



Review

Carcinosarcoma of the ovary: A review of the literature

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ABSTRACT

Objective. Carcinosarcoma of the ovary is a rare tumor with a grim prognosis. This article critically reviews the literature pertinent to the pathology, pathogenesis, diagnosis, management, and outcome of patients with ovarian carcinosarcoma (OCS).

Methods. MEDLINE was searched for all research articles published in English between January 1, 1981 and August 30, 2011 which reported on patients diagnosed with carcinosarcoma of the ovary. Given the rarity of this tumor, studies were not limited by design or number of reported patients.

Results. Patients with OCS generally present with advanced stage disease, and symptoms similar to those of patients with epithelial ovarian cancer (EOC). Retrospective studies have shown that cytoreductive surgery improves outcomes in patients with OCS. Similarly, platinum-based chemotherapy appears to be active in the treatment of OCS.

Conclusions. Ovarian carcinosarcomas are rare and aggressive tumors, associated with a poor prognosis. The mainstay of treatment remains cytoreductive surgical effort for metastatic disease followed by platinum-based chemotherapy. The role of targeted therapies may be promising in the treatment of OCS.

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Introduction

Epithelial ovarian cancer remains the most lethal gynecologic malignancy, largely because effective screening strategies are lacking

and the diagnosis is commonly made at advanced stage. Approximately 22,000 new cases of ovarian cancer are estimated in the United States for 2011, with close to 15,500 deaths. Although it is the ninth leading cause of cancer in women, it remains fifth leading cause of all cancer-related deaths [1]. Epithelial ovarian carcinoma comprises 90–95% of all cases, while sex cord-stromal tumors and malignant ovarian germ cell tumors are relatively rare. Numerous randomized controlled clinical trials have been executed and their results largely guide the management of most women with epithelial

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ovarian cancer. These trials will not be discussed in the current review.

Ovarian carcinosarcoma (OCS), also known as malignant mixed mesodermal tumors or malignant mixed müllerian tumors (MMMT) comprise one of the rarest and most challenging histologic subtypes of ovarian cancer. Carcinosarcomas arising from the ovary may account for only 1–4% of all ovarian cancer [1–6]. Given the rarity of OCS, attempts to conduct prospective trials to illuminate treatment strategies have been mostly elusive. Its management has been extrapolated from the management experience of epithelial ovarian cancer, anecdotal experience or small retrospective published series. This article is based on a comprehensive review of the last 30 years of published literature with the intent to offer clinicians an overview of the pathology, pathogenesis, presentation, and management of women diagnosed with ovarian carcinosarcoma.

Methods

This article reviews the English language literature for studies on ovarian carcinosarcoma. A 30-year period MEDLINE (PubMed) search of English literature published between January 1981 and August 30, 2011 was performed. All publications with the keyword “ovary” were combined and then searched for the keyword “carcinosarcoma,” “malignant mixed mesodermal tumors,” and “malignant mixed müllerian tumors.” Additional publications were identified via systematic review of all reference lists within publications retrieved from the MEDLINE search. Given the rarity of this tumor, and the concomitant lack of data in the form of large trials, all peer reviewed original report publications with an appropriate number of subjects was considered and included.

Pathology

Carcinosarcomas contain both carcinomatous (malignant epithelial) and sarcomatous (mesenchymal) elements. Although the epithelial component is usually serous, endometrioid, or undifferentiated adenocarcinoma, it can also be clear cell adenocarcinoma or squamous cell carcinoma. The sarcomatous component can be homologous (tissue native to the ovary) or heterologous (tissue not native to the ovary) [7,8]. Homologous elements include fibrosarcoma, and leiomyosarcoma. Heterologous elements include chondrosarcoma, rhabdomyosarcoma, osteosarcoma, or liposarcoma [7,8]. The clinical utility of this dichotomous classification is unclear. Some studies have reported that the presence of heterologous sarcomatous elements is associated with a poor prognosis [9,10]. However, others have noted that the heterologous component does not impact survival [5,11–13].

