EJGO European Journal of Gynaecological Oncology

Carcinosarcoma of the ovary: a single institution experience and review of the literature

M.J. Kanis, V. Kolev, J. Getrajdman, K. Zakashansky, C. Cohen, J. Rahaman

Mount Sinai School of Medicine, New York, NY (USA)

Summary

Purpose: To evaluate the management and outcome in patients with advanced stage primary carcinosarcoma (CS) of the ovary in a single institution. *Materials and Methods:* The authors performed a retrospective analysis of all patients treated for CS of the ovary between 1994 and 2011. The medical records, operative reports and pathology records were abstracted for baseline characteristics, surgical staging, degree of cytoreduction and chemotherapy regimens used. Standard statistical methods for analysis of the data were used. *Results:* A total of 33 patients with ovarian CS were identified. Of these, 28 records were available for analysis. One patient was Stage I (3.5%), two were Stage II (11.1%), 20 were Stage III (71.4%), and five (17.9%) were Stage IV. The early stage (Stage I and II) patients were excluded from analysis. Of the 25 advanced stage (III and IV) patients, 21 (84.0%) were optimally cytoreduced to a residual disease of < one cm and four (16.0%) were suboptimally cytoreduced. The median progression free survival (PFS) and overall survival (OS) were ten and 21 months, respectively, for advanced stages. Twenty-one (75%) patients received adjuvant chemotherapy and 62% (13 of 21) of treated patients received paclitaxel/carboplatin (T/C) as first-line chemotherapy. The median PFS and OS were 15.6 and 31.7 months, respectively, for those treated with T/C. There was no difference in PFS ($p = 0.42$) and OS ($p = 0.91$) between the patients who received T/C *vs.* other chemotherapy regimens as a first-line adjuvant chemotherapy. Patients with optimal cytoreduction had an improved PFS compared to those with suboptimal cytoreduction (ten *vs.* four months $p = 0.015$); however, there was no difference in OS (21 *vs.* 13 $p = 0.117$). The two-year OS was 48.0%. In the preset study, PFS was improved in patients who were optimally cytoreduced at the time of diagnosis. *Conclusion:* T/C is an active regimen in the treatment of ovarian CS and has the potential to be the backbone for addition of biologic targeted therapies in the future. For advanced ovarian CS the authors recommend optimal cytoreductive surgery followed by T/C chemotherapy.

Key words: Ovarian carcinosarcoma; Carboplatin; Cytoreductive surgery; Paclitaxel.

Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer. There are an estimated 22,000 new cases with 14,000 deaths in the United States for 2014 [1]. Carcinosarcomas (CS) are rare tumors of the gynecologic tract, comprising approximately 1% of all ovarian malignancies [2, 3]. More frequently, they arise from the uterus, but cases of the vagina, peritoneum, and cervix have been documented as unusual primary sources. Formerly termed malignant mixed Müllerian tumors (MMMT), they are comprised of epithelial (carcinomatous) and sarcomatous (mesenchymal) components. The proposition that it is the epithelial component that undergoes sarcomatous differentiation is supported by in vivo studies. CS are further characterized as homologous or heterologous based on the origin and histology of the mesenchymal components such as cartilage or muscle [4, 5].

Patients with ovarian CS present clinically similarly to those with epithelial ovarian cancer (EOC) with non-specific complaints including abdominal distention, pain, and weight changes. However, those with CS tend to be of older age and have poorer prognoses, reflecting the aggressive nature of disease. Prognostic factors include age, stage, size of residual tumor after surgical cytoreduction, and performance status [2-8]. Literature review initially showed a survival benefit in homologous tumors compared to heterologous, although more recent studies question this theory [8]. Compared to EOC, survival is significantly lower stage for stage and the overall five-year survival for ovarian CS ranges from 7-20% [3]. Furthermore, at time of diagnosis, 90% of patients will have disease beyond the ovary, and 75% will have pelvic or distant metastases (Stage III or IV) due to serosal and peritoneal seeding [4].

