C, Carvia RE, et al. Ovarian endometrioid tumors with yolk sac tumor component, an unusual form of ovarian neoplasm. Analysis of six cases. Am J Surg Pathol 1996;20:1056-66.
30. Oh C, Kendler A, Hernandez E. Ovarian endodermal sinus tumor in a postmenopausal woman. Gynecol Oncol 2001;82:392-4.
31. Parker VL, Sanderson P, Naik V, et al. Post-menopausal presentation of yolk sac germ cell tumour. Gynecol Oncol Rep 2015;11:16-9.
32. Pliskow S. Endodermal sinus tumor of the ovary: review of 10 cases. South Med J 1993;86:187-9.
33. Roma AA, Przybycin CG. Yolk sac tumor in postmenopausal patients: pure or associated with adenocarcinoma, a rare phenomenon. Int J Gynecol Pathol 2014;33:477-82.
34. Roth LM, Talerman A, Levy T, et al. Ovarian yolk sac tumors in older women arising from epithelial ovarian tumors or with no detectable epithelial component. Int J Gynecol Pathol 2011;30:442-51.
35. Sukumaran R, Somanathan T, Mathews A, et al. Primary extragonadal pure yolk sac tumor in a post-menopausal female. South Asian J Cancer 2013;2:178.
36. Takizawa K, Kawana T, Kakinoki S, et al. Case report of a 69-year-old woman with double cancers: Primary yolk sac tumour of the right ovary and primary serous surface papillary carcinoma of the peritoneum. Int J Clin Oncol 1996;1:190-4.
37. Zaloudek C. Yolk Sac Tumour of the Ovary and Extragonadal Sites in Females: Lessons Learned From an Unusual

Case. In: Soslow R, Tornos C, editors. Diagnostic Pathology of Ovarian Tumours: Springer Science + Business Media, LLC; 2011. p. 155-91.
38. Hembah-Hilekaan S, Mbaave T. A rare case of dysgerminoma in a 58-year old postmenopausal woman in Makurdi, North Central Nigeria. Internet J Oncol 2012;8.
39. Giuliani J, Marzola M, Pizzutilo P, et al. Ovarian endometrioid adenocarcinoma with a yolk sac tumour component in a postmenopausal woman: case report and review of the literature. Clin Ovarian Gynecol Cancer 2012;5:31-2.
40. Chen Q, Chen X. Bilateral ovarian mixed epithelial adenocarcinoma in a postmenopausal woman with unilateral ovarian yolk sac tumor component. Int J Clin Exp Pathol 2014;7:8259-65.
41. Yu XJ, Zhang L, Liu ZP, et al. Ovarian malignant mixed germ cell tumor with clear cell carcinoma in a postmenopausal woman. Int J Clin Exp Pathol 2014;7:8996-9001.
42. Gershenson DM, Del Junco G, Herson J, et al. Endodermal sinus tumor of the ovary: the M. D. Anderson experience. Obstet Gynecol 1983;61:194-202.
43. Tewari K, Cappuccini F, Disaia PJ, et al. Malignant germ cell tumors of the ovary. Obstet Gynecol 2000;95:128-33.
44. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol 2007;25:2938-43.
45. Mitchell PL, Al-Nasiri N, A'Hern R, et al. Treatment of nondysgerminomatous ovarian germ cell tumors: an analysis of 69 cases. Cancer 1999;85:2232-44.
46. Kawai M, Kano T, Kikkawa F, et al. Seven tumor markers in benign and malignant germ cell tumors of the ovary. Gynecol Oncol 1992;45:248-53.
47. Ishiguro T, Yoshida Y, Tenzaki T, et al. AFP in yolk sac tumor and solid teratoma of the ovary: significance of postoperative serum AFP. Cancer 1981;48:2480-4.
48. Kawai M, Kano T, Furuhashi Y, et al. Prognostic factors in yolk sac tumors of the ovary. A clinicopathologic analysis of 29 cases. Cancer 1991;67:184-92.
49. Slayton RE, Park RC, Silverberg SG, et al. Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). Cancer 1985;56:243-8.
50. Williams SD, Blessing JA, Moore DH, et al. Cisplatin, vinblastine, and bleomycin in advanced and recurrent ovarian germ-cell tumors. A trial of the Gynecologic Oncology Group. Ann Intern Med 1989;111:22-7.
51. Culine S, Lhomme C, Michel G, et al. Is there a role for second-look laparotomy in the management of malignant germ cell tumors of the ovary? Experience at Institut Gustave Roussy. J Surg Oncol 1996;62:40-5.
52. Mathew GK, Singh SS, Swaminathan RG, et al. Laparotomy for post chemotherapy residue in ovarian germ cell tumors. J Postgrad Med 2006;52:262-5.
53. Gershenson DM, Copeland LJ, Kavanagh JJ, et al. Treatment of malignant nondysgerminomatous germ cell tumors of the ovary with vincristine, dactinomycin, and cyclophosphamide. Cancer 1985;56:2756-61.
54. Vriesendorp R, Aalders JG, Sleijfer DT, et al. Treatment of malignant germ cell tumors of the ovary with cisplatin, vinblastine, and bleomycin (PVB). Cancer Treat Rep 1984;68:779-81.
55. Dimopoulos MA, Papadimitriou C, Hamilos G, et al. Treatment of ovarian germ cell tumors with a 3-day bleomycin, etoposide, and cisplatin regimen: a prospective multicenter study. Gynecol Oncol 2004;95:695-700.
