

Chemotherapy for Uterine Carcinosarcoma with Carboplatin, Ifosfamide and Mesna

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Abstract. *Background/Aim:* Uterine carcinosarcomas (UCSs) are highly aggressive, rare, biphasic tumors composed of epithelial and mesenchymal elements. Surgery remains the mainstay of treatment in early-stage disease. Adjuvant pelvic radiotherapy improves locoregional control without proven overall survival (OS) benefit. Although adjuvant ifosfamide-based combination chemotherapy with cisplatin or paclitaxel has shown superiority to radiotherapy or single-agent chemotherapy in randomized controlled trials, there is no consensus on a standard regimen due to toxicities. The aim of this retrospective study was to assess the efficacy and toxicity of a novel combination chemotherapy using carboplatin, ifosfamide and mesna (CIM) and compare with other regimens for patients with UCSs in both the adjuvant and palliative setting. *Patients and Methods:* Between 1997 and 2010, 60 patients with UCS, 70% of whom with international federation of gynecology and obstetrics (FIGO) stage III/IV disease, were treated with adjuvant or palliative chemotherapy. Two groups were identified: Group 1 (n=22) included patients receiving CIM chemotherapy; and group 2 (n=38) receiving other regimens (carboplatin/paclitaxel/cisplatin/doxorubicin/epirubicin). *Results:* After a median follow-up of 60 months, disease in seven patients in group 1 (CIM) and 20 patients in group 2 had progressed/relapsed. Out of these, six patients in group 1 and 13 patients in group 2 had died. The progression-free survival (PFS) and OS for patients treated with adjuvant or palliative CIM was 35 months [95% confidence interval (CI) =0.26-0.43] and 47 months (95% CI=0.38-0.56; log-rank, p=0.001) respectively, whereas for group 2 patients treated with other regimens,

PFS was 27.48 months (95% CI=0.20-0.33) and OS was 30 months (95% CI=0.21-0.38; log-rank, p=0.001). While none of the patients in group 1 experienced neurotoxicity or other grade 3 or 4 toxicities, 3/38 patients in group 2 experienced grade 3 neutropenia, 4/38 had peripheral sensory neuropathy, 6/38 patients had treatment deferred due to toxicities or allergic reaction to paclitaxel. *Conclusion:* In the phase III randomized controlled trial combination of ifosfamide and taxanes has shown PFS and OS benefit when compared to single-agent ifosfamide at the expense of significant toxicities. Results from our study show that the combination of CIM is an effective and safe alternative regimen for patients with advanced UCSs. In addition to improved OS and PFS, the main advantage of this regimen over taxane-based regimens includes minimal neuropathy, less use of steroids, and low risk of allergic reaction. CIM should be considered in future prospective studies looking at the treatment of UCS.

Uterine carcinosarcomas (UCSs), previously called malignant mixed Müllerian tumors, are highly aggressive, rare, biphasic tumors composed of epithelial and mesenchymal elements believed to arise from a monoclonal origin (1). Although representing less than 5% of all uterine tumors, UCSs account for 16.4% of all deaths caused by a uterine malignancy (2, 3). Despite advances in imaging and adjuvant therapies in the past 30 years, five-year disease-free survival by stage remains poor (stage I, 56%; stage II, 31%; stage III, 13%; stage IV, 0%) with most patients developing extrapelvic disease (4, 5). The primary management of UCS limited to the abdomen is surgery for both staging and initial treatment (6). However, high rates of recurrence (40-60%) and distant metastases with poor prognosis suggest a need for effective adjuvant and palliative treatment. Although well-recognized as improving locoregional control, the role of postoperative radiation in improving overall survival (OS) outcomes remains undecided (7-9).

