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Efficacy and tolerability of combination cisplatin and ifosfamide chemotherapy with vaginal cuff brachytherapy in the first line treatment of uterine carcinosarcoma

M.M. Abu-Khalaf[1], M.A. Raza[2], C. Hatzis[1], H. Wang[3], K. Lin[4], S. Higgins[5], E. Ratner[6], D.A. Silasi[6], M. Azodi[6], T.J. Rutherford[6], A.D. Santin[6], P.E. Schwartz[6]

[1] Section of Medical Oncology, Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT
[2] Regional Cancer Center, ProHealth Care Medical Associates, Milwaukee, WI
[3] Department of Hematology and Oncology, Harvard Vanguard Medical Associates, Boston, MA
[4] Department of Obstetrics & Gynecology, Division of Gynecologic Oncology, University Texas Southwestern Medical Center, Dallas, TX
[5] Department of Therapeutic Radiology, Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT
[6] Department of Obstetrics, Gynecology &, Reproductive Sciences. Section of Gynecologic Oncology, Yale University School of Medicine, Yale Comprehensive Cancer Center, New Haven, CT (USA)

Summary

Purpose of investigation: A retrospective study to evaluate six cycles of cisplatin 40 mg/m^2 on day 1 and ifosfamide 1,200 mg/m^2 daily on days 1 to 4 with Mesna every four weeks as first line treatment for 29 patients with a diagnosis of uterine carcinosarcoma. *Materials and Methods:* A total of 23 of 29 patients received high dose rate intracavitary vaginal cuff brachytherapy (VCBT) with two fractions of seven Gy each. Median age was 65 years (range 40-82); 13 (44.8%) had Stage I disease, three (10.3%) had Stage II, eight (27.6%) had Stage III, and five (17.2%) patients had Stage IV disease. *Results:* Most common toxicities were anemia grade 1 (35%)/grade 2 (45%), and neutropenia grade 3 (17%)/grade 4 (6.9%). Eleven dose modifications, four treatment discontinuations, and one patient withdrawal occurred. At a median follow up of 45 months (range 9 to 144), Progression free survival (PFS) was 20% and overall survival (OS) was 40% for Stage IV, PFS 75% and OS 62.5% for Stage III, compared to a PFS 75 % and OS 72.2% for Stages I-II. Median OS for the entire group was 12.43 years (95% CI 3.69 to inf); for Stage I-III 12.4 years (6.1 to inf), and for Stage IV 15.6 months (95% CI 9.4 to inf). *Conclusions:* Cisplatin and ifosfamide chemotherapy with VCBT was well tolerated and has promising activity in uterine carcinosarcoma.

Key words: Cisplatin; Ifosfamide; Vaginal brachytherapy; Uterine carcinosarcoma.

Introduction

Uterine carcinosarcoma, also termed malignant mixed Müllerian tumor, is a rare biphasic gynecologic neoplasm consisting of epithelial and mesenchymal tissues. It carries a poor prognosis due to a tendency for metastasis and a high rate of recurrence. The annual incidence of uterine carcinosarcoma is one to three per 100,000 women in the US. It comprises 1.5% of corpus uteri cancers though 16.4% of deaths from uterine malignancy are attributed to carcinosarcoma [1, 3]. It is currently believed that the carinomatous component of the neoplasm primarily determines tumor behavior. Uterine carcinosarcomas are categorized as either homologous type or heterologous type based on whether the sarcomatous component arises from tissue native or non-native to the uterus [4]. Although approximately half of the patients diagnosed with uterine carcinosarcoma have Stage I or II upon presentation, up to 53% of these tumors recur and the five-year survival rate in Stage I disease rarely exceeds 50% [5, 6]. Few patients with metastatic, extra-uterine disease at the time of diagnosis have long-term survival despite therapy. Given these poor outcomes, studies have focused on the development of effective chemotherapy.

