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Ovarian carcinosarcoma: Current developments and future perspectives

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ABSTRACT

Ovarian carcinosarcoma (OCS) constitute uncommon malignancies accounting for only 1–4% of ovarian cancers. Patients more often present with advanced stage disease and symptoms similar to those of epithelial ovarian cancers (EOC). Optimal tumor cytoreduction appears to be an important determinant of survival. Platinum-based chemotherapy remains the most commonly employed adjuvant treatment. The uncertain origin and poor prognosis of OCS motivate determination of the molecular basis of carcinosarcomas aggressive behavior in the hope of developing novel and effective treatment modalities. The present review summarizes the current knowledge on the epidemiology, pathology, prognostic factors, clinical presentation, and therapeutic interventions including future potential therapeutic targets.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death in women, with 22,280 cases and 15,500 deaths in 2012 (Siegel et al., 2018). Ninety percent of ovarian cancer are of an epithelial cell type and comprise multiple histologic types with various specific molecular changes, clinical behavior, and treatment outcomes (Kurman and Shih, 2011). Ovarian carcinosarcoma (OCS), also known as mixed malignant Müllerian tumors are rare, biphasic, but challenging histologic subtypes accounting for only 1–4% of all ovarian cancer (del Carmen et al., 2012). A number of observational studies have suggested that OCS follow a distinct natural history compared to other more common epithelial carcinomas (del Carmen et al., 2012; Rauh-Hain et al., 2011). Their prognosis is dismal and most patients relapse within one year after completion of initial treatment. The median overall survival (OS) time range from 8 to 26 months (Rauh-Hain et al., 2011; Berton-Rigaud et al., 2014), with reported five-year, disease specific survival rate of 29.8% (Rauh-Hain et al., 2013; George et al., 2013).

Histologically, carcinosarcomas are composed of an epithelial as well as a sarcomatous component. The contribution of each element in the development of the malignancy is in different extent and for this reason, the preoperative diagnosis of the disease cannot be reliably made by core biopsy or fine-needle aspiration.

Various prognostic factors have been defined, including overriding sarcomatoid element more than 25%, the expression of vascular endothelial growth factor (VEGF), the mutation of p53 (Liu et al., 1994; Zorzou et al., 2005), Ki-67 overexpression (Ariyoshi et al., 2000), age under 65 years, disease stage, tumor grade (Paulsson et al., 2013), and residual disease after surgery; however, there is no consensus about these factors.

Although prospective data are lacking, the management has been extrapolated from the experience of epithelial ovarian cancers (EOC), anecdotal evidence or small retrospective published series. Aggressive surgical debulking is still the mainstay therapy and should be followed by adjuvant chemotherapy in advanced stage disease (del Carmen et al., 2012). Given the rarity of OCS, determination of the best adjuvant therapy remains difficult. Although platinum and taxane based chemotherapy are often used, some retrospective studies have suggested that ifosfamide should be incorporated into the treatment of OCS. As second line treatment options are limited, there is a significant unmet need to clarify and understand the biology of the disease, common genetic alterations and activated molecular pathways in an attempt to improve treatments and ultimately survival. This review summarizes the published literature on the epidemiology, pathology, prognostic factors clinical presentation, and therapeutic interventions including novel agents.

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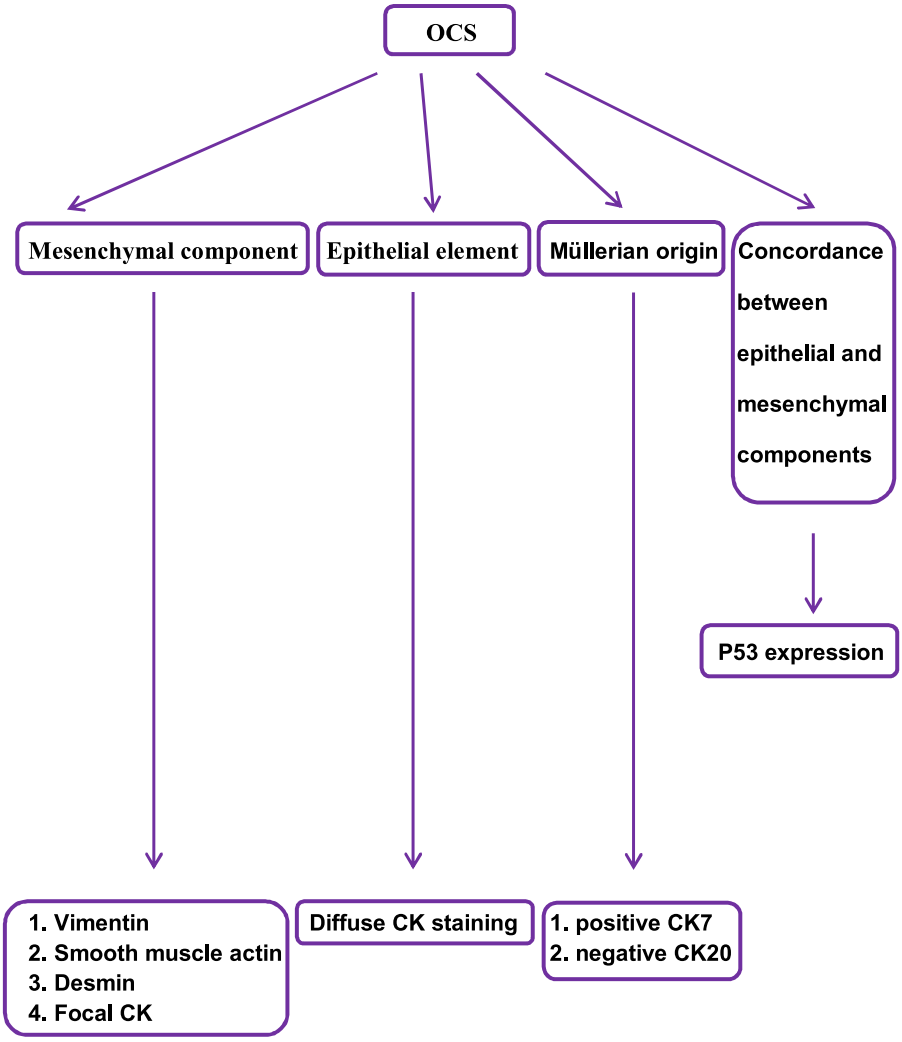

Fig. 1. Immunohistochemical staining of OCS.
Abbreviations. OCSovarian carcinosarcoma, CKcytokeratin

2. Methods

This article reviews the literature for studies on OCS. All publications with the keyword "ovary" were combined and then searched for the keyword "carcinosarcoma", "malignant mixed mesodermal tumors", and "malignant mixed müllerian tumors". Publications between December 1982 and August 2018 were eligible for inclusion. Original papers, review articles and case reports were included. Language restrictions were not used. We also searched registers of clinical trials, and abstracts of scientific meetings.