Gynecologic Oncology Group (GOG) phase II and III trials exploring various combinations of adjuvant chemotherapy regimens using ifosfamide plus mesna, paclitaxel and cisplatin have shown superiority in terms of response rate (RR) and progression-free survival (PFS) when

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compared to whole abdominal-pelvic radiation or single agents. Ifosfamide, mesna and paclitaxel combination also provided OS benefit. However, none of these regimes are widely used in view of grade 3/4 myelo- and neurotoxicity. Therefore, the optimal adjuvant chemotherapy regimen is yet to be determined (10-13).

In patients with advanced, persisting, recurrent or metastatic UCSs, active single-agent chemotherapies include ifosfamide [response rate (RR)=29% to 36%], carboplatin (32%), cisplatin (28% to 42%), paclitaxel (18%), and doxorubicin (10% to 25%) (14-20). Further phase II trial by GOG using carboplatin and paclitaxel led to a total overall response rate of 54% (95% CI=37% to 67%) (21). However, to our knowledge, there exist no studies using the combination of carboplatin, ifosfamide plus mesna (CIM) chemotherapy in patients with UCSs.

The aim of this retrospective study was to assess the efficacy and toxicity of a novel combination chemotherapy using CIM and compare with other regimens for patients with UCSs in both the adjuvant and palliative setting.

Patients and Methods

Between 1997 and 2010, 60 patients with endometrial carcinosarcoma (CS) were treated with chemotherapy at our institution. Two distinct patient groups were identified: Group 1 (n=22) included patients treated with CIM chemotherapy, adjuvantly (n=14) or palliatively (n=8); group 2 (n=38) included patients treated with other chemotherapy regimens adjuvantly (n=21) or palliatively (n=17). All patients treated with adjuvant chemotherapy underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal washings, omentectomy with or without lymph node sampling or dissection (LND). All patients treated with palliative chemotherapy had biopsy-confirmed disease.

Additionally, 64% of patients in group 1 (n=9) and 66% in group 2 (n=14) received postoperative pelvic external beam radiotherapy some time during their treatment pathway. External beam radiotherapy was delivered to a dose of 45-50.4 Gy in 25-28 fractions, five days a week in 1.8 Gy fractions over five to five and half weeks using an isocentric technique with standard 4-field plan. Further vaginal vault low dose rate brachytherapy boost was given to some (n=8) of these patients (three in group 1 and five in group 2 respectively) delivering 15 Gy to 0.5 cm from the surface of applicator.

Baseline characteristics of the 60 patients are summarized in Table I.

The glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula. The chemotherapy regimen in group 1 consisted of a combination of carboplatin area under the curve (AUC 5), ifosfamide (3 g/m²) and mesna (1 g/m²) delivered intravenously on day 1 as out patient treatment every three weekly for 4-6 cycles. The primary end-point was PFS, and secondary end-points were toxicity and overall survival OS. PFS was calculated from the date of surgery or biopsy only to the date of disease recurrence or progression. OS was calculated using the Kaplan-Meier method and defined as the time from initial surgery or biopsy only to death from any cause or censored at the date of last follow-up visit.

Chemotherapy-related toxicities were calculated by means of the common Toxicity Criteria of the National Cancer Institute (version 3.0) (22). All patients were reviewed three-weekly during chemotherapy and weekly during radiotherapy. Data for OS were obtained from the National Health Service strategic tracking service. Response was assessed by means of Response Evaluation Criteria in Solid Tumors (RECIST) criteria (23).

Results

Patients' characteristics. Sixty patients with a median age of 69 years (range=46-83 years) were included for analysis in this study. Of these, 22 patients in group 1 received CIM; 14 patients as adjuvant treatment and the remaining eight with palliative intent. The remaining 38 patients in group 2 received various other chemotherapy regimens; 21 of these patients were treated adjuvantly and 17 patients palliatively. The regimens included carboplatin as single-agent (n=22), in combination with either paclitaxel (n=11) or epirubicin (n=3); and ifosfamide in combination with doxorubicin (n=1) or cisplatin (n=1). The median number of cycles were 4 per patient (range=1-8).