Risk factors for the development of uterine carcinosarcoma are age (median age at time of diagnosis is 62 years), obesity, nulliparity, prolonged use of exogenous estrogen or tamoxifen, and prior pelvic radiation [7-9]. African-American women have a two- to three-fold higher risk of developing uterine carcinosarcoma, however, Caucasian women still account for 60% to 70% percent of all cases in large case series [4, 10]. Clinical symptoms of carcinosarcomas are often non-specific and may include abnormal vaginal bleeding (sometimes with resultant anemia), a vaginal discharge of blood or cellular debris, pelvic or abdominal pain, and a palpable mass on examination with an enlarged uterus. Histology is required to confirm the diagnosis of uterine carcinosarcoma, and endometrial sampling does not always result in the proper diagnosis; thus some cases are confirmed

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only after hysterectomy [11]. Up to 30% to 40% of women have advanced disease (extra-uterine) at time of diagnosis and stage remains the most significant prognostic factor. Factors affecting prognosis include the extent of myometrial invasion, adnexal or serosal disease, lymphovascular invasion, and lymph node involvement [12].

Primary standard treatment for curative stage disease is an extrafascial total hysterectomy and bilateral salpingo-oophorectomy with pelvic/para-aortic lymphadenectomies. A high rate of relapse after surgery alone (up to 60%, local failure and distant metastatic disease) has led to the use of sequential adjuvant radiotherapy and chemotherapy [13], however, consensus guidelines remain under investigation as to what is the optimal adjuvant therapy

Adjuvant radiotherapy has been shown to decrease the risk of local recurrence in early stage disease though with mixed data regarding improvement in overall survival (OS), and it is uncertain what method of RT is most effective and best tolerated [14]. Data regarding single agent and combination chemotherapy has also been published with cisplatin-based combinations showing improved survival endpoints [15, 16]. Ifosfamide, cisplatin, and paclitaxel have been shown to have cytotoxic activity in uterine carcinosarcoma. Ifosfamide is the most active agent with a response rate of 32% to 36% [17, 18]. The other two agents are less effective. Paclitaxel has a response rate of 21.2%, while cisplatin has a response rate of 18% to 19% [19-21].

The present center has previously investigated the use of etoposide, cisplatin, and doxorubicin for the treatment of uterine carcinosarcoma in both early stage (Stages I and II), advanced (Stages III and IV), and recurrent carcinosarcoma with encouraging findings. For early-stage carcinosarcoma, the two-year OS was 92%. For advanced and recurrent carcinosarcoma, two-year OS was 33% and two-year progression free survival (PFS) was 20%. Overall, the combination chemotherapy appeared to be highly effective in early-stage carcinosarcoma [22]. The purpose of this retrospective study is to report the efficacy and tolerability of combination cisplatin and ifosfamide chemotherapy with vaginal cuff brachytherapy (VCBT) in the first line treatment for patients with a diagnosis of uterine carcinosarcoma treated at the Yale Comprehensive Cancer Center.

Materials and Methods

Patients

The medical records of 54 patients diagnosed with uterine carcinosarcoma at the Yale Comprehensive Cancer Center between 1996 and 2008 were retrospectively reviewed. Patients who received palliative care only (n=4), patients who were not treated at the present center after initial diagnosis (n=5), and patients who received a chemotherapy regimen other than the study regimen cisplatin/ifosfamide (n= 16), were excluded from this analysis. The data for our retrospective review is derived from the remaining 29 patients. Patients had Stage I – IV disease (Stage I n=13, Stage II n=3, Stage III n =8, and Stage IV n=5). The diagnosis of a uterine carcinosarcoma was confirmed by detailed pathology review of biopsy and surgical specimens at the present institution. Patients were identified through the Tumor Board Registry of Yale-New Haven Hospital. Demographic and clinical data included the tumor stage, histologic grade, chemotherapy dose, number of cycles received, required dose reductions, and treatment related toxicities. Of the total of 29 identified patients treated with cisplatin and ifosfamide, 23 of 29 patients received VCBT. Toxicity results were available for all patients who received chemotherapy. PFS was calculated as time from the initial diagnosis to date of disease recurrence, progression or last contact. OS was calculated as the time from the initial diagnosis to the date of death or date of last documented contact for living patients.