Immunohistochemistry (IHC) staining for cytokeratin shows diffuse strong staining of the epithelial element, while vimentin staining exhibits rare staining of the epithelial component and diffuse strong staining of the mesenchymal element [14]. Müllerian origin would be supported by positive CK7 staining and negative CK20 staining. Additional IHC stains for muscle-specific actin and desmin may help distinguish other “pure” sarcomas with smooth muscle differentiation from OCS [15]. CD34 staining may help distinguish OCSs from epithelioid sarcomas, which strongly express CD34 [16].

Pathogenesis

The genetic origin of OCS remains unclear. Several mechanisms have been proposed to explain the biphasic, carcinomatous–sarcomatous nature of these tumors [17,18]. Three main theories have been postulated: 1) the collision theory suggests that the two tumor types, epithelial and sarcoma, evolve independently and then collide, suggesting that the carcinoma and sarcoma are two independent tumors; 2) the combination theory supports the notion of a common

stem cell precursor giving rise to a carcinoma and a sarcoma, both components derived from a single stem cell undergoing divergent differentiation early in tumor evolution; 3) the conversion theory states that the sarcomatous element arises from the carcinoma during tumor evolution or that an original stem cell differentiates into one cell type, in turn, differentiating into a second cell type. Most of the data addressing the genetic origin of CS in gynecologic tumors comes from studies of uterine CS specimens.

The hypothesis that a common epithelial clone can mediate an epithelial-to-mesenchymal transformation is supported by a study of a single case of uterine carcinosarcoma [19]. The authors report similar immunoreactivity for p53 in the carcinoma and sarcoma components of the tumor, and disruption of the basement membrane profile in areas of transition between carcinoma and sarcoma. In a study evaluating X-chromosome inactivation, microsatellite analysis, and p53 mutations in 12 uterine and 3 ovarian carcinosarcoma specimens, the authors showed that all OCS were monoclonal, supporting the combination theory [20]. This study supports the combination theory, with all OCS noted to be monoclonal in origin. The authors also report 2 uterine carcinosarcomas with biclonal origin, supporting the collision theory.

However, the data is conflicting regarding the origin of these tumors. Several studies support the monoclonal theory. In a study of comparative genomic hybridization and fluorescence *in situ* hybridization of 30 OCS, chromosome amplification of the *c-myc* proto-oncogene on chromosome 8q and 20q was noted, supporting the monoclonal theory [21]. This study, however, also showed genetic aberrations to be similar to those seen in serous carcinomas, documenting that these tumors could also be metaplastic and lending support to the conversion theory. The study by Sonoda et al. supports the combination theory, with a case of OCS showing clonal loss of BRCA2 allele and a somatic mutation in p53 in both the carcinoma and sarcomatous elements [22]. The consistent concordance of p53 staining between the carcinomatous and sarcomatous elements in uterine CS (p53 protein expression is either negative or positive for both components) supports the theory of common origin for the epithelial and mesenchymal elements [23]. The monoclonal origin of these tumors is further supported by cell culture and heterotransplantation studies in cell lines from patients with uterine CS. For example, one study investigated 2 different cell lines from 2 patients with heterologous uterine CS [24]. Cell line FU-MMT-2 was a mixture of carcinoma and sarcoma cells, with carcinoma cells predominating. FU-MMT-1 had only a sarcoma component, with rhabdomyoblastic differentiation. The sarcoma component of each cell line expressed myogenic and mesenchymal antigens as well as epithelial antigens. In the FU-MMT-2 specimen, the carcinoma cells were positive for both epithelial antigens and vimentin (mesenchymal antigen) and negative for desmin and myoglobin (mesenchymal antigens). The observation that epithelial antigens were seen in both the carcinoma and sarcomatous components supports the theory that both components arise from a common stem cell.

In a study of 3 cases of primary peritoneal CS, several oncoproteins, including p53, p16, BCL2, Cerb-B2, E-cadherin, P-cadherin, and N-cadherin, were evaluated [25]. P16 was seen in all 3 cases, with less consistent expression of the other markers. There was no differential expression between the carcinoma and sarcoma elements, lending support to the theory favoring a single pluripotent malignant clone. In ultrastructural analyses of uterine CS, focal epithelial differentiation (desmosomes and/or bundles of cytokeratin tonofilaments in the sarcoma element, with blending of the stromal and epithelial elements and transitional forms between the two) have been reported [26,27]. These findings support a monoclonal origin for CS.