56. Gershenson DM, Morris M, Cangir A, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. J Clin Oncol 1990;8:715-20.
57. Williams S, Blessing JA, Liao SY, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. J Clin Oncol 1994;12:701-6.
58. Patterson DM, Murugaesu N, Holden L, et al. A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites. Int J Gynecol Cancer 2008;18:43-50.
59. Zanagnolo V, Sartori E, Galleri G, et al. Clinical review of 55 cases of malignant ovarian germ cell tumors. Eur J Gynaecol Oncol 2004;25:315-20.
60. Williams SD, Blessing JA, Hatch KD, et al. Chemotherapy of advanced dysgerminoma: trials of the Gynecologic Oncology Group. J Clin Oncol 1991;9:1950-5.
61. Colombo N, Peiretti M, Garbi A, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii20-6.
62. Network NCC. NCCN Clinical Guidelines in Oncology - Ovarian Cancer Version 2.2015. 2015; Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp - site
63. Williams SD, Kauderer J, Burnett AF, et al. Adjuvant therapy of completely resected dysgerminoma with carboplatin and etoposide: a trial of the Gynecologic Oncology Group. Gynecol Oncol 2004;95:496-9.
64. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 1997;15:1844-52.
65. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol 1993;11:598-606.
66. Gobel U, Schneider DT, Calaminus G, et al. Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. Ann Oncol 2000;11:263-71.
67. Baranzelli MC, Bouffet E, Quintana E, et al. Non-seminomatous ovarian germ cell tumours in children. Eur J Cancer 2000;36:376-83.
68. Marina NM, Cushing B, Giller R, et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: A Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 1999;17:2137-43.
69. Cushing B, Giller R, Ablin A, et al. Surgical resection alone is effective treatment for ovarian immature teratoma in children and adolescents: a report of the pediatric oncology group and the children's cancer group. Am J Obstet Gynecol 1999;181:353-8.
70. Dark GG, Bower M, Newlands ES, et al. Surveillance

policy for stage I ovarian germ cell tumors. J Clin Oncol 1997;15:620-4.
71. Bonazzi C, Peccatori F, Colombo N, et al. Pure ovarian immature teratoma, a unique and curable disease: 10 years' experience of 32 prospectively treated patients. Obstet Gynecol 1994;84:598-604.
72. Meisel JL, Woo KM, Sudarsan N, et al. Development of a risk stratification system to guide treatment for female germ cell tumors. Gynecol Oncol 2015;138:566-72.
73. Selle F, Gligorov J, Richard S, et al. Intensive chemotherapy as salvage treatment for solid tumors: focus on germ cell cancer. Braz J Med Biol Res 2015;48:13-24.
74. Munkarah A, Gershenson DM, Levenback C, et al. Salvage surgery for chemorefractory ovarian germ cell tumors. Gynecol Oncol 1994;55:217-23.
75. Quaglia A, Tavilla A, Shack L, et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. Eur J Cancer 2009;45:1006-16.
76. Trillsch F, Woelber L, Eulenburg C, et al. Treatment reality in elderly patients with advanced ovarian cancer: a prospective analysis of the OVCAD consortium. J Ovarian Res 2013;6:42.
77. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004;22:4626-31.
78. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014;15:396-405.
79. Pignata S, Breda E, Scambia G, et al. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer. A Multicentre Italian Trial in Ovarian cancer (MITO-5) study. Crit Rev Oncol Hematol 2008;66:229-36.
80. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged >or=70 years with advanced ovarian cancer--a study by the AGO OVAR Germany. Ann Oncol 2007;18:282-7.
81. de Vos FY, Nuver J, Willemse PH, et al. Long-term survivors of ovarian malignancies after cisplatin-based chemotherapy; cardiovascular risk factors and signs of vascular damage. Eur J Cancer 2004;40:696-700.
82. Delanoy N, Pecuchet N, Fabre E, et al. Bleomycin-induced pneumonitis in the treatment of ovarian sex cord-stromal tumors: a systematic review and meta-analysis. Int J Gynecol Cancer 2015;25:1593-8.
83. Comis RL. Bleomycin pulmonary toxicity: current status and future directions. Semin Oncol 1992;19:64-70.
84. Feldman DR, Voss MH, Jacobsen EP, et al. Clinical features, presentation, and tolerance of platinum-based chemotherapy in germ cell tumor patients 50 years of age and older. Cancer 2013;119:2574-81.
85. Thomsen FB, Bandak M, Thomsen MF, et al. Survival and toxicity in patients with disseminated germ cell cancer aged 40 years and older. Cancer 2014;120:43-51.
86. Wheater MJ, Manners J, Nolan L, et al. The clinical features and management of testicular germ cell tumours in patients aged 60 years and older. BJU Int 2011;108:1794-9.
87. Murugaesu N, Schmid P, Dancey G, et al. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodality treatment. J Clin Oncol 2006;24:4862-6.
88. de La Motte Rouge T, Pautier P, Rey A, et al. Prognostic factors in women treated for ovarian yolk sac tumour: a retrospective analysis of 84 cases. Eur J Cancer 2011;47:175-82.
89. Umezu T, Kajiyama H, Terauchi M, et al. Long-term outcome and prognostic factors for yolk sac tumor of the ovary. Nagoya J Med Sci 2008;70:29-34.