

Current management of ovarian carcinosarcoma

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Abstract. Mano MS, Rosa DD, Azambuja E, Ismael G, Braga S, D'Hondt V, Piccart M, Awada A. Current management of ovarian carcinosarcoma. *Int J Gynecol Cancer* 2007;17:316–324.

Ovarian carcinosarcomas (OCS), also known as malignant mixed müllerian tumors, are uncommon malignancies that carry a poor prognosis. The presentation of OCS is usually indistinguishable from that of epithelial ovarian cancer. Due to its low frequency, prospective trials have been difficult to perform, but there is evidence that OCS are sensitive to platinum-based chemotherapy. Recent studies have shown encouraging results with platinum–ifosfamide and platinum–taxane schedules, which are usually considered the treatment of choice. However, poor performance status at presentation is also a common problem, so that many patients may be unsuitable for combination chemotherapy but may still benefit from single-agent platinum or ifosfamide or, occasionally, from nonplatinum schedules such as ifosfamide plus paclitaxel. Aggressive cytoreductive surgery appears to have a positive impact on outcome and should probably be offered to most patients. However, this procedure has been associated with higher rates of complication in OCS and should only be attempted by experienced (gynecological) surgeons in centers with expertise in the management of gynecological malignancies.

KEYWORDS: carcinosarcoma, female genital tract, chemotherapy, radiotherapy.

Ovarian cancer (OC) is the most lethal disease affecting the female genital tract (FGT) mainly because effective screening methods are lacking and the diagnosis is usually made at advanced stages. Epithelial cancers represent the vast majority of the cases of OC, and the management of these patients has been established by numerous controlled clinical trials, which will not be further discussed in this review. However, the ovary may also be subject to a wide range of less common malignancies, such as granulosa cell tumors, stromal sex cord tumors, and carcinosarcomas (CS), all having distinct clinical behavior, prognosis, and treatment.

Ovarian carcinosarcomas (OCS), also known as malignant mixed mesodermal tumors or malignant mixed müllerian tumors (MMMT), are among the rarest and most challenging malignancies arising from the FGT. This tumor is estimated to account for only 1–4% of all ovarian malignancies^(1–6). With rare exceptions, attempts to run prospective clinical trials in this disease have been elusive, and randomized clinical trials will probably never be performed. Therefore, the manage-

ment of these patients is usually based on data from anecdotal reports, small retrospective series, or, occasionally, extrapolated from CS of other sites, such as the uterus, where this histology is more commonly found.

We performed a comprehensive review of the literature accumulated over the past three decades to provide some guidance for physicians managing women diagnosed with this uncommon and aggressive malignancy.

Pathology

CSs are complex tumors, containing both carcinomatous and sarcomatous elements. The diagnosis of primary OCS is usually established by conventional microscopy. Tumors may present variable amounts of carcinomatous and sarcomatous components, and some physicians find this information useful particularly to assist with decisions on the type of chemotherapy. Tumors that present sarcomatous elements only are normally referred to as “pure sarcomas.” They should probably be managed similarly to sarcomas of other sites and are not the focus of this review. In the past, it was common practice to report the presence of ovarian only (homologous tumors) or ovarian plus nonovarian components (heterologous tumors). The utility of this classification (based on the origin of the

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doi:10.1111/j.1525-1438.2006.00760.x

mesenchymal tissue) is currently unclear^(4,7-11) and it has been less commonly used in daily practice. Occasionally, the diagnosis may be suggested or confirmed by immunohistochemistry (IHC), particularly in case of poorly differentiated tumors. Typically, IHC staining for cytokeratin demonstrates diffuse strong staining of the epithelial component, and staining with vimentin demonstrates rare staining of the epithelial component and diffuse strong staining of the mesenchymal component⁽¹²⁾. A positive staining for CK7 but negative for CK20 would support a müllerian origin. Sometimes, the IHC profile may overlap with that of other epithelial FGT tumors⁽¹³⁾. Additional immunohistochemical stains for muscle-specific actin and desmin may help to exclude other "pure" sarcomas with smooth muscle differentiation. Occasionally, CD34 staining may help distinguish FGT CS from epithelioid sarcomas, which strongly express CD34⁽¹⁴⁾.