3. Epidemiology

OCS are usually diagnosed at an older age and have higher rates of advanced International Federation of Gynecology and Obstetrics (FIGO) stage at presentation (del Carmen et al., 2012). They carry a significantly worse prognosis than their epithelial counterparts which is illustrated in a large study of the Surveillance, Epidemiology, and End Results (SEER) Program. Data from 18 registries between 1998 and 2009 identified women with OCS and high grade papillary serous carcinoma of the ovary. Overall, women with OCS had a worse five-year, disease specific survival rate; 28.2% compared to 38.4% ($P < 0.001$) (Rauh-Hain et al., 2013). This difference persisted for each FIGO disease stage, with five year survival consistently worse for women with OCS compared with papillary serous carcinoma. In a previous, similar study, George et al. (2013) analyzed women diagnosed between 1988 and 2007. A total of 27,737 women, including 1763 (6.4%) with OCS and 25,974 (93.6%) with serous carcinomas, were identified. After adjusting for other prognostic factors, women with OCS were 72% more likely to die from their cancer [Hazard Ratio (HR) = 1.72; 95% Confidence Interval (CI), 1.52–1.96]. Five-year survival for patients diagnosed with stage I OCS was 65.2% (95% CI, 58.0–71.4%) compared to 80.6% (95% CI, 78.9–82.2%) for papillary serous tumors. Furthermore, five-year survival for stage IIIC patients was 18.2% (95% CI, 14.5–22.4%) for OCS compared to 33.3% (95% 32.1–34.5%) for papillary serous carcinomas. These findings are in accordance with the available literature on median survival, ranging between 16 and 24 months, which is much inferior to serous tumors (Rauh-Hain et al., 2011; Sood et al., 1998).

4. Pathology and pathogenesis

Macroscopically, OCS are solid and/or cystic, fleshy and haemorrhagic and frequently spread beyond the ovary and over peritoneal surfaces by the time of surgery. They differ from EOC in that they contain both carcinomatous - arising from the epithelial tissue - and sarcomatous - arising from the connective tissue - elements. The epithelial and mesenchymal elements in OCS are usually randomly admixed with one another. Both are high-grade but the mesenchymal component occasionally can be composed of relatively bland spindle

cells. The more frequently encountered epithelial components are serous, endometrioid, or undifferentiated adenocarcinoma. OCS are classified according to the homologous or heterologous derivation of the mesenchymal tissue in their stromal element. Homologous carcinosarcomas contain sarcomatous elements differentiate towards tissues physiologically native to the ovary and include fibrosarcoma, and leiomyosarcoma. The heterologous components usually contain malignant osteoid, chondroid or rhabdomyoid cells that are physiologically foreign to the primary site (Athavale et al., 2007; Barakat et al., 1992; Hellström et al., 1999; Inthasorn et al., 2003; Scully et al., 1998).

Immunohistochemistry is typically not required to establish the diagnosis of OCS, although it may be required to distinguish the tumor from a sarcomatoid carcinoma. Immunohistochemistry staining for cytokeratin shows diffuse strong staining of the epithelial element. The mesenchymal component usually stains for vimentin, smooth muscle actin, desmin, and focal cytokeratin (Clement and Young, 2000). Both the sarcomatous and carcinomatous components often coexpress epithelial markers and vimentin to varying degrees (Geisinger et al., 1987; Meis and Lawrence, 1990; de Brito et al., 1993). Müllerian origin would be supported by positive CK7 and negative CK20 staining. CD34 staining may help distinguish OCS from epithelioid sarcomas, which strongly express CD34 (Costa and Guinee, 2000). P53 expression typically shows concordance between epithelial and mesenchymal components, supporting a monoclonal origin (Mayall et al., 1994; Szukala et al., 1999). The associated immunohistochemical profiling is designed in Fig. 1. Estrogen receptor and progesterone receptor expression have been reported in some cases (Ansink et al., 1997). Variable expression of epidermal growth factor receptor, HER-2/neu (Livasy et al., 2006), and c-kit (Winter et al., 2003) has also been reported.

The genetic origin of OCS remains unclear. Several mechanisms have been proposed to explain the biphasic, carcinomatous–sarcomatous nature of these tumors. However, there are limited data regarding the molecular alterations associated with OCS. Three theories for the origin of carcinosarcomas have been proposed (del Carmen et al., 2012). The collision theory suggests that the tumors are biclonal arising from separate cells that later merge. The combination theory assumes that a common precursor differentiates bidirectionally and the conversion theory posits that a single cell undergoes metaplasmic differentiation (del Carmen et al., 2012). Clonality studies patterns, genomic analysis, and loss of heterozygosity studies support the conversion hypothesis (Armstrong et al., 2009). Most of the data addressing the genetic origin of carcinosarcomas in gynecologic tumors comes from studies of uterine carcinosarcomas specimens.