Outcomes. After a median follow-up of 60 months (range=15-123 months), the PFS and OS for patients in group 1 (adjuvant and palliative CIM) was 35 months (95% CI=0.26-0.43) and 47 months (95% CI=0.38-0.56; *p*=0.01), respectively. Disease in seven patients had relapsed/progressed (in four treated adjuvantly; three palliatively). Of these, two (42%) had local recurrence (one patient from adjuvant CIM; one from palliative CIM), four (57%) had distant recurrence (two in each setting for CIM), and the remaining patients (14%) had both local and distant recurrence (palliative CIM). Out of the seven patients whose disease had progressed on CIM, six died (four from the adjuvant arm and two from the palliative arm). Of all group 1 patients treated with palliative CIM (n=8), 37.5% (n=3) had complete response, 25% (n=2) had stable disease and a further 37.5% (n=3) had progressive disease. The median time-to-recurrence for patients treated with adjuvant CIM was 37.79 months and the median OS was 54.7 months. The median time-to-progression and OS for patients treated with palliative CIM was 8 months and 23 months, respectively.

The median PFS and OS for patients of Group 2 was 27.48 months (95% CI=0.20-0.33) and 30 months (95% CI=0.21-0.38; *p*-value 0.01) respectively. Of the 21 patients treated adjuvantly with other regimens, 14 experienced relapse, out of whom 13 died of progressive disease. In terms of sites of recurrence, two had local recurrence, five had distant recurrence and seven patients had both local and distant recurrence. Of the remaining 17 patients in group 2 treated palliatively, two patients had stable disease, six had complete response and another six had progressive disease. The median time-to-recurrence for patients (n=21) treated

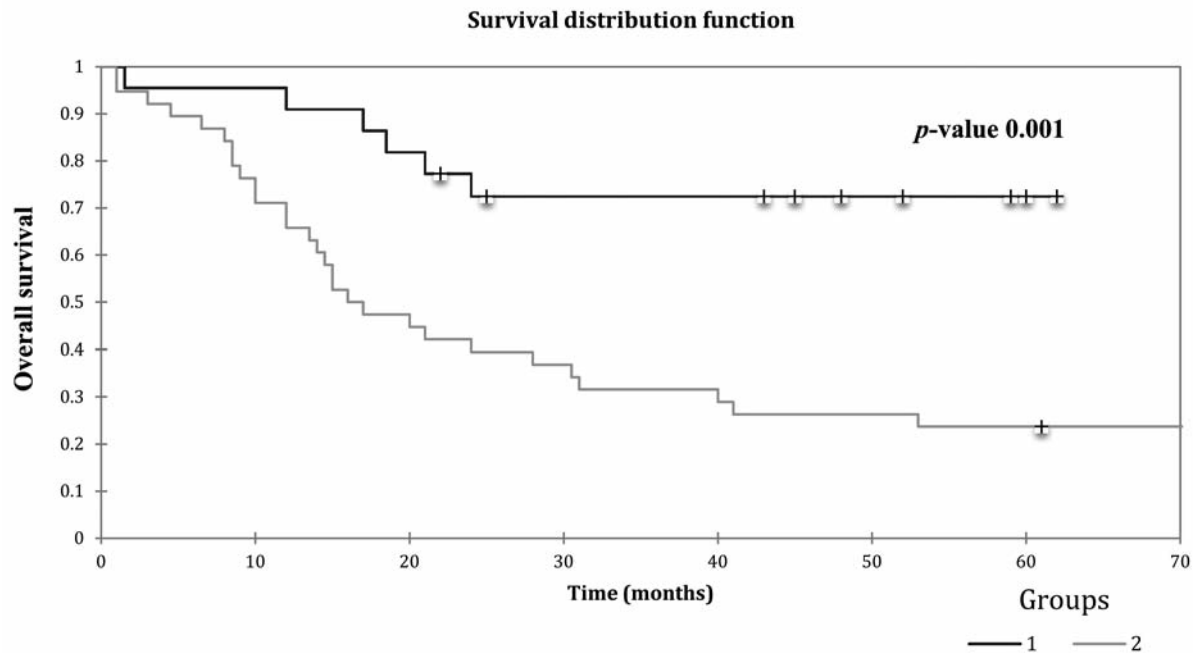


Figure 1. Cumulative overall survival for Group 1 (carboplatin,ifosfamide and mesna) and Group 2 (other regimens).