Pathogenesis

Various pathogenetic mechanisms have been postulated to explain the biphasic carcinomatous-sarcomatous appearance of MMMTs, but the nature of these neoplasms is still unclear. It has been postulated that these tumors arise from pluripotent müllerian mesenchymal cells, which differentiate into malignant epithelial and stromal elements^(15,16). In contrast, there is evidence suggesting that MMMTs usually arise from preexisting carcinomas⁽¹⁷⁾, and these tumors should be regarded as dedifferentiated carcinomas of the ovary or endometrium⁽¹⁸⁾.

There are four main theories regarding the histogenesis of uterine carcinosarcomas (UCSs)⁽¹⁹⁾, namely (1) the collision theory, which suggests that the carcinoma and sarcoma are two independent neoplasms, (2) the combination theory, suggesting that both components are derived from a single stem cell that undergoes divergent differentiation early in the evolution of the tumor, (3) the conversion theory, which suggests that the sarcomatous element derives from the carcinoma during the evolution of the tumor, and (4) the composition theory, suggesting that the spindle cell component is a pseudosarcomatous stromal reaction to the presence of the carcinoma. The fourth theory was already left behind because, in these neoplasms, the sarcomatous component exhibits malignant histologic features.

The study of a single case of uterine MMMT containing extensive rhabdomyosarcomatous elements⁽²⁰⁾ revealed a similar immunoreactivity for p53 in both the carcinomatous and the sarcomatous components, expression of epithelial markers in the sarcomatous cells, and disruption of the basement membrane profile

in areas of transition between carcinomatous and sarcomatous tissue. These findings suggest an origin from a common epithelial clone and an epithelial-to-mesenchymal transformation mechanism in the development of this tumor.

The frequent concordance of p53 staining between the carcinomatous and the sarcomatous components in UCS (ie, p53 protein expression is either positive or negative in both components) provides further support for a common origin for the epithelial and mesenchymal components because, if these were true collision tumors, such concordance in all cases would be extremely unlikely⁽¹⁹⁾.

Cell culture and heterotransplantation studies using cell lines established from patients with UCS also support the monoclonal theory of histogenesis⁽²¹⁻²⁷⁾. One study evaluated two different cell lines established from two patients with heterologous MMMT of the uterus⁽²¹⁾. Morphologically, the cell line called FU-MMT-2 was a mixture of carcinoma cells and sarcoma cells with predominance of carcinoma cells; the cell line FU-MMT-1 had only a sarcomatous element with distinct rhabdomyoblastic differentiation. Immunohistochemically, the sarcoma cells of each cell line expressed myogenic and mesenchymal antigens (desmin, myoglobin, and vimentin) and also epithelial antigens, including epithelial membrane antigen and keratin. The carcinoma cells in FU-MMT-2 were positive for the epithelial antigens and vimentin and negative for desmin and myoglobin. The presence of epithelial antigens in the sarcomatous and carcinomatous elements seemed to support the hypothesis that both elements are derived from a common stem cell.

The expression of several oncoproteins (p53, p16, BCL2, *Cerb-B2*, E-cadherin, P-cadherin, and N-cadherin) were studied in three cases of primary peritoneal MMMTs⁽²⁸⁾. All three cases expressed p16 but showed less consistent expression of other markers, with one case expressing p53 and one expressing BCL2. All cases were negative for membrane expression of *Cerb-B2*. The three classical cadherins were expressed in two cases with one case showing only weak N- and P-cadherin expression. There were no differences in antigen expression between areas of epithelial or sarcomatous differentiation, supporting a single pluripotential malignant clone in the histogenesis of MMMTs.

Ultrastructural studies of UCS showed focal epithelial differentiation, in the form of desmosomes and/or bundles of cytokeratin tonofilaments, in the sarcomatous component, with a blending of the epithelial and stromal elements and transitional forms between the two^(29,30). These data may also suggest a monoclonal origin for UCSs.

The analysis of p53 and K-ras mutations as well as patterns of chromosome X inactivation in 25 cases of UCSs were identical in both carcinomatous and sarcomatous components in 21 tumors, indicating that they represent combination tumors⁽³¹⁾. However, three tumors showed different patterns of chromosome X inactivation between the carcinomatous and the sarcomatous components, suggesting that although most CSs are combination tumors, some develop as collision tumors.

It may be of prognostic importance to identify those UCSs that are likely to represent true collision tumors. With a true collision tumor, the ultimate prognosis will depend on the most aggressive component, and the outcome may be better than for a similar stage CS⁽¹⁹⁾.