Given the low incidence of this disease, there are few randomized trials available, and surgical and chemotherapeutic therapy is frequently extrapolated from data available from epithelial ovarian cancer. Most Gynecologic Oncology Group (GOG) trials exclude tumors with CS histology, particularly those of ovarian origin. However, it has been demonstrated that a survival advantage is conferred to those who undergo optimal cytoreduction and tumor debulking [3, 4, 9, 10]. There is no standardized treatment protocol for this disease; however, most gynecologic oncologists recommend treatment with chemotherapy, similar to the man-

Revised manuscript accepted for publication February 10, 2015

Table 1. — *Patient characteristics, surgical and medical treatments, and outcomes of those with ovarian carcinosarcoma.*

Patient No.	Age	Stage	Optimal debulking status <1 cm	Chemo protocol	PFS (mos)	OS (mos)
1	67	IIIB	Yes	I/Cs	143	178
2	75	IIIC	Yes	T/C	16	27
3	64	IIIB	Yes	T/C	28	49
4	54	IIIB	Yes	I/Cs	10	30
5	72	IV	Yes	T/C	14	45
6	63	IV	Yes	T/C	4	17
7	55	IIIC	Yes	T/C	28	106
8	57	IIIB	Yes	T/C	6	14
9	57	IIIC	Yes	T/C	1	1
10	59	IIIC	Yes	I/Cs	8	15
11	77	IIIC	Yes	None*	1	1
12	55	IIIC	Yes	T/C	21	21
13	59	IIIC	Yes	I/Cs	8	8
14	55	IIIC	Yes	T/C	17	53
15	66	IIIC	Yes	None*	1	1
16	74	IIIC	Yes	T/C	36	36
17	80	IIIC	Yes	T/C	10	10
18	73	IV	Yes	T/C	8	8
19	70	IV	Yes	G/D	16	31
20	73	IIIC	No	None*	2	2
21	84	IIIC	No	None*	4	4
22	69	IIIC	No	I/Cs	28	28
23	71	IIIC	No	T/C	14	22
24	56	IIIC	Yes	I/Cs	1291	1291
25	66	IIIC	Yes	I/Cs	42	42

*Four patients did not receive chemotherapy due to rapid progression of disease.
T/C = taxol/carboplatin; I/Cs = ifosfamide/cisplatin;
G/D= gemcitabine/docetaxel.

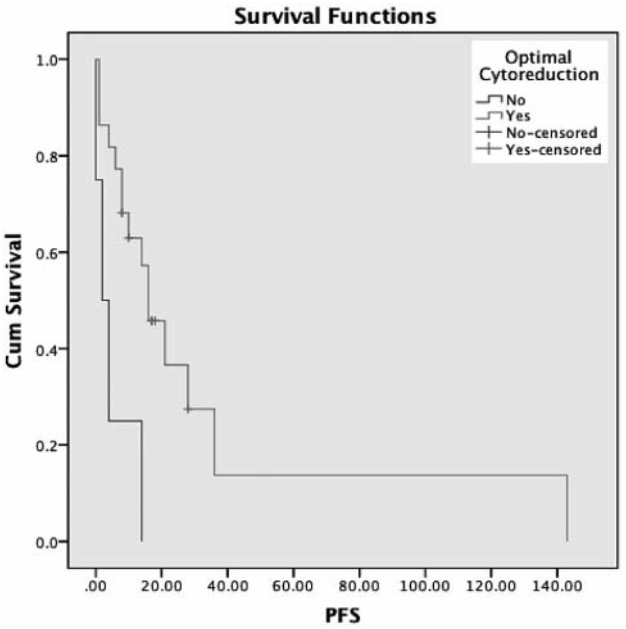

Figure 1. — Survival analysis. Optimal cytoreduction improved PFS but not OS.

agement of EOC or uterine CS. While EOCs are best treated with a platinum and taxane combination with excellent response of up to 75-80%, a lower response rate and higher rate of recurrence in CS has been shown compared to EOCs [3, 4, 9]. Alternative chemotherapeutic options such as ifosfamide-based combinations have been used, based on established data from uterine CS [11].

In this paper, the authors offer their experience in treating advanced stage CS of the ovary.