Pre-treatment evaluation

A gynecologic oncologist, and in most cases a radiation oncologist, examined the patients and a clinical examination, pathology review, diagnostic imaging interpretation, laboratory findings, and treatment plan were documented in the patient's record. Staging evaluation including laboratory data and diagnostic imaging were available for all cases. The International Federation of Obstetricians and Gynecologists (FIGO) staging of uterine cancer was used.

Treatment

Planned treatment included cisplatin 40 mg/m^2 on day 1 and ifosfamide 1,200 mg/m^2 daily on days 1 to 4 with Mesna every four weeks for six cycles. Prior to each infusion, patients had laboratory testing which included a complete blood count, hepatic function, and renal function tests. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better. Patients were evaluated for toxicity prior to each infusion. A total of 23 patients received high-dose rate intracavitary VCBT delivered with a vaginal cylinder. These patients were treated with high-dose rate intracavitary vaginal brachytherapy as per the present institutional protocol. For patients who received chemotherapy, two fractions of seven Gy each were delivered to the upper two-thirds of the vagina, to a depth of 0.5 cm. The first fraction was delivered approximately one week before and the second one week after the second cycle of chemotherapy.

Results

Median age of patients was 65 years (range 40-82); 13 patients (44.8%) had Stage I disease, three patients (10.3%) had Stage II, eight patients (27.6%) had Stage III, and five patients (17.2%) had Stage IV disease. A total of 11 instances of dose modification were recorded; six were for ifosfamide, three for cisplatin, and two for both ifosfamide and cisplatin (Table 1). Ifosfamide dose reduction was due to fatigue (n =1), hematuria (n= 2), nausea/vomiting (n=1), febrile neutropenia (n=2), or physician's decision (n=2). Cisplatin dose reduction was due to renal toxicity (n=3) or physician's decision (n=1). Table 2 summarizes treatment related toxicities as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v 2.0 (NCI CTC V2.0). Anemia was the most common grade 1 (35%) and grade 2 toxicity (45%), and neutropenia was the most common grade 3 (17%) and grade 4 toxicity (6.9%). Four patients had treatment discontinuation for the following toxicities: grade 3 fatigue (five cycles completed): grade 3 neutropenia and grade 2 renal dysfunction (five cycles); grade 2 delirium (one

Table 1. — *Dose modifications.*

# of required dose reduction	dose reduction	Cycle # with dose reduction	Toxicity
1	I 1200 mg/m^2/d on days 1-3	5-6	Grade 3 nausea/vomiting
1	I 1200 mg/m^2/d on days 1-3	3-6	Grade 3 fatigue
1	I 1200 mg/m^2/d on days 1-3	1	Grade 2 hematuria
1	I 1200 mg/m^2/d on days 1-3	5	Grade 1 hematuria
1	C 20mg/m^2 on day 1	1-2	Physician's decision
1	C 32mg/m^2 on day 1	3-6	Grade 1 renal toxicity
1	C 32mg/m^2 on day 1	1-2	Baseline renal toxicity
2	1: I 1200 mg/m^2/d on days 1-3	2-6	Neutropenic fever
	2: C dose reduction (unknown dose)	6	Grade 1 renal toxicity
2	1: I 1200 mg/m^2/d on days 1-3	2-5	Neutroenic fever and grade 3 pulmonary edema
	2: I 1200 mg/m^2/d on day 1 I 1500 mg/m^2/d on day 2	6	Physician's decision