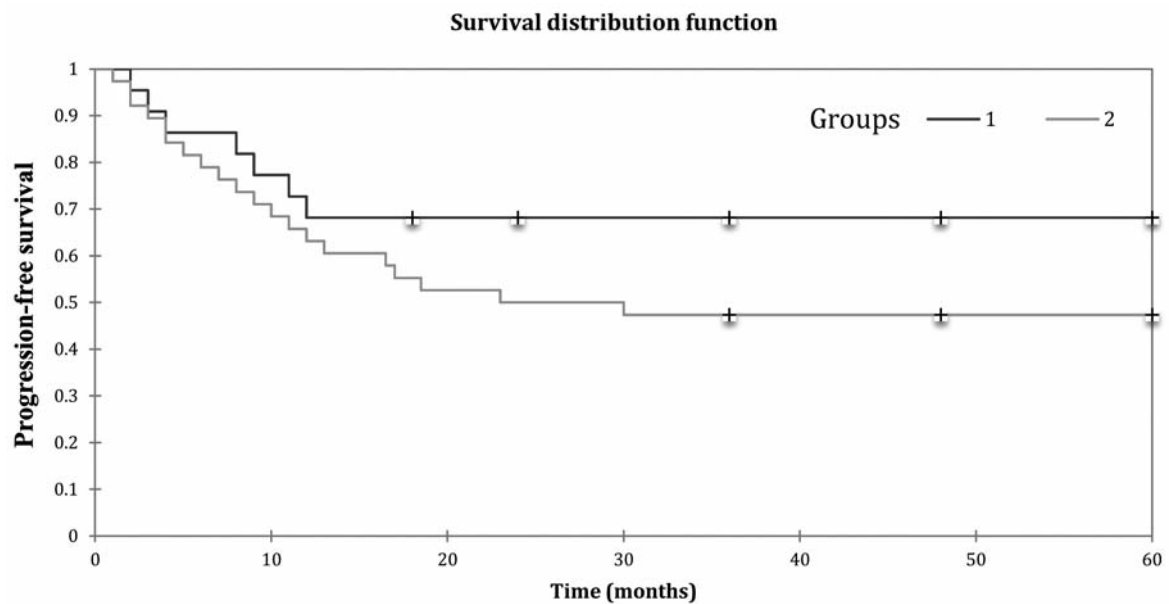


Figure 2. Cumulative progression-free survival for Group1 (carboplatin,ifosfamide and mesna) and Group 2 (other regimens).

with other adjuvant chemotherapy regimens was 18 months (range=8-31 months) and the median OS was 40 months. The median time-to-progression and OS for palliative chemotherapy patients (n=17) in group 2 was 5 months (range=2-10 months) and 9 months respectively.

Cumulative PFS and OS for group 1 and 2 are illustrated in Figures 1 and 2, respectively.

Toxicity. None of the patients in the CIM-treated group experienced grade 3 or 4 toxicities. Grade 1 or 2 neutropenia

Table I. Baseline demographics and characteristics (n=60).