In 25 cases of uterine CS, p53 and K-ras mutations, and patterns or X chromosome inactivation were identical for both the carcinoma and sarcoma elements in 21 tumors [28]. In the study by Growden et al., broad genotyping was conducted in cases of gynecologic CS in

order to identify tissue-specific somatic mutational profiles [29]. Cancer gene mutations were identified in 46% of the 52 cases, including TP53 (23%), PIK3CA (19%), KRAS (15%), CTNNB1 (4%), and NRAS (2%). The authors also reported on comparative evaluation of the carcinoma and sarcoma components within a tumor, showing similar mutation signatures. In this study, the frequency of TP53 and CTNNB1 mutations were similar across CS arising from the uterus and the ovary, while activating mutations in PIK3CA, KRAS, and NRAS were exclusive to uterine CS.

The conversion theory finds support in a study of 2 ovarian serous epithelial carcinomas recurring as OCS. Evaluation of loss of heterozygosity, p53 mutation, and microsatellite analysis revealed identical findings in both the primary and recurrent tumors [30]. Ultimately, the observation that some gynecologic CS over express certain therapeutically relevant mutations may help direct targeted treatments for some of these tumors.

Clinical presentation

OCS share similarities but also can be distinctly different from epithelial ovarian cancer (EOC). Patients with OCS tend to present at an older age when compared to women diagnosed with EOC. Median age at diagnosis for OCS has been reported to range from 60 to 70, with at least two studies citing an older age for women diagnosed with OCS when compared to those diagnosed with EOC [4,6,10,31]. OCS is staged according to FIGO criteria for ovarian cancer. Most patients present with symptoms of advanced stage disease, FIGO stage III or IV [3,4,6,10,31]. These symptoms include pelvic and/or abdominal pain, early satiety, bloating, abdominal distention, and gastrointestinal complaints [6,10]. Patients' performance status at the time of presentation is usually poorer when compared to women with EOC, and after adjusting for stage [3,6].

On initial examination, a palpable mass may be appreciated. It has been estimated that over 90% of women will have disease that has spread beyond the ovary, with one-third of cases involving both ovaries with ascites present [6,32]. Several authors have reported lymph nodal metastases in over one half of patients at the time of initial diagnosis [3,4,6]. Lung and brain metastases are rare in OCS, unlike its uterine counterpart [3,4]. Serum CA-125 levels tend to be elevated and may be useful in evaluating response to treatment [3,6]. In the study by Sood et al., over 90% of patients had an elevated CA-125 level, with a pre operative level of >75 U/mL associated with poor outcome [10]. CA-125 has not been validated as a marker of response to systemic treatment [2]. Both epithelial and sarcoma elements are seen in metastatic disease. When compared to EOC, OCS has a worse survival rate, with median survival estimated to be less than 18 months [3,4,6,10,31].

Prognostic factors

Although previous studies reported worse outcomes in patients with OCS whose tumors had heterologous elements, in more recent reports histology (homologous vs heterologous elements) has no clear influence on patient outcome [5,10,11,13,30]. Similarly, other histologic factors, such as grade and mitotic index, have not been associated with outcome or the ability to predict metastatic disease [17]. However, the histologic features of the tumor's epithelial element may be predictive of outcome. Metastatic disease may be related to grade and myometrial vascular invasion [33]. In one study, serous epithelial elements were noted to have a worse outcome than nonserous epithelial components [34]. The presence of greater than 25% sarcoma composition as well as a high number of small vessels in the primary tumor have also been linked to worse outcome [34,35]. In a study of 25 patients with uterine and ovarian CS, increased VEGF, VEGFR-3 expression and increased number of vessels were associated with poor survival [35]. Ovarian CS has been reported

to over express p53 and to do so at a higher proportion than other gynecologic cancers [36]. P53 over expression was associated with advanced stage, and worse overall survival [36].