Presentation and diagnosis

The median age at diagnosis has ranged from 60 to 70 years in different series^(6,32). In at least two reports, patients diagnosed with OCS tended to be significantly older than those with epithelial ovarian cancer (EOC)^(1,6). The staging of OCS is similar to that of EOC and is usually performed according to the FIGO classification⁽³³⁾. Patients with OCS are usually diagnosed with advanced stage disease (FIGO stages III and IV)^(1,2,6,32,34); however, the performance status at presentation tends to be poorer as compared with EOC (even after matching for stage)^(2,6). The clinical presentation is usually indistinguishable from EOC, with pelvic and/or abdominal pain, abdominal distension and occasionally intestinal symptoms, and palpable pelvic mass^(6,32), which explain why the diagnosis is frequently established only postoperatively. In one study, ascites was a less frequent finding in patients with OCS⁽⁶⁾. Patients also tend to present with increased CA-125, so this finding is usually unhelpful for the differential diagnosis with EOC^(2,6). Although the CA-125 has not been validated as a marker of response to chemotherapy in OCS, Brown *et al.*⁽⁶⁾ suggested it could be used for this purpose.

Natural history and prognosis

Contrary to UCS, which often metastasizes to the lungs, the spread of OCS is similar to that of primary EOC, with serosal and peritoneal seeding as early sites of metastasis⁽¹⁵⁾.

Despite some conflicting data⁽³⁵⁾, patients diagnosed with OCS appear to have a worse outcome as compared with EOC, even after matching for stage^(1,6). However, the risk of selection bias in small, nonrandomised, retrospective series should always

be carefully considered. In one of the largest series ($n = 47$)⁽³²⁾, 72% of the patients developed recurrence, at a mean time of 10.5 months. Virtually, all recurred within the first 2 years. The median survival (MS) for all patients was 16 months, in contrast to 24–36 months for patients diagnosed with advanced EOC. In this study, the outcome was apparently better for patients who were optimally debulked (the strongest prognostic factor in the multivariate analysis), in those with lower CA-125 at baseline, in patients treated with platinum-based chemotherapy as compared to nonplatinum-based chemotherapy, and in those with homologous tumors. In another large report⁽⁶⁾, the MS was 8.2 months with a 2-year survival rate of 23% and a 5-year survival rate of 15%. The median time to recurrence was 6.4 months. In this study, 50% of the patients with FIGO stage I and virtually all the patients with more advanced disease eventually developed recurrence⁽⁶⁾. In another study of 18 OCS patients, the MS was only 11 months⁽³⁴⁾. In a larger report ($n = 31$), the MS after a median follow-up of 28 months was 21 months⁽⁷⁾. In a recent study of 40 patients treated in a single institution, the MS was only 8.7 months⁽²⁾, and the outcome was generally worse in patients with bulky residual disease and in those with advanced FIGO stage. Poor outcome has also been associated with the presence of heterologous elements^(18,32,36). However, in most studies, histology (homologous vs heterologous) had no clear influence on patient outcome^(4,7–10,37,38). These findings were recently confirmed by the two largest reports^(2,6).

The most important report so far on the epidemiology of patients with OCS consists of an analysis of the data from the population-based Surveillance, Epidemiology and End Results of patients diagnosed with primary invasive OC in the United States. Out of 13,996 cases, 382 were OCSs. These tumors appeared to be particularly rarer than EOC in women less than 50 years old; stage at presentation was similar with 66–68% diagnosed with advanced disease. The prognosis of women diagnosed with OCS was poor even for early-stage disease. In line with previous reports, the MS was significantly shorter for OCS even after adjustment for stage⁽¹⁾.

Treatment

Surgery

The role of cytoreductive surgery (CRS) in patients with OCS has not been prospectively evaluated. In some earlier small series, CRS has not been shown to improve outcome^(37,39,40). However, other studies have

showed exactly the opposite^(2,9,32,38,41,42). In a recent report ($n = 31$), optimal CRS was associated with improved outcome in patients with FIGO stage IIIC OCS⁽⁷⁾. In a larger report, patients with stage III disease who were optimally debulked had a significantly longer MS (14.8 vs 3.1 months, $P < 0.001$)⁽⁶⁾. However, it has also been suggested that surgery for OCS can be difficult and associated with high morbidity⁽³²⁾. Tumors tend to be fleshy and hemorrhagic with heavy blood loss happening commonly⁽²⁾, raising questions about the potential role of anti-angiogenic agents in this disease.