Materials and Methods

After approval by the Institutional Review Board, the authors performed a retrospective analysis of all patients treated for CS of the ovary between 1994 and 2011. Data from electronic medical records was abstracted for baseline characteristics including age, histology, tumor grade, stage, type of chemotherapy, and recurrences. Data regarding surgical staging and extent of cytoreduction was also obtained from the operative report. Optimal cytoreduction was defined as residual disease less than one cm at the end of the procedure. In all cases, surgery was performed by Board certified gynecologic oncologists at a major academic medical center with comprehensive staging and an aggressive attempt at optimal cytoreduction. A histologic diagnosis of CS was made by slide review by a gynecologic pathologist. Progression free survival (PFS) was defined as the interval from the date of the primary surgery to the date of documented recurrence. Overall survival (OS) was defined as the date of surgery to the date of death or date of last follow-up. Responses following chemotherapy were assessed by Response Evaluation Criteria in Solid Tumors (RECIST). Standard statistical methods for analysis of the data were used with SPSS 19.

Results

A total of 33 patients with ovarian CS were identified. Five patients were lost to follow-up after surgery. All patients underwent surgical cytoreduction and comprehensive staging based on the FIGO system. One patient was Stage I (3.5%), two were Stage II (11.1%), 20 were Stage III (71.4%), and five (17.9%) were Stage IV (see Table 1). Three patients that were Stage I and II were excluded in treatment and survival analysis. Twenty-five patients with advanced stage (III and IV) were included in final analysis. The mean age of diagnosis was 68 years.

Cytoreduction

Of the 25 patients, 21 (84%) were optimally cytoreduced, defined by residual disease less than one cm. Four (16%) patients were suboptimally cytoreduced. Median survival was 15 and 13 months for optimal and suboptimal debulking, respectively. There was no statistically significant difference in the OS based on the cytoreductive status ($p = 0.117$); however, there was a difference in the PFS ($p = 0.015$) (Figure 1).

Chemotherapy

Twenty-one (75%) patients received chemotherapy and four did not receive any adjuvant treatment due to rapid progression of disease and prohibitive co-morbidities with progression and death within four months of surgery (Table 1). Two patients had suboptimal cytoreduction with residual disease involving the bowel and mesentery. Two patients decompensated postoperatively and were not candidates to receive chemotherapy. Twenty (95%) patients received a platinum-based chemotherapeutic agent as first line treatment. Thirteen (62%) received T/C as first-line treatment. Seven patients received ifosfamide/cisplatin, and one was treated with gemcitabine and docetaxel. The median PFS and OS were 15.6 and 31.7 months, respectively, for those treated with T/C. There was no difference in PFS ($p = 0.197$) and OS ($p = 0.453$) between the patients who received T/C *vs.* other regimens as a first-line adjuvant chemotherapy.

Survival

The median PFS and OS were ten and 21 months, respectively, for all stages. PFS and OS for Stages III and IV were eight and 14 months, and 15 and 18 months, respectively. Only three out of 23 (13.0%) patients survived five years. The two-year survival was 48%.

Table 2. — *Effect of surgical cytoreduction on survival from retrospective studies in primary ovarian carcinosarcoma.*

Author	Publication Year	Definition of optimal debulking	Number of patients	Impact of optimal debulking on survival
Terada [29]	1989	< 1.5 cm	15	None
Plaxe [7]	1990	< 2 cm	15	None
Barakat [12]	1990	< 2 cm	24	None
Ariyoshi [30]	2000	< 2 cm	14	None
Leiser [31]	2007	< 1 cm	29	None
Silasi [18]	2008	< 1 cm	22	None
Morrow [20]	1986	NR	30	Improved PFS
Anderson [22]	1987	NR	14	Improved PFS
Muntz [10]	1994	< 2 cm	23	Improved PFS
Sood [6]	1998	< 1 cm	41	Improved PFS
Duska [15]	2002	< 2 cm	14	Improved PFS
Harris [32]	2003	< 2 cm	40	Improved PFS
Rauh-Hain [3]	2011	< 1 cm	50	Improved PFS
Brown [4]	2004	< 2 cm	41	Improved OS
Rutledge [17]	2006	< 1 cm	19	Improved OS
Chun [19]	2011	No visible tumor	40	Improved OS
Loizi [29]	2011	< 2 cm	13	Improved OS
Yi [33]	2011	< 2 cm	16	Improved OS
Current series	2015	< 1 cm	23	Improved PFS

NR = not recorded.