5. Prognostic factors

In terms of histo-pathological prognostic factors, the significance of the presence or absence of a heterologous mesenchymal component is unclear. Some studies have reported that the presence of heterologous sarcomatous elements is associated with a poor prognosis (Sood et al., 1998), whilst other presented that the heterologous component does not impact survival (Ariyoshi et al., 2000; Chang et al., 1995; Morrow et al., 1984; Muntz et al., 1995). However, the histologic features of the epithelial element may be predictive of outcome. Metastatic disease may be related to grade and myometrial vascular invasion (George et al., 1995). The presence of greater than 25% sarcomatous component as well as a high number of small vessels in the primary tumor have also been associated with worse survival (Athavale et al., 2007; Näyhä and Stenbäck, 2008). In addition, tumors with serous epithelial components adversely affected the survival compared with non-serous components (Athavale et al., 2007). In a study of 25 patients with uterine and OCS, increased VEGF, VEGFR-3 expression and vessel number were correlated with poor survival (Näyhä and Stenbäck, 2008). OCS have been reported to over express p53 in relatively higher proportion as compared to other gynecologic cancers, and this was associated with advanced stage, and worse OS (Liu et al., 1994). Liu et al. presented that in 21 out of 33 patients with uterine and OCS were revealed mutations in the p53 gene (64%) (Liu et al., 1994). The corresponding overexpression of P53 has been found in approximately 10–15% of early and 40–50% of advanced ovarian and endometrial adenocarcinomas (Berchuck et al., 1994). An additional smaller study demonstrated that p53 overexpression affect OS (Zorzou et al., 2005). Ki67 is a nuclear protein related to cellular proliferation, and its reactivity was estimated in 22 patients with OCS. All the specimens demonstrated staining for Ki67 and half of them presented a high Ki67 labeling index. The 5-year survival rate was 15.9% for the high Ki67 index group and 36.4% for the low index group, respectively (Ariyoshi et al., 2000).

Several clinical prognostic factors associated with poor outcome have been detected including older age, advanced stage at presentation and suboptimal surgical debulking (Rauh-Hain et al., 2011; Inthasorn et al., 2003; Scully et al., 1998; Rutledge et al., 2006). Inthasorn et al, reported that age older than 65 years was an indicator for a poor prognosis using univariate analysis (Inthasorn et al., 2003). However, this was not consistent with the findings reported by Rutledge et al, who found that age did not affect survival (Rutledge et al., 2006). Interestingly enough, no studies to date have been able to demonstrate that stage is a prognostic factor using multivariate analysis (Sood et al., 1998; Chang et al., 1995; Rutledge et al., 2006). The rarity of early-stage cases reduce the statistical power in reported case series. Hellstrom et al, found that patients with stage I or II had a better survival than those with stage III or IV disease (Hellström et al., 1999). The analysis of data from SEER (George et al., 2013) showed that stage II and more advanced-stage disease had a poor OS, with HR for death of 1.91 to 5.88. Optimal cytoreductive surgery is the best strategy to improve patient survival in OCS (Rauh-Hain et al., 2011); nevertheless, the reported survival benefit in patients with OCS who underwent optimal cytoreduction is more variable as compared to EOC. (Duska et al. (2002)) showed that optimal surgery increased the progression free survival (PFS), but not the OS. In a case series of 47 patients with OCS, the achieved median survival of women who underwent optimal cytoreduction was 25 months compared to 8 months in those with suboptimal debulking. This is the only available study demonstrated survival benefit of optimal debulking surgery, as an independent prognostic factor, by multivariate analysis. Patients with OCS represented 15% of participants in the study (Sood et al., 1998). Similar results were presented by Rutledge et al. with 2-year survival of 70% as compared to 43% ($P = 0.02$) for patients underwent optimally and suboptimally debulked surgery, respectively (Rutledge et al., 2006). Furthermore, Rauh-Hain et al, reported a median OS of 47 months for women with only microscopic residual tumors, 18 months in patients with optimal but macroscopic residual tumors, and 8 months in patients with suboptimal cytoreduction (residual tumor larger than 1 cm; $P = 0.02$) (Rauh-Hain et al., 2011). However, this survival benefit was revealed only in univariate analysis. Table 1 demonstrates data on the survival benefit of optimal debulking surgery in patients with OCS.

A study designed to evaluate the expression of PD-L1 and intratumoral CD8 + T lymphocytes by immunohistochemistry from 19 OCS patients, demonstrated a prognostic value of CD8 + T lymphocytes and PD-L1 expression, particularly remarkable in mesenchymal component in OCS (Zhu et al., 2017). These results suggest that, positive tumoral CD8 + T lymphocytes and mesenchymal PD-L1-negative expression seem to be associated with better survival in OCS. In this regard, immunotherapy targeting PD-L1 pathway could be effective treatment modality. Indeed, recently has been reported that pembrolizumab provided some tumor control, in a patient heavily pretreated for metastatic OCS; nevertheless, the effects were short-lived (Zibetti Dal Molin et al., 2018).

It has been reported that a higher proportion of patients with OCS has normal level of CA-125 at initial diagnosis, as compared to those with EOC; nevertheless, this difference is not statistically significant, and there is not prognostic importance of CA-125 (Brown et al., 2004).

Table 1
Summary of studies investigated the effect of debulking surgery on survival in ovarian carcinosarcoma.

Reference number/author	Publication year	Definition of optimal debulking	Number of patients	Effect on survival	Median OS (months)
(Rauh-Hain et al., 2011)/Rauh-Hain JA, et al.	2011	< 1 cm	50	Improvement	47 vs. 18 vs. 8
(Ariyoshi et al., 2000)/Ariyoshi K et al.	2000	< 2 cm	14	None	5-year survival 45% vs. 8%
(Sood et al., 1998)/Sood AK, et al.	1998	< 1 cm	41	Improvement	5-year survival 44% vs. %
(Barakat et al., 1992)/Barakat RR, et al.	1990	< 2 cm	24	None	10 vs. 11.7
(Morrow et al., 1984)/Morrow CP et al.	1986	NR	30	Improvement	NR
(Muntz et al., 1995)/Muntz HG, et al.	1994	< 2 cm	23	Improvement	10 vs. 24
(Rutledge et al., 2006)/Rutledge TL, et al.	2006	< 1 cm	19	Improvement	2-year survival 70% vs. 43%
(Duska et al., 2002)/Duska LR et al.	2002	< 2 cm	14	Improvement	NR
(Brown et al., 2004)/Brown E, et al.	2004	< 2 cm	41	Improvement	14.8 vs. 3.1
(Anderson et al., 1987)/Anderson B, et al.	1987	NR	14	Improvement	NR
(Lu et al., 2014)/Lu CH, et al.	2014	< 1 cm	61	Improvement	NR
(Cicin et al., 2016)Cicin İ, et al.	2016	< 2 cm	24	Improvement	32.5 vs. 19.5
(Doo et al., 2014)/Doo DW, et al.	2014	< 1 cm	33	Improvement	57 vs. 31 vs. 3
(Leiser et al., 2007)/Leiser AL, et al.	2007	< 1 cm	29	None	NR
(Petru et al., 2015)Petru E, et al.	2015	< 1 cm	26	None	NR
(Harris et al., 2003)/Harris MA et al.	2003	< 2 cm	40	Improvement	5-year survival 29% vs. 8%
(Plaxe et al., 1990)/Plaxe SC et al.	1990	< 2 cm	15	None	18 vs. 16
(Terada et al., 1989)/Terada KY, et al.	1989	< 1.5 cm	15	None	NR

Abbreviations. OS: overall survival, NR: not reported.