In short, the limited available evidence supports the role of maximal CRS in improving the prognosis of patients with OCS. The surgical management of these patients should be similar to that of patients diagnosed with EOC. Ideally, these patients should undergo cytoreduction by experienced (gynecological) surgeons in highly specialized centers^(32,39,43,44).

Radiotherapy

There have been anecdotal reports of patients with OCS treated with radiotherapy, in addition to or instead of chemotherapy^(2,4,32,45). There is little rationale for the use of radiotherapy in a disease that is usually diagnosed at advanced stages and usually behaves like OC (ie, spreading through the peritoneal surface). Nevertheless, one should not dismiss the fact that whole-abdominal radiotherapy (WAR) has been considered a valid approach in the adjuvant treatment of diseases, such as papillary serous uterine cancer [Gynecologic Oncology Group (GOG 94)], an unusually aggressive tumor, which also tends to spread like OC^(46,47). Similarly, patients with advanced endometrial carcinoma that have been optimally debulked to less than 2 cm can also derive some benefit from the use of WAR; in a recent randomized trial (GOG 122), this treatment was considered inferior, but significantly less toxic than "adjuvant chemotherapy" consisting of cisplatin and doxorubicin⁽⁴⁸⁾. Similar results have been recently reported in patients with UCS⁽⁴⁹⁾.

The role of radiotherapy in patients with early-stage OCS is unknown, but it should probably not replace chemotherapy. In UCS, pelvic failures have been a problem in earlier trials of adjuvant chemotherapy⁽⁵⁰⁾. Radiotherapy may be appropriate for patients with chemotherapy-refractory recurrent or persistent disease, restricted to the pelvis.

Chemotherapy

A number of small, retrospective studies and anecdotal reports have supported the role of chemotherapy

in the management of patients with OCS. Although most of these reports included highly heterogeneous groups of patients treated with numerous different regimens, platinum-based chemotherapy seems to be particularly active in this disease. A number of different schedules have proven activity in CS of the FGT, though toxicity has often been a limiting problem⁽⁵¹⁾ (Table 1).

In a retrospective study of 47 patients with CS and pure sarcomas of the ovary⁽³²⁾, adjuvant chemotherapy was given to 85% of the patients (consisting of numerous different agents/regimens). The response rate (RR) and MS were reportedly better in patients who received platinum-based chemotherapy ($n = 27$) rather than nonplatinum-based chemotherapy (RR = 80% vs 12% [$P = 0.008$] and MS = 15 vs 6.6 months [$P = 0.03$]). A similar trend for a better outcome in patients treated with platinum-based vs nonplatinum-based chemotherapy was reported in a large, single institution experience⁽²⁾.

The GOG has recently reported the results of the only large trial prospectively assessing the role of chemotherapy in patients with OCS⁽⁵⁷⁾. Median age of patients (with measurable disease, $n = 44$) was 62 years; 27 (50%) had FIGO stage III/IV/recurrent disease and 27 had early-stage disease. One hundred thirty-six patients received cisplatin 50 mg/m² thrice weekly until unacceptable toxicity or disease progression. Among the 44 patients with measurable disease, responses were observed in 20%, with an additional 23% experiencing stable disease. The median duration of response and stable disease was 3.5 and 4.1 months, respectively. The median progression-free survival (PFS) and overall survival (OS) among 130 patients evaluable for efficacy was 5.2 months and 11.7 months, respectively. In an exploratory analysis performed in patients considered evaluable for response ($n = 44$), MS was apparently longer in responders as compared to nonresponders (19 vs 4.7 months). The results of this trial are consistent with previous reports^(2,4,6). The most important conclusion from this GOG trial is that OCS are definitely sensitive to platinum compounds. Another conclusion—based on the fact that it took GOG 20 years to recruit a little more than 100 patients into this trial—is that prospective trials cannot be performed in this disease due to its rarity, and data should instead be extrapolated from trials in UCS.