Several clinical prognostic factors associated with poor outcome have been described in the literature including older age, advanced stage at presentation and suboptimal surgical resection [6,18,31,37]. In one of the largest series (n=50), Rauh-Hain et al. report a median disease free survival of 11 months for patients with OCS compared to 16 months among controls with EOC [31]. Median overall survival was also significantly decreased for women with OCS, 24 months, compared to 41 months for controls with EOC [31]. In this study, optimal surgical resection was associated with a significant survival advantage [31]. In another retrospective study of 47 patients with OCS, 72% of patients developed recurrent disease, mean time of 10.5 months [10]. Mean survival time was 16 months for patients with OCS, compared to 24–36 months for women with EOC [10]. The authors also reported improved survival associated with optimal debulking, as well as those with lower CA-125 levels, those with homologous tumors and those treated with platinum-based chemotherapy regimens [10]. In a study of 40 patients with OCS treated at a single institution, median survival was 8.7 months, with worse outcome reported in those with advanced stage and bulky residual disease [3]. Data from the population-based Surveillance, Epidemiology and End Results (SEER) of patients with primary ovarian cancer, included 13,996 cases, out of which 382 were OCSs [38]. This analysis showed that OCS cases were more rare than EOC in women younger than age 50, of similar stage at presentation (66–68% diagnosed with advanced stage disease) and of poor prognosis, even for early-stage disease [38]. The study also documented a shorter median survival associated with OCS when compared to EOC [38].

Treatment

Surgery

Given the rarity of OCS, the role that cytoreductive surgery plays in its management has not been prospectively evaluated. In earlier retrospective studies, cytoreductive surgery was not associated with improved outcome [13,39–42]. However, in the last 15 years, retrospective reviews have reported an improved outcome benefiting patient with OCS who undergo an optimal debulking procedure [3,10,11,31,43–45].

In the study by Rauh Hain et al., among 50 patients with OCS, a significant difference in disease-free survival (DFS) and overall survival (OS) was noted between patients undergoing an optimal debulking procedure when compared to those who had a sub-optimal operation [31]. The authors defined an optimal procedure as one where less than or equal to 1 cm of residual disease was left behind at the completion of primary surgery. The reported DFS for patients with only microscopic residual disease (n=11) was 19 months, compared to 10 months for patients with an optimal operation (residual disease ≤1 cm) but with macroscopic disease left behind (n=26) and 5 months for those with a sub-optimal operation (n=10; p=0.01) [31]. The median OS for patients with microscopic disease was 47 months, 18 months for those with an optimal surgery who had macroscopic disease ≤1 cm and 8 months for those patients with a sub-optimal procedure (p=0.02) [31]. Rutledge et al. reported a 25-month median OS in patients who underwent an optimal debulking primary surgery, compared to only 16 months amongst those whose surgery was sub-optimal [37]. Duska et al., in a series of 28 patients with OCS reported that optimal cytoreduction (<2 cm residual disease) was significantly associated with longer time to recurrence (p=0.001) but not time to death (p=0.89) [44]. In another retrospective review, median survival in patients who underwent an optimal primary surgery was 46 months, compared to 27 months in patients whose tumors were suboptimally resected [46]. Table 1

Table 1
Retrospective studies on effect of debulking surgery on survival in ovarian carcinosarcoma.

Reference number/author	Publication year	Definition of optimal debulking	Number of patients	Impact of optimal debulking on survival
[13]/Ariyoshi et al.	2000	<2 cm	14	None
[40]/Plaxe et al.	1990	<2 cm	15	None
[41]/Terada et al.	1989	<1.5 cm	15	None
[39]/Barakat et al.	1990	<2 cm	24	None
[42]/Leiser et al.	2007	<1 cm	29	None
[45]/Anderson et al.	1987	NR	14	Improved
[44]/Duska et al.	2002	<2 cm	14	Improved
[43]/Muntz et al.	1994	<2 cm	23	Improved
[11]/Morrow et al.	1986	Not reported	30	Improved
[10]/Sood et al.	1998	<1 cm	41	Improved
[3]/Harris et al.	2003	<2 cm	40	Improved
[31]/Rauh-Hain et al.	2011	<1 cm	50	Improved
[37]/Rutledge et al.	2006	<1 cm	19	Associated with survival advantage
[6]/Brown et al.	2004	<2 cm	41	Associated with survival advantage

summarizes data on the effect of surgical debulking on survival in patients with OCS. In summary, most of the available retrospective studies support the role of cytoreductive surgery in the management of OCS, with optimal debulking improving survival and prognosis. Operative management of these tumors should resemble that for EOC and should be undertaken by experience gynecologic oncologist and specialized centers [10,40,47,48].