I = Ifosfamide C = Cisplatin

Table 2. — *Grade 1-4 toxicities.*

Toxicity	Grade (NCI CTC v2.0): (#/%)			
	1	2	3	4
Neutropenia	5 (17%)	3 (10%)	5 (17%)	2 (6.9%)
Anemia	10 (35%)	13 (45%)	4 (14%)	0
Thrombocytopenia	6 (21%)	0	1 (3.4%)	0
N/V	5 (17%)	3 (10%)	1 (3.4%)	0
GI, other	2 (6.9%)	1 (3.4%)	1 (3.4%)	0
Renal	2 (6.9%)	2 (6.9%)	0	0
GU, other	7 (24%)	1 (3.4%)	1 (3.4%)	0
Cardiac	0	2 (6.9%)	1 (3.4%)	0
Pulmonary	0	1 (3.4%)	1 (3.4%)	0
Neurotoxicity	0	6 (21%)	2 (6.9%)	0
Fever	0	1 (3.4%)	0	0
Fatigue	4 (14%)	2 (6.9%)	2 (6.9%)	0

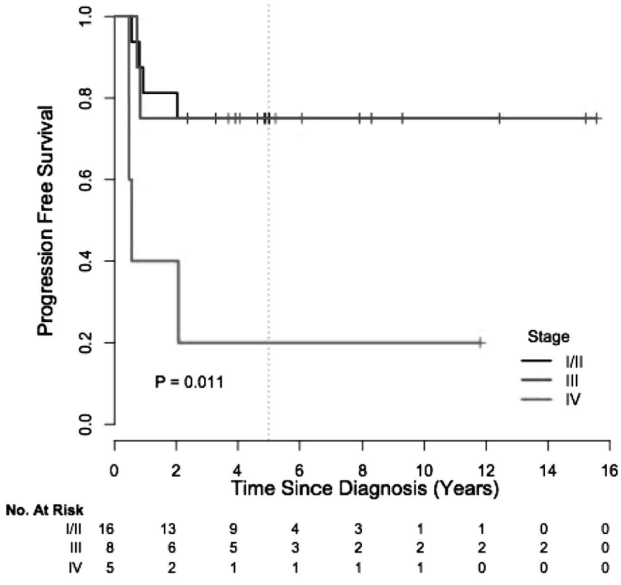

Figure 1. — Progression free survival by stage.

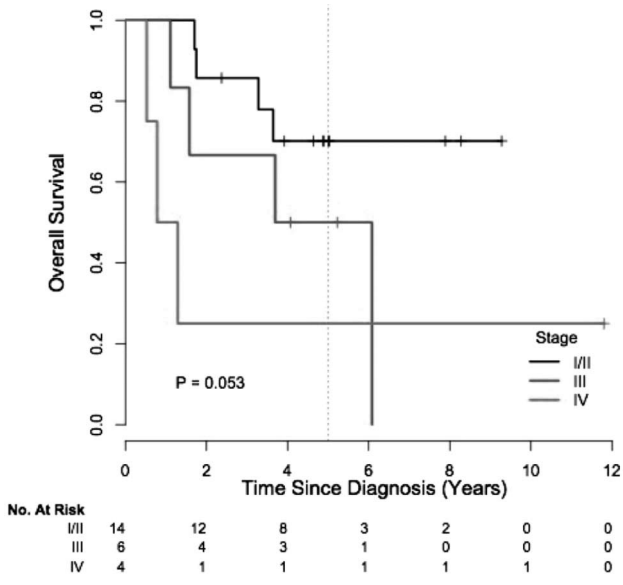

Figure 2. — Overall survival by stage.

cycle); grade 3 cardiac event and grade 2 renal dysfunction (two cycles). One patient withdrew from treatment.

The median PFS was not reached for Stages I-III. Median PFS was 6.7 months for Stage IV patients (95% CI 5.7 to inf). The median OS for the entire group is 12.43 years (95% CI 3.69 to inf); for Stage I-III was 12.4 years (6.1 to inf) and for Stage IV was 15.6 months (95% CI 9.4 to inf). At a median follow up of 45 months (range 9 to 144 months), PFS was 67.9% and OS 63.7% for all stages (Figures 1 and 2). PFS was 20% and OS was 40% for Stage IV, and the PFS was 75% and OS 62.5% for Stage III, compared to a PFS of 75 % and OS 72.2% for Stages I-II (Table 3).

