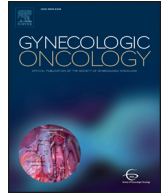




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Salvage chemotherapy with taxane and platinum for women with recurrent uterine carcinosarcoma

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HIGHLIGHTS

- Survival after recurrence was examined in women with recurrent uterine carcinosarcoma.
- Salvage therapy with taxane/platinum (TP) regimen was compared to non-TP regimens.
- Survival after recurrence was higher in TP regimen compared to non-TP regimen.
- Longer disease-free interval was associated with TP response.

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ABSTRACT

Objective. To examine survival after recurrence (SAR) among women with recurrent uterine carcinosarcoma who received a taxane/platinum doublet as the first-line salvage chemotherapy.

Methods. We retrospectively examined 148 women with recurrent uterine carcinosarcoma who received salvage chemotherapy within a cohort of 906 uterine carcinosarcomas. An independent association of salvage chemotherapy type and SAR was examined with multivariate analysis.

Results. There were 71 (48.0%) women who received a taxane/platinum regimen. On univariate analysis, women who received a taxane/platinum doublet had a higher 2-year SAR rate compared to women who received non-taxane/platinum regimens (55.5% versus 34.8%, $P < 0.001$). On multivariate analysis, use of taxane/platinum regimen was independently associated with improved SAR compared to the non-taxane/platinum regimens (adjusted-hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.35 to 0.91, $P = 0.02$). When stratified by disease-free interval, women with a disease-free interval ≥ 6 months who received a taxane/platinum doublet had a higher 2-year SAR rate compared to those who received non-taxane/platinum regimens (61.9% versus 40.0%, HR 0.46, 95% CI 0.28 to 0.75, $P = 0.002$); conversely, in women with a disease-free interval < 6 months, 2-year SAR rates were similar between the two groups (20.5% versus 18.4%, HR 0.80, 95% CI 0.33 to 1.90, $P = 0.61$). Among women who received a taxane/platinum doublet as adjuvant chemotherapy, re-treatment with taxane/platinum doublet as salvage chemotherapy remained beneficial (2-year SAR rate, 62.1% versus 39.7%, HR 0.40, 95% CI 0.18 to 0.86, $P = 0.019$).

Conclusion. Our study suggests that taxane/platinum doublet may be a more effective chemotherapy regimen compared to other regimens among women with recurrent uterine carcinosarcoma, especially for those who had a disease-free interval of ≥ 6 months.

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1. Introduction

Uterine carcinosarcoma is a high-grade endometrial cancer that has undergone an epithelial-mesenchymal transition with the sarcoma component arising from a dedifferentiated carcinoma component [1, 2]. The aggressiveness of uterine carcinosarcoma is clearly reflected in the considerably high incidence of disease recurrence after initial treatment. Nearly half of women with uterine carcinosarcoma experience a disease recurrence despite a comprehensive treatment approach [1,3].

Currently, there is no standard consensus for treatment strategy in women with recurrent uterine carcinosarcoma. The use of systemic chemotherapy plays a pivotal role in salvage therapy; more specific treatment considerations may be dependent on patient and tumor factors. Cisplatin, carboplatin, ifosfamide, and paclitaxel are all considered active agents for the treatment uterine carcinosarcoma [4].

One of the commonly used chemotherapy regimens for uterine carcinosarcoma is a paclitaxel with carboplatin doublet. Less toxicity, fewer adverse events, and ease of administration compared to other regimens such as an ifosfamide-based regimen make this a favorable option [1]. A combination regimen of paclitaxel with carboplatin has been reported to be effective for women with uterine carcinosarcoma in multiple clinical trials [5–8], with overall response rates ranging from 54% to 67%. These studies predominantly evaluated the effectiveness of this regimen in advanced stage disease *via* single arm cohorts; and recurrent disease accounting for only 17 to 57% of their study subjects [5–8]. Currently, there is no clinical trial reporting superiority of a taxane/platinum regimen over others in uterine carcinosarcoma.

Given differences in tumor biology between primary and recurrent tumors, a study solely examining recurrent disease is useful in the management of uterine carcinosarcoma. The objective of the study was to examine survival after recurrence (SAR) among women with recurrent uterine carcinosarcoma who received a taxane/platinum doublet as the first-line salvage chemotherapy.

2. Patients and methods

2.1. Systematic literature review

We first performed a systematic literature search examining a public search engine PubMed/MEDLINE with the entry keywords “uterine carcinosarcoma” OR “malignant mixed müllerian tumor” AND “carboplatin”

AND “paclitaxel” limited to English literature (searched on July 24, 2017). We used the MOOSE guideline to summarize the search results [9]. There were 56 articles identified in the initial search (Fig. S1), with seven articles examining the efficacy of carboplatin and paclitaxel in advanced stage, persistent, and recurrent uterine carcinosarcoma (Table S1) [5–8,10–12]. We found no prior study comparing a taxane/platinum regimen to other non-taxane/platinum regimens in a recurrent uterine carcinosarcoma population.

2.2. Study Eligibility

We utilized a previously organized database for uterine carcinosarcoma [3,13–15]. In this retrospective cohort study, we collected consecutive cases of uterine carcinosarcoma anywhere it was available between 1993 and 2013 from 26 institutions in the United States and Japan. The database consisted of 906 women with stage I–IV uterine carcinosarcoma who underwent primary hysterectomy-based surgical staging. Institutional Review Board approval was obtained at each participating institution. We consulted the STROBE guidelines to outline the results of the cohort study [16].

Within this surgical database, women who had no residual disease at the time of initial hysterectomy-based surgical treatment and who eventually developed disease recurrence were included in our analysis of salvage chemotherapies. We excluded women with residual disease at surgical treatment because prognosis is distinctively different compared to those who had complete resection [3,17]. Among those who were eligible for analysis, characteristics and outcomes of women who received the first-line salvage chemotherapy with taxane/platinum doublet were compared to those who received other regimens.

2.3. Clinical information

We examined information from the initial diagnosis of uterine carcinosarcoma and from the time of the first recurrence. Variables ascertained from the initial uterine carcinosarcoma diagnosis were country, ethnicity, cancer stage, histologic subtypes (carcinoma and sarcoma), surgery type and the extent of residual disease, type of postoperative chemotherapy (taxane/platinum versus others), and type of postoperative radiotherapy (whole pelvic irradiation versus others).

Variables abstracted at the time of disease recurrence included age at recurrence, the histology type of the recurrence (carcinoma versus

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