Discussion

Ovarian CS are more rare than their uterine counterparts, representing an aggressive cancer that is routinely widely metastatic at the time of initial presentation. Patient characteristics from the present study are similar to that of other published reports. The average age of presentation was 68 years, and 85% of the present patients had advanced stage of disease at presentation, both of which are consistent with other published series. The median survival was 21 months in this study with a 13% five-year survival rate, which is higher than the reported median survival of 8-16 months [4, 11]. Barakat *et al.* found a median survival of 104.8 months in those with Stage I or II disease and only 9.5 months in those with Stage III or IV disease in a review of 31 patients at Memorial Hospital [12]. Similarly, Barnholtz *et al.* reported a median survival of 64 months for early stage and 13 months for advanced stage disease in a retrospective analysis of the SEER database of 382 patients with ovarian CS [13].

Cytoreduction

There is no uniform agreement about the optimal treatment of these malignancies except that achieving optimal debulking at the time of initial surgery is associated with significantly improved overall survival. [3-4, 6, 10, 14-19]. The present authors found 84% of their patients were optimally cytoreduced to less than one cm of residual disease, with a statistically significant PFS of ten months, which is higher than reported in the literature [10, 15-22]. Duska *et al.* found that 50% of were optimally cytoreduced to less than two cm of residual disease leading to an improved PFS but not OS [15]. Brown *et al.* found a 43% optimal debulking rate to less than two cm. Among 19 patients with Stage III disease, median survival was 14.8 months with a 39% two-year survival, compared to a 0% two-year survival and three-month median survival in those with suboptimal disease [4]. Yi *et al.* found an OS advantage with optimal cytoreduction, although the majority of retrospective reviews only found an improved PFS, similar to the present results [4, 16-18]. Table 2 provides a summary of the reported impact of surgical debulking on survival.

Not only do many of these studies define optimal cytoreduction as residual disease less than two cm, compared to the present one cm, they also report a lower optimal debulking rate. This may explain the lower survival rate found in the literature, particularly of advanced stage disease. Surgical cytoreduction, therefore, may be a crucial factor to improving PFS.

Chemotherapy

Due to the rarity of these tumors, there are few reports investigating ideal chemotherapy regimens. There is no standardized treatment protocol for this disease; however, most gynecologic oncologists recommend treatment with chemotherapy, similar to the management of EOC or uterine CS [23, 24]. In uterine CS, GOG trials have demonstrated response rates of 25% for ifosfamide, 18% for paclitaxel, and 17% for cisplatin as single agents [25].

Table 3. — *Use of paclitaxel/carboplatin as first line treatment in ovarian CS in all stages.*

Author	Year	Study type	# of patients receiving T/C	PFS/OS (months)	Statistical significance
Sit [11]	2000	Retrospective	3	NR/19	NR
Duska [15]	2002	Retrospective	13*	NR/27.1	NR
Silasi [18]	2008	Retrospective	4	6/38	No
Loizzi [29]	2011	Retrospective	5	11/17	No
Chun [19]	2011	Retrospective	16	35/53	Yes
Dai [16]	2011	Retrospective	4	3.8/NR	Yes
Current series	2015	Retrospective	13	14.7/30	No

*Rauh-Hain (2011) series was an update of the series by Duska (2002), however the number of patients receiving T/C was not specified. NR = not recorded.

GOG-0108 evaluated the combination of ifosfamide-mesna with or without cisplatin as first-line therapy in patients with advanced, persistent, or recurrent uterine CS. The combination regimen demonstrated a significantly improved overall response rate (54%) when compared to the single-agent regimen (36%) [26].

Findings from GOG-0161 were recently published. There was a 31% decrease in the adjusted hazard of death [hazard ratio (HR) = 0.69; $p = 0.03$] and a 29% decrease in the adjusted hazard of death or progression (HR = 0.71; $p = 0.03$) in those patients receiving paclitaxel-ifosfamide /mesna-growth factor relative to ifosfamide alone for uterine CS [27]. Thus, paclitaxel /ifosfamide became the standard arm for future GOG studies testing combination chemotherapy for uterine CS. The GOG Phase II trial (GOG-0232B) formally tested the efficacy of T/C in 55 patients with advanced uterine CS. The proportions of patients with confirmed complete and partial responses were 13% and 41%, respectively, resulting in a total overall response rate of 54% (95% CI, 37% to 67%) with a median PFS of 7.0 months and median survival of 14.4 months [28]. Thus, the GOG current Phase III trial for uterine CS (GOG 261) was designed to test the efficacy of T/C compared to paclitaxel/ifosfamide and also allowed ovarian CS to be enrolled.