Chemotherapy

Following primary surgical debulking, the consensus has been to recommend adjuvant chemotherapy for women with OCS. As is the case with surgery, the role of chemotherapy in the treatment of OCS has evolved primarily based on the reported experience from retrospective studies, inclusive of heterogeneous patients treated, with various stages of disease and treated with different regimens. OCS are usually excluded from GOG and other phase I/II trials. The available data supports the use of platinum-based systemic therapy [2,17]. It remains unclear as to whether platinum should be used alone or in combination. Historically, treatment regimens have included platinum and/or paclitaxel, platinum and/or ifosfamide, and platinum with doxorubicin and dacarbazine [2,17].

Data from three prospective GOG trials suggests that doxorubicin is not sufficient and that combination cisplatin with ifosfamide is an active doublet in the treatment of OCS [49–51]. The first of these trials evaluated the role of doxorubicin among 31 patients with OCS, with a 10% reported response rate (RR) and only one partial response [49]. The second trial investigated the role of ifosfamide and mesna among 28 patients with OCS [50]. The authors reported 1 complete response, 4 partial responses, and a 17.9% overall response rate [50]. In the most recent GOG trial, 136 eligible patients with OCS were treated with cisplatin (50 mg/m²) every 3 weeks until disease progression or unacceptable toxicity. Only 44 patients were evaluable for treatment response. One patient had a complete response, 8 had a partial response and 25 had progression of disease on the trial [51]. The authors reported a 20% response rate with cisplatin, similar to the response rate seen in uterine CS [51]. Median PFS and OS in 130 patients evaluable for these endpoints were 5.2 and 11.7 months, respectively [51]. This trial provided the first objective data to show that cisplatin is an active agent in the primary systemic treatment of OCS. The study also demonstrated the difficulty in completing prospective trial in this rare disease. Accrual of 136 patients into this trial took 20 years of recruitment [51].

Retrospective studies have also supported the role of platinum-based chemotherapy in the treatment of OCS. In a study of 47 patients with OCS, 85% of patients received adjuvant chemotherapy, using

several different regimens [10]. Twenty-seven patients receiving platinum-based therapy were compared to those treated with non-platinum based regimens and noted to have a higher response rate and median survival (RR=80% vs 12%, $p=0.008$; median survival 15 vs 6.6 months, $p=0.03$) [10]. Given that combination carboplatin–paclitaxel chemotherapy has proven to be effective in the treatment of EOC, investigators have suggested this regimen as effective in the treatment of OCS. In a study of 26 patients treated with first-line carboplatin and paclitaxel for OCS, 16 (55%) of patients achieved a complete response, and 6 patients were documented to have a partial response, with a 72% total response rate and 27-month overall median survival reported by the authors [44]. In contrast, Brown et al. demonstrated a lower objective response rate to platinum-based chemotherapy in patients with OCS when compared to those with serous EOC [6]. In one of the largest retrospective series published to date, Rauh Hain et al. reported a 62% overall response rate to carboplatin and paclitaxel based chemotherapy among 50 patients with OCS treated with this regimen post operatively [31]. In this study, 18 patients (36%) with OCS experienced progression of disease, 28 patients (56%) had a complete response, and 3 patients (6%) had a partial response while on chemotherapy [31]. In contrast, among 100 matched controls with serous EOC, the response rate was 83%, including 75 patients (75%) with a complete response ($p=0.03$) [31].