The rationale for the conclusion above is the fact that the clinical behavior and prognosis of patients with OCS are very similar to those of patients with UCS, which is relatively more frequent⁽³⁴⁾. Furthermore, the activity observed with single-agent cisplatin

Table 1. Activity of chemotherapy in OCS: largest series and prospective studies

Author	Type of chemotherapy	n	RR	Comments
Retrospective studies				
Brown 2004 ⁽⁶⁾	Platinum based	12 (stage III/IV and MD)	25%	RR = 41% (n = 17) based on CA-125 (Rustin criteria)
Harris 2003 ⁽²⁾	Nonplatinum based	6	NR	Overall MS = 8.7 m
	Platinum based	26	42%	
Sood 1998 ⁽³²⁾	Nonplatinum based	6	33%	MS for platinum/nonplatinum CT = 15 vs 6.6 m (P = 0.03)
	Platinum based	27	80%	
Rutledge 2006 ⁽⁷⁾	Nonplatinum based	11	12%	PFS (P = 0.005) and 2-year OS (P = 0.03) better with platinum-ifo-based CT
	Platinum-ifo based	11	NR	
Morrow 1986 ⁽⁵²⁾	Platinum-taxane based	16		
	Dox 75 mg/m ²	31 (10 with MD)	1/10	
Morrow 1984 ⁽³⁸⁾	VAC	8	2/8	
	Dox	6	1/6	
Plaxe 1990 ⁽³⁹⁾	Cis-dox based	13 (all FIGO III/IV)	NR	MS = 16 m for CT treated
Duska 2002 ⁽⁴²⁾	Carboplatin-paclitaxel	28 (most FIGO III/IV)	72% (55% CR)	MS = 27 m
Sit 2000 ⁽⁵³⁾	Carboplatin-paclitaxel	6 (1 with MD)	1/1	MS carboplatin-paclitaxel PC/platinum-ifo = 33 vs 23 m
Moore 1986 ⁽⁵⁴⁾	Platinum-ifo	8 (3 with MD)	3/3	
	CYVADIC or CAP	15	9/15 (60%)	
Prospective studies				
Sutton 1994 ⁽⁵⁵⁾	Ifo/mesna	31	5/28 (18%)	Prior platinum-based CT, G3 neurotoxicity: 2/28, G3/4 neutropenia: 35%
Crotzer 2003 ⁽⁵⁶⁾	Cis-ifo	8	NR	Median PFS = 15 m, MS = 17 m
Thigpen 2004 ⁽⁵⁷⁾	Cis	136	20%	MS longer in responders 20 years to recruit

CT, chemotherapy; MD, measurable disease; NR, not reported; Ifo, ifosfamide; Cis, cisplatin; VAC, vincristine, dactinomycin, cyclophosphamide; Dox, doxorubicin; CR, complete response; CAP, cisplatin, cyclophosphamide, doxorubicin; CYVADIC, cyclophosphamide, vincristine, doxorubicin, and dacarbazine; G, grade.

in OCS (at doses typically used for the treatment of uterine cancers) is similar to that observed with this same agent in UCS⁽⁵⁷⁾. In phase II trials, the most active agents in UCS were ifosfamide (RR = 32% in previously untreated patients)⁽⁵⁸⁾ and cisplatin (RR = ±20%)^(59–61). At least two previous randomized trials have failed to demonstrate the superiority of combination over single-agent chemotherapy in UCS^(62,63). In a small nonrandomized trial, the RR to the combination of ifosfamide and cisplatin was 33%⁽⁶⁴⁾. The GOG has subsequently performed a large phase III trial comparing single-agent ifosfamide, so far the most active agent in UCS, to the combination of cisplatin and ifosfamide. This trial has shown superior activity and only slightly improved PFS with the combination, with no difference in terms of survival and at the cost of increased toxicity⁽⁶⁵⁾. In a nonrandomized study, the GOG has also evaluated the role of the doublet ifosfamide/cisplatin as adjuvant treatment after successful surgery for early-stage UCS (FIGO stage I and II), with encouraging results. However, high rates of pelvic failures have been reported in this trial in which patients did not receive adjuvant radiotherapy⁽⁵⁰⁾. In

a recently reported GOG trial, this same regimen was compared to WAR in 224 patients with optimally debulked UCS. Although the outcome was poor in both arms, chemotherapy reduced recurrence rates and improved survival over WAR⁽⁴⁹⁾. In conclusion, based on the data above, the doublet cisplatin/ifosfamide should be considered as upfront treatment for suitable patients diagnosed with OCS. As previously mentioned, OCS patients tend to have a poorer performance status, and in at least one report, few were able to tolerate ifosfamide given in combination with a platinum compound⁽²⁾. In one of the rare prospective studies performed in OCS, the GOG demonstrated an overall response of 18% to ifosfamide and mesna, with acceptable toxicity⁽⁵⁵⁾. It is worth noting that the GOG has recently reported the results of a phase III trial in patients with advanced, recurrent or persistent, previously untreated UCS comparing ifosfamide single agent (2.0 g/m² intravenously daily for 3 days) to a nonplatinum regimen consisting of ifosfamide (1.6 g/m² intravenously daily for 3 days) and paclitaxel (135 mg/m² by 3-h infusion on day 1) with growth factor support (in the combination arm only)⁽⁶⁶⁾.