In ovarian CS, Sutton *et al.* reported a 17.9% response rate with ifosfamide and mesna and Morrow *et al.* demonstrated that doxorubicin had limited efficacy with only a 10% response rate [20-21]. More recently, a GOG study treated 136 patients diagnosed with ovarian CS with cisplatin 50 mg/m^2 every three weeks as a single agent until disease progression or unacceptable toxicity, and demonstrated a median survival of 11.7 months [19]. The response rate was 20%, similar to that in uterine CS. Subsequently, various studies on small sample sizes have documented responses to platinum-based chemotherapy ranging from 50-100% with a median survival of 16-18 months [2]. At Mount Sinai Hospital, Plaxe *et al.* reported on 15 cases of advanced ovarian CS cases, 13 of which received doxorubicin and cisplatin chemotherapy with an 85% progression-free response rate and a median survival of 16 months.

In the last two decades, reports of the utility of T/C or other platinum/taxane chemotherapy for ovarian CS have emerged. Sit *et al.* in 2000 reported a 19-month survival rate using the T/C in six patients, although it was first line chemotherapy in only three [11]. Duska *et al.* in 2002 found a 55% complete response rate and 6% partial response rate among 16 patients in Boston with Stage I-IV disease treated with first line platinum/taxane chemotherapy [15]. Furthermore, Chun *et al.* in 2006 reviewed 40 patients of whom 16 were treated with T/C and two patients received paclitaxel plus cisplatin. They concluded that the use of platinum and taxane improves outcome. PFS improved from 12 to 35 months and OS from 21 to 53 months [19].

Silasi *et al.* recently published their experience and review of the literature (nine other studies included) for a total of 417 patients. They compared the six patients receiving ifosfamide/cisplatin to the group of four patients receiving paclitaxel/carboplatin and there was no statistically significant difference in survival [18, 21]. Rauh-Hain *et al.* retrospectively reviewed 50 patients (an update of the Boston experience) with ovarian CS and reported a 62% overall response rate to platinum/taxane combination chemotherapy (although the number of patients receiving T/C was not specified). Interestingly, they compared responses to platinum/taxane chemotherapy for ovarian CS to patients with EOC and found a lower response rate at six-months of treatment in the CS cohort [3].

While multiple protocols were used, the majority of patients (13 of 21) treated at the present institution did receive T/C following surgical debulking. Table 3 is an updated list of the reported use of T/C as first line treatment in ovarian CS in all stages. Because ovarian CS is such a rare entity, the data on the efficacy of chemotherapy will always be limited. The data from the present series is therefore quite important and adds to the growing body of data that suggests that T/C is an active and reasonable option in the treatment of ovarian CS.

Biologic "targeted therapies" have been successful in the treatment of other cancers and might have utility in improving outcomes in ovarian CS. Overexpression of several receptors and genes have been documented in ovarian CS including EGFR (30%), c-kit (16-25%), Her-2-neu (40-56%), Cox-2 (33%), and VEGF (44%). The biologic agents directed at these targets may hold promise and include cetuximab (EGFR), imitinib (c-kit), traztuzamab (Her-2Neu), and bevacizumab (VEGF)[18]. In other disease sites these biologic agents have already demonstrated efficacy as single agents as well as in combination with chemotherapy. The present authors anticipate that the next generation of clinical trials in ovarian CS will address the incorporation of these biologic agents and that T/C has the potential to emerge as the best backbone chemotherapy regimen.

Conclusion

Most patients with ovarian CS present with advanced stage disease and require optimal cytoreductive surgery followed by adjuvant chemotherapy. In the present study, PFS was improved in patients who were optimally cytoreduced at the time of diagnosis. T/C is an active regimen in treatment of CS and has the potential to be the backbone chemotherapeutic regimen for the addition of biologic targeted therapies.

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Address reprint requests to:
M.J. KANIS, M.D.
Mount Sinai School of Medicine
1176 Fifth Ave
Box 1173
New York, NY 10029 (USA)
e-mail: mjkanis@gmail.com