6. Clinical presentation

OCS share similarities but also can be distinctly different from EOC. The average age at the time of disease onset is between sixty to seventy years with at least two studies citing an older age for women diagnosed with OCS when compared to those diagnosed with EOC. At the time of diagnosis, the FIGO stage is usually III-IV. Initial symptoms include pelvic and/or abdominal pain, early satiety, bloating, abdominal distention, and gastrointestinal complaints (Rauh-Hain et al., 2011; Sood et al., 1998; Brown et al., 2004). Patients' performance status at the time of presentation is usually poorer when compared to women with EOC, and after adjusting for stage (Brown et al., 2004).

On initial examination, a palpable mass may be revealed. It has been estimated that over 90% of women present with disease spread beyond the ovary, with one-third of cases involving both ovaries (Brown et al., 2004; Silverman et al., 1986). One in two patients are diagnosed with pelvic and para-aortic lymph node metastases (Brown et al., 2004). Almost all patients will be expressing the antigen CA-125, at a value above 75 U/ml (Sood et al., 1998). This could be useful in evaluating response to treatment (Brown et al., 2004). Both epithelial and sarcoma elements are present in metastatic disease.

7. Treatment

7.1. Surgery

Women with early-stage tumors should undergo comprehensive surgical staging (Berton-Rigaud et al., 2014). The role of cytoreductive surgery in the management of OCS has not been prospectively evaluated. Most of the available retrospective studies support the role of surgical cytoreduction, and there does seem to be a trend toward better survival with optimal debulking surgery (Rauh-Hain et al., 2011; Sood et al., 1998; Morrow et al., 1984; Muntz et al., 1995; Rutledge et al., 2006; Duska et al., 2002; Brown et al., 2004; Silverman et al., 1986; Anderson et al., 1987; Lu et al., 2014; Cicin et al., 2016; Doo et al., 2014) (Table 1). This procedure includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and appendectomy, para-aortic and pelvic lymphadenectomy to the left renal vein. Peritoneal, paracolic, subdiaphragmatic and minor pelvis biopsies are recommended. In individual cases may be given preoperatively three or six cycles of chemotherapy in order to achieve an optimal surgical result.

A retrospective study by Lu CH et al, supported that cytoreduction to no gross and no more than 1 residual tumors trend toward an improved survival, even though not statistically significant (P = 0.144 and 0.137, respectively) (Lu et al., 2014). The operative approach of these tumors should resemble the management of EOC, and should be undertaken in specialized institutions (del Carmen et al., 2012; Berton-Rigaud et al., 2014).

The role of lymphadenectomy in the management of OCS has not yet been clarified due to the rarity of the disease. In a recent study, a cohort of 363 patients with early stage OCS was divided into two groups; 186 patients underwent lymphadenectomy, whereas 177 did not, respectively (Wang et al., 2018). Multivariate analysis identified an independent positive association of early American Joint Committee on Cancer (AJCC) T, and lymphadenectomy with OS. A higher survival benefit was observed in the group of the patients who underwent lymphadenectomy than in those who did not in AJCC T2 (P = 0.002 for OS); nevertheless, but there was no statistically significant difference between either group in AJCC T1 disease (P = 0.582 for OS).

7.2. First line systemic treatments

In the absence of randomized data, chemotherapy options for patients with OCS are based primarily on data extrapolated from other ovarian and sarcoma subtypes, as well as retrospective data. Studies that have included patients diagnosed with different stages and treated various chemotherapy regimens within the same study, represent a major barrier and the optimal systemic treatment for patients with OCS remains elusive (Shylasree et al., 2013). Response rates ranging from 18% to 100% were noted for ifosfamide and cisplatin administered either as single agents or in combination (Rutledge et al., 2006; Sit et al., 2000; Sutton et al., 1994; Crotzer et al., 2007). Given the activity of both cisplatin and ifosfamide, several studies have compared the outcomes between patients treated with platinum-taxane combinations and ifosfamide-based regimens; nevertheless, the results remained controversial (Rauh-Hain et al., 2011; Sood et al., 1998; Inthasorn et al., 2003; Chang et al., 1995; Rutledge et al., 2006; Duska et al., 2002; Brown et al., 2004; Silverman et al., 1986; Anderson et al., 1987; Lu et al., 2014; Cicin et al., 2016; Sit et al., 2000; Crotzer et al., 2007; Leiser et al., 2007; Mok et al., 2006; Cicin et al., 2008; Petru et al., 2015; Yalcin et al., 2018; Brackmann et al., 2018).

Data from three prospective Gynecologic Oncology Group (GOG) trials demonstrated that doxorubicin is not sufficient and cisplatin as well as ifosfamide represent reasonable treatment options in OCS (Sutton et al., 1994; Tate Thigpen et al., 2004; Morrow et al., 1986). In the first study, the GOG evaluated doxorubicin at a dose of 75/m^2.

Among 10 evaluable cases with measurable disease, there was one partial response and no complete responses. Four out of 21 patients with non-measurable cancer remained clinically disease free from 2 to 45 months. There were two treatment-related deaths. The authors concluded that doxorubicin alone as first-line chemotherapy in patients with OCS was not sufficient (Morrow et al., 1986). In the second trial was conducted ifosfamide and mesna in patients who had previously received platinum-containing chemotherapy; 31 were evaluable for toxicity and 28 for response. The achieved overall response rate was 17.9% in this cohort of patients with recurrent disease (Sutton et al., 1994). In the most recent GOG trial, among 136 patients, treated with cisplatin (50 mg/m^2) every 3 weeks until disease progression or unacceptable toxicity, 44 were evaluable for treatment response (Tate Thigpen et al., 2004). One patient achieved a complete response, 8 experienced a partial response and 25 had progression of disease on the trial. The reported response rate was 20%. Median PFS and OS in 130 patients evaluable for these endpoints were 5.2 and 11.7 months, respectively (Tate Thigpen et al., 2004). This trial provided the first objective data to show that cisplatin is an active agent in the primary systemic treatment of OCS.