Although patients treated with the combination had significantly more alopecia and neuropathy, the combination resulted in superior RR (odds of response 2.21 times that of ifosfamide single agent; $P = 0.017$), PFS (HR = 0.71, 95% CI = 0.51–0.97, $P = 0.03$), and OS (HR = 0.69, 95% CI = 0.49–0.97, $P = 0.03$), so that this schedule may also be considered a reasonable (nonplatinum) alternative for suitable patients with advanced OCS.

There have been anecdotal reports suggesting encouraging activity with platinum–taxane combinations in both UCS and OCS^(7,42,67,68). In a recent retrospective report of 29 women with OCS treated with adjuvant chemotherapy, those who received ifosfamide/cisplatin ($n = 11$) had a significantly longer PFS as compared to patients treated with carboplatin/paclitaxel ($n = 16$) (12 months for carboplatin/paclitaxel vs not yet reached for ifosfamide/cisplatin; $P = 0.005$). There was also a similarly positive effect of ifosfamide–platinum-based therapy on OS (2-year OS, 55% for carboplatin/paclitaxel vs 81% for ifosfamide/cisplatin; $P = 0.03$)⁽⁷⁾. The majority of long-term survivors (>2 years) in this study were ifosfamide/cisplatin-treated patients. However, such reports are potentially biased by patient selection; in this report, for instance, patients treated with ifosfamide/cisplatin tended to have earlier stage disease and had been more often optimally debulked. In a similar but much smaller report, patients treated with platinum–paclitaxel-based chemotherapy ($n = 6$) seemed to have similar outcome to those treated with platinum–ifosfamide-based chemotherapy ($n = 8$)⁽⁵³⁾. In another small retrospective study ($n = 11$), OCS patients who received post-operative carboplatin–paclitaxel had similar outcome to those who received cisplatin–ifosfamide, which was also more toxic⁽⁶⁹⁾. In a recent small ($n = 8$), prospective study in which patients with primary or recurrent OCS were treated with ifosfamide and cisplatin, an encouraging MS of 21 months was reported⁽⁵⁶⁾. Finally and most importantly, in a recently retrospective study of 28 OCS patients, the RR to paclitaxel–platinum chemotherapy was 72%, with 55% of complete clinical responders. The MS for these patients was 27 months⁽⁴²⁾. In view of the established role of the doublet carboplatin/paclitaxel in patients with EOC and of the lack of data with regard to the best agent for use in combination with a platinum compound in OCS (in patients suitable for combination chemotherapy), platinum–taxane doublets are considered by some oncologists a reasonable and certainly better tolerated option in this disease.

Occasionally, oncologists have attempted to estimate the amount of sarcomatous elements in the

tumor as guidance for the choice of the chemotherapy. This is mainly based on the assumption that tumors with a predominance of sarcomatous elements might be particularly sensitive to anthracyclines and could derive a larger benefit from platinum–anthracycline combinations. One could also consider the use of platinum–taxane–anthracycline triplets (such as carboplatin–epirubicin–paclitaxel, recently shown equivalent, but more toxic than carboplatin–paclitaxel in two phase III trials in patients with EOC^(70,71)), particularly in selected cases such as young and reasonably fit women. However, such arguments are purely theoretical. It should also be noted that single-agent doxorubicin has shown disappointing activity in previous phase II trials in both UCS⁽⁶²⁾ and OCS^(38,52), though two retrospective studies reported some benefit from doxorubicin–cisplatin-based chemotherapy, usually given as a sort of adjuvant treatment to patients with OCS^(16,39). Furthermore, since pathologists cannot assess every single piece of tumor in detail, histologic heterogeneity could further jeopardize the validity of this approach. Some authors have also suggested that CS arise from the müllerian epithelium, with subsequent differentiation/metaplasia to sarcomatous elements, which would further support the assumption that OCS should be treated more like EOC⁽⁹⁾.