Table 3. — *Progression free survival and overall survival for Stages I-II, III, and IV.*

	PFS at 45 months		OS at 45 months	
	Mean	95% CI	Mean	95% CI
All	0.655	(0.503-0.853)	0.637	(0.481-0.845)
Stage I/II	0.750	(0.565-0.995)	0.722	(0.524-0.996)
Stage III	0.750	(0.503-1)	0.625	(0.365-1)
Stage IV	0.200	(0.035-1)	0.400	(0.137-1)

Table 4. — *Time to first recurrence/disease progression.*

Disease stage at diagnosis	Time to disease recurrence/ Progression (months)
IB	9.7
IC	24.4
IIA	6.7
IIIA	8.8
IV	6.7
IV	5.7
IV	5.6
IV	24.9

Disease recurrence or progression occurred in eight patients who received cisplatin/ifosfamide plus VCBT. The site of first recurrence for patients with Stages I-III included peritoneal implants in a Stage IB patient; lung, omentum, spleen, and retroperitoneal lymphadenopathy in a Stage IC patient; and lung metastasis in two patients (Stages IIA and IIIB) There were no isolated vaginal failures identified with VCBT. Table 4 shows the time to recurrence/progression for patients with Stages I-IV.

Discussion

The optimal chemotherapy agents for treatment of uterine carcinosarcoma have yet to be determined. Previous studies have shown five-year survival rates between 33% and 60% with surgery alone [23]. Postoperative pelvic radiotherapy has been shown to reduce local recurrence compared to surgery alone though an improvement in OS is not certain [24]. The 2010 National Comprehensive Cancer Network (NCCN) guidelines recommend treatment for all stages of carcinosarcoma except for Stage IA [25]. Treatment recommendations include chemotherapy with or without radiation or whole abdominal radiation with or without vaginal brachytherapy. Ifosfamide has been evaluated in combination with paclitaxel or cisplatin. The Gynecologic Oncology Group (GOG) trial 161 randomly assigned 179 women with previously untreated Stage III to IV, recurrent or advanced disease to single agent ifosfamide (2 g/m^2 daily for three days) or ifosfamide (1.6 g/m^2 daily for three days) plus paclitaxel (135 mg/m^2 on day 1) in 21-day cycles [26]. The combination of ifosfamide plus paclitaxel resulted in a higher response rate (45 *vs* 29 percent) and an improvement in median OS (14 *vs* 6 months, HR 0.69, 95% CI 0.49-0.97). Sensory neuropathy (grades 1-4) was significantly higher with combination therapy (30% *vs* 8%). The GOG evaluated the efficacy of carboplatin (area under the curve = 6) plus paclitaxel (175 mg/m^2) every three weeks (GOG 232B) in 55 women as first line therapy for Stage III or IV, persistent, or recurrent carcinosarcoma [27]. Of 46 evaluable patients, the overall response rate was 54% (13% complete response rate). The median PFS and OS were eight and 15 months, respectively. Serious (grade 3/4) toxicities included neutropenia (85%), thrombocytopenia (11%), and sensory neuropathy (11%). Currently, the GOG is conducting a randomized, phase III trial of paclitaxel plus carboplatin versus ifosfamide plus paclitaxel in chemotherapy-naïve women with newly diagnosed Stage I–IV uterine carcinosarcoma.

A randomized phase III trial (GOG 108) evaluated ifosfamide (1.5 g/m^2/day) for five days every three weeks for eight cycles with Mesna uroprotection, with or without cisplatin (20 mg/m^2/day) for five days in patients with advanced, persistent or recurrent carcinosarcoma [28]. The combination arm resulted in a higher response rate (54% *vs* 36%) and a significant improvement in median PFS (6 *vs* 4 months, RR 0.73, $p = 0.02$), without an improvement in median OS (9 *vs* 8 months, RR 0.80, $p = 0.07$). Combination therapy resulted in more serious (grade 3/4) events compared to single agent ifosfamide, including anemia (17% *vs* 8%) and peripheral neuropathy (12% *vs* 1%).