Retrospective studies have also supported the role of platinum based chemotherapy in the treatment of OCS. Indeed, given the efficacy of the combination of carboplatin/paclitaxel chemotherapy in the treatment of EOC, investigators have examined this regimen in the treatment of OCS. A recent study evaluated the impact of optimal cytoreductive surgery followed by platinum-taxane combination chemotherapy on the survival of patients with OCS matched to a control group of patients with high grade serous EOC (Yalcin et al., 2018). The median PFS for OCS patients was 29 months (95% CI 0–59 months) compared to 27 months (95% CI 22.6–31.3 months) in the high grade serous EOC group (P = 0.76). OS was also similar in both groups; median OS was 62 months in the OCS group compared to 82 months in the high grade serous EOC group (P = 0.53). As such, optimally debulked OCS could be considered as responsive as high grade serous EOC to platinum plus taxane combination chemotherapy, and the therapeutic approach could be identical for patients with either diagnosis. In addition, the study indicated that platinum resistance seems to be an independent prognostic factor for decreased OS in OCS patients (HR 5.05; 95% CI 2.32–11, P < 0.001). In another study of 28 OCS patients treated with first-line carboplatin and paclitaxel, 16 women (55%) had a complete response and 6 patients (23%) had a partial response. The reported median OS was 27 months and the total response rate 72% (Duska et al., 2002). However, Brown et al. demonstrated a lower objective response rate to platinum-based chemotherapy in patients with OCS when compared to those with serous EOC (Brown et al., 2004). In addition, in a large retrospective case–control study, among 50 patients with OCS, the overall response rate to carboplatin and paclitaxel based chemotherapy was 62% (Rauh-Hain et al., 2011). In this study, 18 patients (36%) with OCS experienced progression of disease, 28 (56%) achieved a complete response, and 3 (6%) had a partial response while on chemotherapy. 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) (Rauh-Hain et al., 2011).

Another recent retrospective study investigated 31 patients with OCS, treated with first-line chemotherapy, consisting of either carboplatin/paclitaxel, ifosfamide/paclitaxel, or even a different regimen, respectively (Brackmann et al., 2018). The choice was based on common clinical use of chemotherapy doublets ifosfamide/paclitaxel and carboplatin/paclitaxel on uterine carcinosarcomas. The group treated with carboplatin/paclitaxel achieved a median PFS of 17.8 months (95% CI: 4.0–31.6 months), which is statistically significant improved compared to 8.0 months (95% CI: 2.4–13.7 months) for ifosfamide/paclitaxel cohort (P = 0.025). OS was similar between groups, with a median OS of 23.2 months (95% CI: 22.0–24.4 months) for carboplatin/paclitaxel and 19.0 months (95% CI: 16.4–21.6 months) for ifosfamide/paclitaxel (P = 0.350). Taken into consideration that the platinum component of the chemotherapy doublet is critical to the effectiveness of the regimen, there was additionally compared ifosfamide/cisplatin to carboplatin/paclitaxel. No difference in median PFS (13.0 vs 17.8 months, P = 0.750) or OS (20.6 vs 23.2 months, P = 0.657) was revealed between these platinum-containing groups. Taken the lower morbidity, and cost as well as the shorter duration of admission, along with longer PFS, carboplatin/paclitaxel combination could be a reasonable first-line chemotherapy for OCS after primary surgical debulking. In the same context, Rutledge et al. revealed in their retrospective study improved median OS (P = 0.03) and PFS (P = 0.005) rates in favor of cisplatin/ifosfamide compared to carboplatin/paclitaxel when the analysis included all the cases; the median PFS was 12 months in those who received carboplatin and paclitaxel but had not been reached in patients treated with a combination of cisplatin and ifosfamide (Rutledge et al., 2006). However, the results are potentially biased by patient selection; when the analysis was limited to advanced cases, no significant survival benefit was found (P = 0.13). Furthermore, this doublet was also more toxic, with 15–20% of patients developing grade 3 or 4 neutropenia (Rutledge et al., 2006). Similarly, the report by Sit et al with 14 enrolled patients did not reveal significant difference in survival with either regimen; 19 versus 23 months for carboplatin/paclitaxel versus cisplatin/ifosfamide, respectively (Sit et al., 2000). No multivariate analysis has proved the superiority of cisplatin/ifosfamide in terms of survival after controlling for other potential confounding factors. Finally, there is an ongoing front-line phase III study for uterine and ovarian carcinosarcomas [GOG-0261, NCT00954174] aims to determine which doublet combination, carboplatin/paclitaxel or ifosfamide/paclitaxel, is superior. In summary, there is no consensus among researchers about whether cisplatin/ifosfamide is better than carboplatin/paclitaxel. In this regard, comprehensive clinical judgment is required and the choice may depend on potential tolerability and comorbidities.

Furthermore, in a study, the combination of anthracycline, alkylating agent, and cisplatin showed a good response rate but also a high toxicity (Signorelli et al., 2009). Among 41 patients with OCS, 13 were treated with a combination of cisplatin, adriamycin, and cyclophosphamide whereas 28 with a combination of cisplatin, epirubicin, and ifosfamide. Ten out of 22 (46%) evaluable for response patients achieved complete and 3 (13%) partial response (global response rate, 59%). The overall PFS and median OS were 11.8 and 20 months, respectively. Table 2 summarizes the studies of chemotherapy in the treatment of OCS.

In addition, the role of intraperitoneal chemotherapy with cisplatin and hyperthermia (HIPEC) is under consideration, and there are no published data specifically for carcinosarcoma. The combination of intravenous and intraperitoneal chemotherapy administration is also possible.