Finally, there have been anecdotal reports of successful treatment with a combination of CRS, systemic chemotherapy, and intraperitoneal hyperthermic perfusion⁽⁷²⁾. Interestingly, one case report suggested some activity with liposomal doxorubicin⁽⁷³⁾. In a recent study of MMT of the FGT (in which two patients had OCS), the triplet paclitaxel, ifosfamide, and carboplatin has shown promising activity and acceptable toxicity when given with growth factor support⁽⁷⁴⁾.

Future directions

Despite the fact that OCS are relatively chemosensitive tumors, the prognosis of these patients remains poor despite the use of chemotherapy, lagging behind that of patients with EOC matched for stage. New treatment strategies are needed for this population. The use of biological “targeted” therapies has been proven successful in several tumor types. Whether such treatments could also be active in CS of the FGT is a question that would largely depend on the presence of suitable targets for these agents in the tumors. Moreover, the low frequency of this disease represents another challenge for the development of clinical trials of molecular-targeted therapies.

The human epidermal growth factor receptor 2 (HER-2/neu, also called c-erbB-2) is known to be

involved in the development and growth of tumor in many types of cancer. In a recent report, HER-2 overexpression was detected in 9 of 16 cases, though only 1 showed HER-2 gene amplification by fluorescence *in situ* hybridization⁽⁷⁵⁾. In another study, staining for the HER-2 protein was detected in 9 of 28 cases; 4 of these cases expressed HER-2 at +++, all of which also showed HER-2 gene amplification by fluorescence *in situ* hybridization⁽⁷⁶⁾. As expected, in both studies, the staining tended to be stronger within the epithelial component. In other studies, HER-2 overexpression has been reported in 0–88% of the cases^(64,77–79). These data raise questions about the potential role of trastuzumab, a HER-2-targeted monoclonal antibody with proven activity in patients with HER-2-positive breast cancer⁽⁸⁰⁾, in the treatment of patients diagnosed with HER-2 overexpressing and/or amplified OCS.

The epithelial growth factor receptor (EGFR), which is also the target of a number of biological compounds such as cetuximab (and other small tyrosine kinase inhibitors molecules targeting the EGFR pathway), has also been evaluated in small series of cases of CS of the FGT. Epithelial growth factor receptor overexpression has been reported in around 30% of the cases^(79,75). C-Kit, which is one of the targets of the tyrosine kinase inhibitor imatinib, also seems to be expressed in some cases of CS of the FGT, with rates varying from 16% to 25% in different studies^(75,81,82). Finally, the cox-2 enzyme also appears to be expressed in around 33% of the cases⁽⁸²⁾ and could be another potential target for agents such as the cox-2 inhibitors and others.

The vascular endothelial growth factor (VEGF) has also been shown to result in a worse prognosis in a number of tumor types, including OC⁽⁸³⁾. In contrast, there is little information about the impact of VEGF on the outcome of patients with soft tissue sarcomas^(84,85). In a recent report of nine patients with OCS, reactivity for VEGF was observed in four (44%) tumors specimens⁽⁷⁷⁾. However, it is worth noting that in a recent phase II study of doxorubicin in combination with the anti-VEGF antibody bevacizumab in patients with soft tissue sarcomas, the activity was no better than that usually seen with doxorubicin alone⁽⁸⁶⁾.

In one previous study, estrogen receptor and/or progesterone receptor expression was reported in about 24% of the cases of UCS⁽⁶⁴⁾. Geisler *et al.*⁽⁸⁷⁾ observed estrogen receptor expression in six of nine specimens (66.6%) of OCS. In a more recent series, all nine cases were negative for estrogen receptor and progesterone receptor expression⁽⁷⁷⁾. Unfortunately, there is virtually no data on the utility of hormonal manipulations in this disease.

Conclusion

OCSs are rare tumors that are typically associated with a poor prognosis. Prospective trials have been difficult to perform, but there is evidence that these tumors are sensitive to platinum-based chemotherapy. Poor performance status at presentation is a common problem, so that many patients may not be suitable for combination chemotherapy but may still be candidates to single-agent platinum or ifosfamide or, occasionally, nonplatinum regimens such as ifosfamide plus paclitaxel. Maximal CRS appears to have a positive impact on patient outcome and is recommended in most cases. The risk of complications may be higher than in EOC, so that surgery should always be performed by experienced (gynecological) surgeons and in centers with expertise in the management of gynecological malignancies.

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Accepted for publication July 18, 2006

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