Characteristic	No.	%
Median age, years	69	
FIGO stage		
IB	8	13.3%
II	11	18.3%
IIIA	5	8.3%
IIIB	5	8.3%
IIIC	17	28.3%
IVA	10	16.6%
IVB	4	6.6%
Histology		
Carcinosarcoma	60	100%
Grade 3	60	100%
Myometrial invasion		
<50%	2	3.3%
>50%	53	88.3%
Unknown	5	8.3%
Lymphovascular invasion		
Present	40	66.6%
Absent	5	8.3%
Unknown	15	25%
Surgery		
TAH+BSO+peritoneal washings	6	10%
TAH+BSO+omentectomy+peritoneal washings	33	55%
TAH+BSO+omentectomy+peritoneal washings+lymph node dissection	16	26.6%
Biopsy only	5	8.3%

FIGO: International federations of gynecology and obstetrics; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy.

was observed in 13% of patients (n=3). There were no cases of neutropenic sepsis, encephalopathy or enteritis requiring hospitalization. There were no cases of treatment-related renal failure or neuropathy.

In group 2, one patient had thromboembolic stroke after cycle 1. Grade 3-4 neutropenia was noted in three patients after single-agent carboplatin and on its combination with epirubicin needing granulocyte-colony stimulating factor support. Grade 3 anaemia needing blood transfusion in one patient after carboplatin and paclitaxel. Two patients omitted paclitaxel due to grade 3 allergic reaction following cycle 1 and 2, respectively, and continued on carboplatin. For another patient doxorubicin was omitted due to grade 3 fatigue and continued on ifosfamide. In four patients, treatment was deferred and further doses reduced due to persistent grade 2 myelosuppression from carboplatin and significant myalgia and neuropathy when used in combination with paclitaxel. Details of chemotherapy-related grade 3 or 4 toxicities are summarized in Table II.

Table II. Chemotherapy-related grade 3 and 4 toxicities.

Toxicity	Group 1 (CIM) n/N	Group 2 (Other regimens) n/N
Acute toxicity (any)	0/22	
Anaemia		1/38
Neutropenia		3/38
Allergic reaction		2/38
Fatigue		1/38
Cardiovascular		1/38
Late toxicity: Sensory neuropathy	0/22	4/38

CIM: Carboplatin, ifosfamide and mesna.

Discussion

There exist no randomized trials that have evaluated the value of adjuvant chemotherapy especially in women with stage IA disease (24,25). These women have a better prognosis compared to those with IB or later stage disease.

In the first adjuvant phase III trial in 1985 by GOG that included UCSs, 156 women with stage I or II uterine sarcomas were randomly assigned to postoperative surveillance or adjuvant doxorubicin (GOG20). Although adjuvant doxorubicin resulted in a lower recurrence rate (41% vs. 53%, respectively), the result was not statistically significant. In addition, there was no difference in PFS or OS. Toxicities included lymphopenia (33%) and six cases of non life-threatening cardiac toxicity (20).

A phase III randomized controlled trial by Sutton *et al.* compared single-agent ifosfamide (1.5 g/m²/day for 5 days q3w) without mesna protection to combination chemotherapy with cisplatin (20 mg/m²/day for 5 days q3w) in 194 women with advanced or recurrent UCSs (GOG 108). The combination treatment offered a higher response rate (RR, 57% vs. 39%) and a slight prolongation of median PFS (6 months vs. 4 months), at the expense of grade 3 or 4 myelo- and neurotoxicity. However, no statistically significant OS benefit was found between the two arms (12).

Adjuvant cisplatin/ifosfamide with mesna chemotherapy regimen was evaluated in a phase II trial (GOG 117) and reported 2-year PFS of 69% and OS of 82% in 65 patients with stage I-II UCS (10). This regimen was then compared in a phase III RCT involving 206 patients (GOG 150) to whole-abdominal radiation in patients with stage I-IV UCS with optimally debulked tumor to ≤1 cm and without extra-abdominal spread. After a median duration of follow-up of 5 years, the risk of recurrence was lower among those treated with chemotherapy rather than whole-abdominal radiation (hazard ratio [HR]=0.79, 95% CI=0.53-0.79); lower risk of