7.3. Targeted therapies

Obviously, there is a pressing effort to optimize the outcome of OCS by exploring molecular biomarkers that can provide accurate prognosis and targeted therapy. In this regard, targeting pathways like the epidermal growth factor (EGF) family (HER) and the VEGF may be beneficial in OCS. Given the rarity of the disease, there are limited data regarding the relevance of these pathways; nevertheless, the analysis of uterine carcinosarcomas for expression of potentially targetable genes, revealed expression of EGFR in 58.4% of samples, while VEGF expression was found in 100% of patients (Sawada et al., 2003). Several studies with enrollment of OCS patients have also demonstrated variable over expression of C-kit which is targeted by the agent imatinib (Sawada et al., 2003; Caudell et al., 2005; Raspollini et al., 2005; Nakayama et al., 2006; Leath et al., 2004; Menczer et al., 2005; Adams et al., 2007). The COX-2 enzyme also appears to be over expressed and may provide another opportunity for targeted therapy (Raspollini et al., 2005).

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)
(Rauh-Hain et al., 2011)/Rauh-Hain JA, et al.	2011	Retrospective	50	Carboplatin–paclitaxel	CR (28) PR (3) RR (62%)	11/24
(Sood et al., 1998)/Sood AK, et al.	1998	Retrospective	10	Platinum-based	CR (3) PR (5) RR (80%)	NR/15
(Inthasorn et al., 2003)/Inthasorn P, et al.	2003	Retrospective	6	Platinum-based	CR (2) RR (33%)	NR/23
(Chang et al., 1995)/Chang J, et al.	1995	Retrospective	24	Mostly platinum-based regimens	CR (1) PR (7) RR (33%)	NR
(Morrow et al., 1984)/Morrow CP et al.	1984	Retrospective	8	VAC	CR (2) RR (25%)	NR
(Rutledge et al., 2006)/Rutledge TL, et al.	2006	Retrospective	11	Cisplatin/ifosfamide	Improved PFS	NR/81 (at 2 years)
(Duska et al., 2002)/Duska LR et al.	2002	Retrospective	28	Carboplatin/paclitaxel	CR (16) PR (6) RR (78.6%)	NR/27.1
(Brown et al., 2004)/Brown E, et al.	2004	Retrospective	12	Platinum-based	CR (1) PR (2) RR (25%)	6.4/8.2
(Anderson et al., 1987)/Anderson B, et al.	1987	Retrospective	10	Platinum-based	CR (4) PR (2) RR (60%)	NR/16
(Lu et al., 2014)/Lu CH, et al.	2014	Retrospective	61	52 Platinum-based, 37 Paclitaxel-based	CR (19) RR (31.1%)	NR/15.8
(Cicin et al., 2016)Cicin İ, et al.	2016	Retrospective	24	Mostly platinum-based	NR	NR/20.7
(Sit et al., 2000)/Sit AS, et al.	2000	Retrospective	14	8 Platinum/ifosfamide, 6 Platinum/taxane	NR	NR/23 NR/19
(Sutton et al., 1994)/Sutton GP, et al.	1994	GOG/ Prospective	28	Ifosfamide/ mesna	CR (1) PR (4) RR (17.9%)	NR
(Crotzer et al., 2007)/Crotzer DR, et al.	2003	Prospective	8	Cisplatin/ ifosfamide	CR (7) PR (1) RR (100%)	15/17
(Leiser et al., 2007)/Leiser AL, et al.	2007	Retrospective	28	Platinum-based	CR (12) PR (7) RR (67.8%)	12/43
(Mok et al., 2006)/Mok JE, et al.	2006	Retrospective	10	Platinum-based	NR	NR/46
(Cicin et al., 2008)/Cicin I, et al.	2008	Retrospective	22	Platinum-based	NR	NR/26
(Petru et al., 2015)Petru E, et al.	2015	Retrospective	26	Platinum-based (69%)	NR	NR
(Yalcin et al., 2018)/Yalcin I, et al.	2018	Retrospective	54	Platinum/taxane	RR (42.6%)	29/62
(Brackmann et al., 2018)/Brackmann M, et al.	2018	Retrospective	31	7 Ifosfamide/taxane, 15 Platinum/taxane, 6 other agent, 3 no chemotherapy	CR (17) RR (54.8%)	8/19 17.8/23.2
(Tate Thigpen et al., 2004)/Tate Thigpen J et al.	2004	GOG/ Prospective	44	Cisplatin	CR (1) PR (8) RR (20.5%)	5.2/11.7
(Morrow et al., 1986)/Morrow CP et al.	1986	GOG/ Prospective	31	Doxorubicin	PR (1) RR (3.2%)	NR
(Signorelli et al., 2009)Signorelli M, et al.	2009	Retrospective	41	13 Platinum/ Adriamycin/ cyclophosphamide, 28 Platinum/ epirubicin/ ifosfamide	CR (10) PR (3) RR (31.7%)	11.8/20
(Harris et al., 2003)/Harris MA et al.	2003	Retrospective	32	26 Platinum-based, 6 Non-platinum based	RR (40%)	NR/8.7
(Plaxe et al., 1990)/Plaxe SC et al.	1990	Retrospective	13	Cisplatin/ doxorubicin	CR (10) PR (1) RR (84.6%)	17/NR
(Piver et al., 1982)/Piver MS, et al.	1982	Retrospective	11	CYVADIC	CR (1) PR (2) RR (27.2%)	NR
(Moore et al., 1986)/Moore M, et al.	1986	Retrospective	15	CYVADIC or CAP	CR (6) PR (3) RR (60%)	NR
(Prendiville et al., 1994)/Prendiville J, et al.	1994	Retrospective	15	Several regimens, mostly cyclophosphamide	CR (2) PR (5) RR (46.6%)	NR

Abbreviations. 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.