The observation that the combination cisplatin/ifosfamide is effective in the treatment of uterine CS has resulted in the adoption, by some, of this regimen to treat OCS [50,52]. In the GOG prospective study investigating the role of ifosfamide in the treatment of OCS, the reported median survival was 23 months [50]. In the retrospective study by Rutledge et al., 11 patients receiving cisplatin/ifosfamide, first-line chemotherapy, were compared to 16 patients treated with combination carboplatin and paclitaxel [37]. Both PFS and overall survival were improved with the use of cisplatin/ifosfamide [37]. The median progression-free interval for the carboplatin/paclitaxel treated group was 12 months and had not been reached in the ifosfamide/cisplatin treated cohort ($p=0.005$). Similarly, overall survival was significantly improved with the use of ifosfamide ($p=0.03$). This doublet was also more toxic, with 15–20% of patients developing grade 3 or 4 neutropenia [37]. Results from the ongoing GOG phase II trial evaluating the role of carboplatin/paclitaxel in the treatment of uterine CS may help inform treatment choice for OCS. Table 2 summarizes the studies of chemotherapy in the treatment of OCS. Platinum-based regimens have emerged as the most efficacious in several retrospective studies. The choice of paclitaxel vs ifosfamide as the second agent in the doublet may depend on patient factors and potential tolerability.

Radiation therapy

The use of radiation therapy in the treatment of OCS lacks data and is largely based on anecdotal reports [3,5,10]. There is little rationale to use this modality treatment in a cancer that is usually diagnosed at advanced stages and that spreads through peritoneal surfaces [2,17]. In patients with early-stage OCS, the role of radiation therapy remains unknown [2]. This treatment modality may be useful in the management of single, isolated pelvic recurrences, but has not been studied [2,17].

Future directions

It remains clear that patients with advanced OCS have a poorer prognosis and median overall survival when compared to patients with EOC. These tumors may also have a lower response to platinum-based chemotherapy. Novel therapies are needed. Biological “targeted” therapies have been successful in the treatment of other cancers and may be promising in the future management of OCS, if suitable targets are discovered in these tumors. The rarity of this disease is certainly a

Table 2
Summary of chemotherapy studies in the treatment of ovarian carcinosarcoma.

Reference number/author	Publication year	Study type	Number of patients	Chemotherapy regimen	Response (# of patients)	Median PFS/OS (months)
[49]/Morrow et al.	1986	GOG/Prospective	31	Doxorubicin	PR (1)	NR
[50]/Sutton et al.	1994	GOG/Prospective	28	Ifosfamide/mesna	RR (10%) CR (1)	NR
[51]/Thigpen et al.	2004	GOG/Prospective	44	Cisplatin	PR (4) RR (17.9%) CR (1)	5.2/11.7
[53]/Crotzer et al.	2003	Prospective	8	Cisplatin/ifosfamide	PR (8) RR (20%) CR (7)	15/17
[11]/Morrow et al.	1984	Retrospective	8	VAC	PR (1) CR (2)	NR
[54]/Piver et al.	1982	Retrospective	11	CYVADIC	RR (25%) CR (1)	NR
[55]/Moore et al.	1986	Retrospective	15	CYVADIC or CAP	PR (2) CR (6)	NR
[45]/Anderson et al.	1987	Retrospective	10	Platinum-based	PR (3) RR60%) CR (4)	NR/16
[40]/Plaxe et al.	1990	Retrospective	13	Cisplatin/doxorubicin	PR (2) CR (10)	17/NR
[56]/Prendeville et al.	1994	Retrospective	15	Several regimens, mostly cyclophosphamide	PR (1) CR (2)	NR
[5]/Chang et al.	1995	Retrospective	24	Mostly platinum-based regimens	PR (5) CR (1)	NR
[10]/Sood et al.	1998	Retrospective	10	Platinum-based	PR (7) RR (33%) CR (3)	NR/15
[52]/Sit et al.	2000	Retrospective	14	8 Platinum–ifosfamide	RR (80%) NR	NR/23
[44]/Duska et al.	2002	Retrospective	28	6 Platinum–taxane Carboplatin–paclitaxel	CR (16) PR (6) RR (72%)	NR/19 NR/27.1
[3]/Harrie et al.	2003	Retrospective	32	26 Platinum-based 6 Non-platinum based	RR (40%)	NR/8.7
[18]/Inthasorn et al.	2003	Retrospective	6	Platinum-based	CR (2) RR (33%)	NR/23
[6]/Brown et al.	2004	Retrospective	12	Platinum-based	CR (1) PR (2) RR (25%)	6.4/8.2
[37]/Rutledge et al.	2006	Retrospective	11	Cisplatin–ifosfamide	Improved PFS	NR/81% (at 2 years)
[57]/Mok et al.	2006	Retrospective	10	Platinum-based	NR	NR/46
[42]/Leiser et al.	2007	Retrospective	28	Platinum-based	CR (12) PR (7)	12/43
[58]/Cecin et al.	2008	Retrospective	22	Platinum-based	NR	NR/26
[31]/Rauh-Hain et al.	2011	Retrospective	50	Carboplatin–paclitaxel	CR (28) PR (3) RR (62%)	11/24