The present retrospective review revealed that the combination of cisplatin 40 mg/m^2 on day 1 and ifosfamide 1,200 mg/m2 daily on days 1 to 4 with Mesna every four weeks for six cycles was overall well-tolerated. The authors found that grade 3 anemia occurred in only 14% of patients, and no patients had grade 4 anemia. In the present study, grade 3 neurotoxicity occurred in only 6.9%. VCBT resulted in excellent local control. The median PFS was not reached for Stages I-III. The PFS and OS results were favorable for Stage IV disease compared to results from GOG 108, with a median PFS of 6.7 months (95% CI 5.7 to inf) and a median OS of 15.6 months (95% CI 9.4 to inf). Overall, the combination of cisplatin and ifosfamide chemotherapy with VCBT employed in this study was well-tolerated with promising activity for uterine carcinosarcoma.

References

[1] Dinh T., Slavin R., Bhagavan B., Hannigan E.V., Tiamson E.M., Yandell R.B.: "Mixed mullerian tumors of the uterus: A clinicopathologic study." *Obstet Gynecol.,* 1989, *74*, 388.

[2] Ries L.A.G., Young J.L., Keel G.E., Eisner M.P., Lin Y.D., Horner M-J., (eds).: "SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007. Available at: http://seer.cancer.gov/publications/survival/ surv_corpus_uteri.pdf

[3] Gonzalez Bosquet J., Terstriep W., Cliby W., Brown-Jones M., Kaur J., Piodratz K., Keeney G.: "The impact of multi-modal therapy on survival for uterine carcinosarcoma." *Gynecol. Oncol.,* 2010, *116*, 419.

[4] Kanthan R., Senger J.: "Uterine carcinosarcomas (malignant mixed müllerian tumours): a review with special emphasis on the controversies in management". *Obstet. Gynecol. Int.*, 2011, *2011*, 470795. doi: 10.1155/2011/470795. Epub 2011 Oct 5.

[5] Major F., Blessing J., Silverberg S., Morrow C.P., Creasman W.T., Currie J.L., *et al.*: "Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study". *Cancer,* 1993, *71*, 1702.

[6] Kahanpää K., Wahlström T., Gröhn P., Heinonen E., Nieminen U., Widholm O.: "Sarcomas of the uterus: a clinicopathologic study of 119 patients". *Obstet. Gynecol.,* 1986, *67*, 417.

[7] Zelmanowicz A., Hildesheim A., Sherman A.E., Sturgeon S., Kurman R., Barrett R., *et al.*: "Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors". *Gynecol. Oncol.*, 1998, *69*, 253.

[8] Fotiou S., Hatjieleftheriou G., Kyrousis G., Kokka F., Apostolikas N.: "Long-term tamoxifen treatment: a possible aetiological factor in the development of uterine carcinosarcoma: two case reports and review of the literature". *Anticancer Res.,* 2000, *20*, 2015.

[9] Pothuri B., Ramondetta L., Martino M., Alektiar K., Eifel P., Deavers M., *et al.*: "Development of endometrial cancer after radiation treatment for cervical carcinoma". *Obstet. Gynecol.,* 2003, *101*, 941.

[10] Sherman M., Devesa S.: "Analysis of racial differences in incidence, survival and mortality for malignant tumors of the uterine corpus". *Cancer,* 2003, *98*, 176.

[11] Bansal N., Herzog T., Burke W., Cohen C., WrightJ.: "The utility of preoperative endometrial sampling for the detection of uterine sarcomas". *Gynecol. Oncol.,* 2008, *110*, 43. doi: 10.1016/j.ygyno. 2008.02.026. Epub 2008 Apr 29

[12] Yamada S., Burger R., Brewster W., Anton D., Kohler M., Monk B.: "Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus". *Cancer,* 2000, *88*, 2782.