The estimated HER2/neu overexpression range between 25 and 56% in carcinomatous component compared to low to negligible expression in the sarcomatous element (Menderes et al., 2017). One study showed HER-2-over expression in 9 out of 16 cases, with gene amplification by fluorescence in situ hybridization (FISH) demonstrated just in one case (Sawada et al., 2003). Another study revealed HER-2-over expression in 9 of 28 cases, with gene amplification by FISH seen in four cases (Raspollini et al., 2005). The staining was stronger for the epithelial element in both studies (Sawada et al., 2003; Raspollini et al., 2005). In this regard, the role of targets such as trastuzumab (anti-HER2/neu) should be investigated. Schwab et al. demonstrated that the tyrosine kinase inhibitor (TKI) Neratibib - targeting the HER2/neu pathway - inhibited effectively tumor growth and extended survival in a mouse model at an already established safe dosage (Schwab et al., 2015). In addition, T-DM1, a combination of trastuzumab and maytansine (microtubule polymerization inhibitor) was recently demonstrated to be highly effective at targeting and killing HER2/neu OCS in a mouse model (Nicoletti et al., 2015). In addition, a novel Duocarmycin-Based HER2-Targeting Antibody-Drug Conjugate (SYD985) has been demonstrated to be active against carcinosarcomas with low/moderate or heterogeneous HER2/neu expression. Furthermore, SYD985 is significantly more potent than T-DM1, and may also be effective against the mesenchymal components of carcinosarcoma, which commonly have negligible HER2/neu expression. In a recent study, SYD985 and T-DM1 evoked similar levels of antibody-dependent cellular cytotoxicity against HER2/neu expressing carcinosarcoma cell lines in the presence of effector peripheral blood lymphocytes (Menderes et al., 2017); nevertheless, SYD985 was significantly more cytotoxic against primary carcinosarcoma cell lines with HER2/neu expression of 1+ and 3+ in absence of peripheral blood lymphocytes. Specifically, in HER2/neu 3+ cell lines, SYD985 was found to be more than 7 folds more potent than T-DM1 ($P < 0.0001$) in inducing cell death, while in HER2/neu 1+ cell lines, SYD985 was 54 folds more potent than T-DM1. In vivo data in multiple animal models harbouring carcinosarcoma xenografts with 3+ and 1 + HER2/neu expression and patient-derived-xenografts with 3 + HER2/neu expression were compatible with the in vitro results; they provided evidence of high efficacy of SYD985. Encouraging results with SYD985 in patients with locally advanced or metastatic solid tumors have recently been reported in Phase I clinical trials (NCT02277717) (Elgersma et al., 2015), and further research effort in OCS patients is warranted.

VEGF targeting has demonstrated clinical benefit in large prospective randomized trials (GOG-0218 and ICON-7) of EOC; such data are not available for OCS (Perren et al., 2011; Burger et al., 2011). Among 9 patients with OCS in a study, VEGF that is correlated with worse prognosis in several malignancies, including ovarian cancer, was expressed in 4 cases (44%) (Zorzou et al., 2005). The role of bevacizumab in the treatment of OCS requires consideration. Data from a phase II study with enrollment of women with recurrent or metastatic gynecologic carcinosarcomas, including 3 cases of OCS, demonstrated that single agent aflibercept (VEGF Trap) had minimal activity (Mackay et al., 2012).

The rate of BRCA1 and BRCA2 mutations in OCS is difficult to be determined. However, there is compelling evidence that BRCA-wild type tumors can also demonstrate a BRCA-like phenotype, also referred to as BRCAness (Glaser et al., 2015). Using massively parallel genomic sequencing in a study, 4 of 12 OCS tumors demonstrated loss of function mutations in homologous recombination genes (Pennington et al., 2014) and it is possible that PARP inhibition may be effective in this disease.

Less is known about the therapeutic role of insulin-like growth factor receptor-I (IGF-1R) inhibition in OCS; however, overexpression of IGF-1R and IGF-II was reported in a uterine carcinosarcoma (Roy et al., 2000). In EOC, the IGF-1R inhibitor BMS-754807 inhibits mesenchymal, epithelial, and hematopoietic tumor growth, with reported activity in a xenograft model (Weroha and Haluska, 2008). Therefore, there is indirect evidence suggestive of IGF pathway involvement in OCS.

Gynecologic Oncology Group (GOG)-230D, a phase II trial of pazopanib for recurrent or persistent uterine carcinosarcoma, reported that the estimated response rate of pazopanib was 0% (0/19), and the median PFS and OS were 2 and 8.7 months, respectively (Campos et al., 2014). As such, GOG did not move forward to perform a phase III trial of pazopanib for uterine carcinosarcoma. On the other hand, a recent study presented 8 cases of recurrent or persistent uterine carcinosarcoma or OCS, with reported response and clinical benefit rate of 25 (2/8) and 50% (4/8), respectively (Nishikawa et al., 2017). This apparent better clinical activity of pazopanib compared to the data of GOG-230D trial, could be explained with the disparate clinical background of patients in both studies. Thus, further evaluation of the efficacy of pazopanib is recommended. Data concerning overexpression of various receptors in OCS with the potential targeted therapies are depicted in Table 3.

8. Future directions

The expression of PD-L1 has been investigated in various malignancies; nevertheless, very limited data have been reported in EOC. Hamanishi et al (Hamanishi et al., 2007) reported the proportion of PD-L1 high expression to be 68.6% in 70 cases most of which were serous, clear cell, and endometrioid carcinomas. Darb-Esfahani et al (Darb-Esfahani et al., 2016), however, presented a higher proportion of PD-L1 expression that reached 75.7% in 202 cases of evaluable high grade serous ovarian cancer. The discrepancy in terms of PD-L1 expression from those studies could be related to different specificity of the antibodies that were used, and the difference in scoring strategies. In the majority of studies on PD-L1 expression, a cut-off of 5% of tumor cells with PD-L1 membrane staining was implemented (Faraj et al., 2015).

There have been conflicting results in the literature regarding the favorable or adverse prognostic factor of PD-L1 expression. Some studies demonstrated that PD-L1 expression is associated with unfavorable prognosis (Chen et al., 2012; Muenst et al., 2014), and other reported an improved OS in malignancies with high expression of PD-L1 (Kluger et al., 2015). In a recent study in the field of OCS, 52.6% of intraepithelial component and 47.4% of mesenchymal component were characterized by PD-L1 positive expression (Zhu et al., 2017). Interestingly enough, favorable effect of intraepithelial PD-L1 expression on outcome, as well as positive prognostic impact of PD-1 and PD-L1 mRNA expression were demonstrated at the same study. Nevertheless, the correlation between mesenchymal CD8 + T lymphocytes and PD-L1 expression was negative (Zhu et al., 2017). The biological significance of this small subpopulation of T cells could be measured by patient prognosis. Overall, the epithelial tumor cells dictate metastatic biologic behavior and the sarcomatous component predominates the prognosis. This in fact could explain the discrepant results of intraepithelial and mesenchymal PD-L1 expression on survival. It seems that PD-L1 inhibitory pathway, regulates both T-cell responses to self-antigens and viral antigens, and tumor-infiltrating CD8 + T-cell responses in OCS (Zhu et al., 2017; Shen et al., 2014).