PFS = progression-free survival.

OS = overall survival.

GOG = Gynecologic Oncology Group.

PR = partial response.

RR = response rate.

NR = not reported.

CR = complete response.

VAC = vincristine, dactinomycin, cyclophosphamide.

CYVADIC = cyclophosphamide, vincristine, doxorubicin, dacarbazine.

CAP = cisplatin, cyclophosphamide, doxorubicin.

major obstacle when considering clinical trials evaluating the role of molecular-targeted therapies.

The epidermal growth factor receptor (EGFR) may be over expressed in OCS and is the target of agents such as cetuximab. Over-expression has been reported to be as high as 30% in these tumors [59,60]. Several studies have also shown over expression of C-kit. C-kit is targeted by the agent imitinib and may be over expressed in 16–25% of OCS [59,61,62]. The COX-2 enzyme also appears to be over expressed and may offer another opportunity for targeted therapy [62].

Her-2-over expression has been reported in carcinosarcomas of the female genital tract. One study showed over expression in 9 of 16 cases, with gene amplification by fluorescence *in situ* hybridization (FISH) seen in only one case [59]. A different study showed Her-2 protein detection in 9 of 28 cases, with gene amplification by FISH seen in four cases [62]. In both studies, staining was stronger for the epithelial element [59,62]. Although the data is limited, the role of targets such as trastuzumab warrants consideration. In a study of 9 patients with OCS, four (44%) of patients were noted to have tumors

Table 3
Over-expression of various genes/receptors in OCS.

Receptor	Reference	Over-expression in OCS (%)	Potential targeted therapeutic agent
EGFR	[50,60]	30%	Cetuximab
c-Kit	[59,61,62]	16–25%	Imitinib
Cox-2	[62]	33%	Cox-2 inhibitors
Her-2-neu	[59,62]	40–56%	Trastuzumab
VEGF	[63,64]	44% ^a	Bevacizumab

EGFR = epidermal growth factor receptor.

VEGF = vascular endothelial growth factor.

^a VEGF over expression in 4 of 9 patients with OCS.

with reactivity for vascular endothelial growth factor (VEGF), which has been shown to correlated with worse prognosis in several malignancies, including ovarian cancer [63,64]. The role of bevacizumab in the treatment of OCS remains elusive. Table 3 summarizes over-expression of various genes/receptors in OCS and potential targeted therapies.

Conclusions

Ovarian carcinosarcomas are rare and aggressive tumors, associated with a poor prognosis. Patients usually present with metastatic disease and symptoms similar to those of patients with EOC. The rarity of this tumor has limited the execution of prospective trials, thus, management recommendations have been made largely based on the experience collected from retrospective studies.

Optimal cytoreductive surgery appears to improve outcome and survival in patients with OCS and should be performed by experienced gynecologic oncologists in centers of excellence with expertise in the management of gynecologic malignancies. Debulking surgery should be followed by platinum-based chemotherapy. The addition of ifosfamide or paclitaxel to the platinum agent should be based on patient factors and toxicities. It is unlikely that these two regimens will be compared via a randomized, prospective trial. Future efforts should focus on the potential role of targeted therapies in the management of OCS and will necessitate a better understanding of the molecular basis of this tumor and the risk factors for its development.

Conflict of interest statement

None of the authors have any conflict of interests to report.

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