[13] Arrastia C., Fruchter R., Clark M., Maiman M., Remi J.C., Macaset M., *et al.*: "Uterine carcinosarcomas: incidence and trends in management and survival". *Gynecol. Oncol.,* 1997, *65*, 158.

[14] Gerszten K., Faul C., Kounelis S., Huang Q., Kelley J., Jones M.: "The impact of adjuvant radiotherapy on carcinosarcoma of the uterus". *Gynecol. Oncol*., 1998, *68*, 8.

[15] Sutton G., Kauderer J., Carson L., Lentz S., Whitney C., Gallion H., Gynecologic Oncology Group: "Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study". *Gynecol. Oncol.,* 2005, *96*, 630.

[16] Wong L., See H.T., Khoo-Tan H.S., Low JS, Nq WT, Low JJ:. "Combined adjuvant cisplatin and ifosfamide chemotherapy and radiotherapy for malignant mixed müllerian tumors of the uterus". *Int. J. Gynecol. Cancer,* 2006, *16*, 1364.

[17] Sutton G., Blessing J., Rosenshein N., Photopulos G., DiSaia P.: "Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus: (a Gynecologic Oncology Group study)". *Am. J. Obstet. Gynecol.,* 1989, *161*, 309.

[18] Sutton G., Brunetto V., Kilgore L., Soper J., McGehee R., Olt G., et al.: "A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study". *Gynecol. Oncol.,* 2000, *79*, 147.

[19] Curtin J., Blessing J., Soper J,, DeGeest K.: "Paclitaxel in the treatment of carcinosarcoma of the uterus: a gynecologic oncology group study". *Gynecol. Oncol.,* 2001, *83*, 268.

[20] Thigpen J., Blessing J., Wilbanks G.: "Cisplatin as second-line chemotherapy in the treatment of advanced or recurrent leiomyosarcoma of the uterus. A phase II trial of the Gynecologic Oncology Group". *Am. J. Clin. Oncol.,* 1986, *9*, 18.

[21] Thigpen J., Blessing J., Beecham J., Homesley H., Yordan E.: "Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent uterine sarcomas: a Gynecologic Oncology Group study". *J. Clin. Oncol.,*1991, *9*, 1962.

[22] Resnik E., Chambers S., Carcangiu M., Kohorn E., Schwartz P., Chambers J.: "A phase II study of etoposide, cisplatin, and doxorubicin chemotherapy in mixed müllerian tumors (MMT) of the uterus". *Gynecol. Oncol.,*1995, *56*, 370.

[23] Kahanpää K., Wahlström T., Gröhn P., Heinonen E., Nieminen U., Widholm O.: "Sarcomas of the uterus: a clinicopathologic study of 119 patients". *Obstet. Gynecol*., 1986, *67*, 417.

[24] Sartori E., Bazzurini L., Gadducci A., Landoni F., Lissoni A., Maggino T., *et al.*: "Carcinoma of the uterus: a clinicopathological multicenter CTF study". *Gynecol. Oncol*., 1997, *67*, 70.

[25] Greer B., Koh W., Abu-Rustum N., Bookman M., Bristow R., Campos S., *et al.*: "Uterine neoplasms. Clinical practice guidelines in oncology". *J. Natl. Compr. Canc. Netw*., 2009, *7*, 498.

[26] Homesley H., Filiaci V., Markman M., Bitterman P., Easton L., Kilgore L., *et al.*: "Gynecologic Oncology Group: Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study". *J. Clin. Oncol., 25*, 526.

[27] Powell M., Filiaci V., Rose P., Mannel R., Hanjani P., Degeest K., *et al.*: "Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study". *J. Clin. Oncol*., 2010, *28*, 2727.

[28] Sutton G., Brunetto V., Kilgore L., Soper J., McGehee R., Olt G., *et al.*: "A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study". *Gynecol. Oncol.,* 2000, *79*, 147.

Address reprint requests to:
MAYSA ABU-KHALAF, M.D.
300 George Street, Suite 120
New Haven, CT 06511 (USA)
e-mail: maysa.abu-khalaf@yale.edu