Table III. Comparison of acute and late chemotherapy related toxicities

Toxicity (Grade3/4)	Study/regimen (Ref)				
	Dandamudi <i>et al.</i> (CIM)	Sutton <i>et al.</i> Cisplatin/ ifosfamide (12)	GOG 150 Cisplatin/ ifosfamide/mesna (10)	GOG161 Paclitaxel/ ifosfamide/mesna (13)	GOG Phase II carboplatin/ paclitaxel (21)
Neutropenia	0/22	56/90	46/99	26/86	39/46
GI Toxicity	0/22		11/99	2/46	
Nausea/vomiting		13/90		3/86	2/46
Diarrhoea		4/90		4/86	1/46
Sensoryneuropathy	0/22	26/90	9/99	8/86	5/46
Cardiovascular	0/22	0/90	4/99	3/86	1/46

CIM: Carboplatin, ifosfamide and mesna; GI: gastro-intestinal.

death (HR=0.79, 95% CI=0.53-1.18), although the difference was not statistically significant (11). Chemotherapy was associated with a higher incidence of vaginal recurrence (10 vs. 4 patients), severe neuropathy (9 vs. 0 patients) and haematological toxicities (RR=0.02, 95% CI=0.00-0.16). In view of the concerns regarding the significant toxicities and lack of OS benefit, this combination is not widely used.

Further adjuvant phase III trial showed OS benefit when ifosfamide and mesna (13) were used in combination with paclitaxel chemotherapy in patients with advanced uterine sarcoma with optimally debulked tumor to ≤ 1 cm and without extra-abdominal spread. This GOG 161 trial enrolled 179 women with previously untreated stage III to IV, recurrent or advanced disease and randomly assigned them to treatment using 21-day cycles of single-agent ifosfamide (2 g/m² daily for three days) or ifosfamide (1.6 g/m² daily for three days) plus paclitaxel (135 mg/m² on day 1) for up to eight cycles. Compared with single-agent ifosfamide, ifosfamide-plus-paclitaxel resulted in a higher response rate (45 vs. 29 percent) and a significant reduction in the risk of death (median overall survival 14 vs. 6 months, HR=0.69, 95% CI=0.49-0.97). However, sensory neuropathy (grade 1 to 4) was significantly worse with combination therapy versus ifosfamide (30% vs. 8%, RR=2.73, 95% CI=0.75-9.94). Serious (grade 3/4) central nervous system toxicity was reported in three patients treated with single-agent ifosfamide and five patients treated with the combination.

Cochrane review included these two trials (GOG 150 and GOG 161) in a meta-analysis (n=373) and concluded that in advanced-stage metastatic UCS, as well as recurrent disease, adjuvant combination chemotherapy with ifosfamide should be considered (HR=0.75, 95% CI=0.60-0.94 and HR=0.72, 95% CI=0.58-0.90 for OS and PFS, respectively). In addition, radiotherapy to the abdomen is not associated with improved survival. The combination chemotherapy with ifosfamide and paclitaxel was associated with lower risk of death compared to ifosfamide alone. However, women who received the combination therapy had a significantly higher

risk of severe nausea or vomiting (RR=3.53, 95% CI=1.33-9.37), higher risk of neuropathy (RR=1.59, 95% CI=0.99-2.55) than women who received ifosfamide. The authors were unable to report on quality-of-life as none of these trials had such assessments as a component (26).

A study by the GOG using paclitaxel and carboplatin for advanced stage (III or IV), UCSs with persistent or recurrent measurable disease, and no prior chemotherapy has been published. The proportion of patients with confirmed response was 54% (95% CI=37-67%). The median PFS and overall survival were 7.6 and 14.7 months, respectively. However, of the 46 evaluable patients, grade 3/4 toxicities were reported in 39 (84.7%) with neutropenia, including one with febrile neutropenia, five with thrombocytopenia, three patients having had allergy, and five patients with sensory neuropathy (21).