A phase I trial (NCT00729664) of BMS-936559, an anti-PD-L1 agent, revealed 1 among 17 patients with ovarian cancer who responded; in addition 3 patients with more than 1 year of follow-up achieved stable disease (≥ 24 weeks) (Brahmer et al., 2012). Nivolumab, an anti-PD-1 antibody, demonstrated an efficacy in patients with relapsed platinum resistant ovarian cancer, with a median PFS and OS time of 3.5 (95% CI, 1.7–3.9 months), and 20 months respectively (Hamanishi et al., 2015). This relatively low overall control rate could be associated with the lack of preexisting tumor-infiltrating lymphocytes in these tumors, leading to insufficient response to PD-1/PD-L1 blockade. As such, combinations would be required to induce an anti-tumor adaptive immune response.

The differential expression and accessibility of EpCAM on

Table 3
Over-expression of various receptors in gynaecological sarcomas.

Receptor	Reference number/author	Publication year	Number of Patients	Over-expression (%)	Potential targeted therapeutic agent
EGFR	(Sawada et al., 2003)/ Sawada M, et al	2003	16	31.3	Cetuximab
	(Costa and Walls, 1996)/Costa MJ, et al	1996	82	26.8	
Her-2-neu	(Zorzou et al., 2005)/ Zorzou MP, et al	2005	9	0	Trastuzumab
	(Sawada et al., 2003)/ Sawada M, et al	2003	16	56.3	
	(Raspollini et al., 2005)/ Raspollini MR, et al	2005	24	29.2	
	(Costa and Walls, 1996)/Costa MJ et al	1996	82	96.3	
c-Kit	(Sawada et al., 2003)/ Sawada M, et al	2003	16	25	Imatinib
	(Caudell et al., 2005)/ Caudell JJ, et al	2005	38	5.2	
	(Raspollini et al., 2005)/ Raspollini MR, et al	2005	24	16.7	
	(Nakayama et al., 2006)/ Nakayama M, et al	2006	26	15.4	
	(Leath et al., 2004)/ Leath CA 3rd, et al	2004	11	100	
	(Menczer et al., 2005)/ Menczer J, et al	2005	20	0	
	(Adams et al., 2007)/ Adams SF, et al	2007	42	2.4	
Cox-2	(Raspollini et al., 2005)/ Raspollini MR, et al	2005	24	33.3	Cox-2 inhibitors
VEGF	(Zorzou et al., 2005)/ Zorzou MP, et al	2005	9	44.4	Bevacizumab
	(Mackay et al., 2012)/Mackay HJ, et al.	2012	63	Unknown	Aflibercept
PDGFR-α	(Adams et al., 2007)/ Adams SF, et al	2007	42	69	Imatinib, sunitib, nilotinib
PDGFR-β	(Caudell et al., 2005)/ Caudell JJ, et al	2005	38	100	
	(Adams et al., 2007)/ Adams SF, et al	2007	42	9.5	
Unknown	(Nishikawa et al., 2017)/ Nishikawa T, et al	2017	8	Unknown	Pazopanib

Abbreviations. EGFR: Epidermal growth factor receptor, Her-2-neu: human epidermal growth factor receptor 2, c-Kit: proto-oncogene c-Kit, Cox-2: Cyclooxygenase-2, VEGF: Vascular endothelial growth factor, PDGFR-α: platelet-derived growth factor receptor α, PDGFR-β: platelet-derived growth factor receptor β.

metastatic/chemotherapy-resistant carcinosarcoma cells compared to normal tissues could offer a new therapeutic perspective with Bispecific T cell engagers (BiTE)-based immunotherapy. The EpCAM expression in solid tumors guided to the development of solitomab which acts by engaging resting polyclonal CD8+ and CD4 + T cells for highly potent redirected lysis of target tumor cells (Brischwein et al., 2006). A study that evaluated EpCAM expression in primary carcinosarcomas cell lines and tumor cells in pleural fluid from patients with gynecologic carcinosarcomas, revealed remarkable solitomab antitumor activity (Ferrari et al., 2015). In addition, a trifunctional anti-EpCAM antibody (catumaxomab), administered intraperitoneally, decreases tumor burden, and ascites accumulation and has been approved in Europe for the treatment of chemotherapy refractory ovarian cancer (Burges et al., 2007).

A recent study demonstrated that carcinosarcomas have mutation profiles similar to those found in epithelial uterine and ovarian cancers (Zhao et al., 2016). A significantly increased frequency of somatic mutations in histone genes and amplifications of the histone gene locus on chr6p, implied that these mutations participate in the development of the sarcomatous elements of these tumors. It is considered that such mutations would guide to modifications in chromatin conformation and reconstruction of gene regulation. In this context, treatments targeting genes and pathways within the carcinomatous components, including PIK3CA, CCNE1, and MYC, may demonstrate efficacy in the treatment of both carcinomatous and sarcomatous elements.

9. Conclusions

OCS are histologically distinct tumors with aggressive tumor biology, associated with worse survival outcomes. Due to the rarity of this entity, management recommendations have been made largely based on the experience collected from retrospective studies. The mainstay of treatment remains cytoreductive surgery followed by platinum-based chemotherapy. The addition of paclitaxel or ifosfamide to platinum in first-line treatment should be based on patient factors and associated toxicities. Further work is needed to examine the patterns of chemotherapy use in women with OCS.

The dismal prognosis of these patients give the motivation to conduct multicenter studies and introduce new and experimental therapies. Further research is needed to identify and target molecular drivers to improve the treatment and survival. PD-L1 expression, and CD8 + T lymphocytes in particular, are biologically and clinically important in OCS. PD-L1 may therefore be used as a new target in designing T cell-based immunotherapy.

Declaration of interest

We declare that we have no conflicts of interest in the authorship of this contribution.

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