Results are awaited from the GOG phase III trial (GOG 261) comparing this regimen (carboplatin and paclitaxel) with ifosfamide and paclitaxel for newly diagnosed UCS stage I to III or those with chemonaïve recurrent disease (27).

The results from our study show a significant reduction in toxicities using the novel CIM regimen (group 1) when compared to other regimens (group 2) and GOG trials in both adjuvant and palliative setting. Table III shows the comparison of acute and late chemotherapy-related toxicities.

Almost 70% (n=41) of the patients in our study had FIGO stage III/IV UCS at diagnosis. CIM chemotherapy led to a median OS of 54.7 and 23 months in the adjuvant and palliative setting, respectively.

Table IV shows the comparison of PFS and OS with other chemotherapy regimens tested in published randomised controlled trials. Even though the number of patients in the study was small due to the rarity of this disease, our results with CIM chemotherapy show efficacy at least as good as any other published series but with better side-effect and safety profiles when compared with other regimens used in published studies. It is much less myelosuppressive than the other ifosfamide-containing

Table IV. Comparison of PFS and OS with published studies.

Study (Ref)	Median PFS (months)	Median OS (months)
Dandamudi <i>et al.</i> CIM regimen		
adjuvant and palliative	35	47
adjuvant	37.79	54.7
palliative (FIGO stage IVB)	8.0	23
Carboplatin+paclitaxel (21) (GOG phase II) FIGO stage III/IV	7.6	14.7
Cisplatin+ifosfamide+mesna (10) (GOG150, phase III)	6.0	9.4
Paclitaxel+ifosfamide+mesna vs. ifosfamide+ mesna (13) (GOG 161, phase III)	5.8 vs. 3.6	13.5 vs. 8.4
Cisplatin+ifosfamide vs. ifosfamide (12) (GOG 108, phase III)	6.0 vs. 4.0	9.4 vs. 7.6

PFS: Progression-free survival; OS: overall-survival; CIM: carboplatin, ifosfamide and mesna; FIGO: international federation of gynecology and obstetrics; GOG: gynecologic oncology group.

regimens. Advantages of this regimen over cisplatin/carboplatin and taxanes, in particular, also include minimal neuropathy, less use of steroids, and a low risk of allergic reaction and alopecia. It should be noted that it is difficult to compare between the different studies as they do contain different patient groups. In addition, patients having CIM chemotherapy would have had normal albumin and glomerular filtration rate ($>50\text{mls/min/1.73m}^2$) which would have invariably included patients with good performance status, while patients treated with single-agent carboplatin mostly would have had poorer performance status, and would have been included in group 2.

Conclusion

In summary, ifosfamide, cisplatin, carboplatin and taxanes appear to be the most active agents for endometrial cancer, and combination chemotherapy leads to improved response rates. There has only been one randomized trial showing superiority of chemotherapy over radiotherapy in advanced UCS. However, the chemotherapy arm was associated with significant toxicity. Although there was better PFS and OS with ifosfamide, mesna and paclitaxel, this was at the expense of increased neurological toxicity.

Our study shows that the combination of CIM is an effective alternative regimen for patients with endometrial carcinosarcoma, especially where taxanes are contraindicated. In addition, treatment-related toxicity with the combination of CIM regimen is minimal when compared to published studies using taxane or cisplatin combination.

Nevertheless, future randomized controlled trials will be vital in deciding the most efficacious combination chemotherapy regimen with minimal toxicity for adjuvant or palliative treatment in patients with endometrial carcinosarcoma. The results from phase III GOG 261 non-inferiority trial comparing paclitaxel with carboplatin or ifosfamide plus mesna in treating patients with newly-

diagnosed chemotherapy-naïve persistent or recurrent uterine, ovarian, fallopian tube, or peritoneal cavity cancer is awaited (27). Until the optimal chemotherapy regimen is established, patients could be considered for this combination and its advantages over taxane- and other ifosfamide-based regimens have already been discussed. CIM chemotherapy should be considered in future prospective studies looking at the treatment UCS.

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