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Phase II trial of adjuvant pelvic radiation "sandwiched" between ifosfamide or ifosfamide plus cisplatin in women with uterine carcinosarcoma☆,☆☆,★

Mark H. Einstein [a,b,*], Merieme Klobocista [a], June Y. Hou [a], Stephen Lee [a], Subhakar Mutyala [c], Keyur Mehta [c], Laura L. Reimers [a], Dennis Y.-S. Kuo [a], Gloria S. Huang [a,b], Gary L. Goldberg [a,b]

[a] Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA
[b] Albert Einstein Cancer Center, Bronx, NY, USA
[c] Department of Radiation Oncology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA

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ABSTRACT

Objective. Uterine carcinosarcoma (CS) is a rare uterine tumor with an extremely poor prognosis. In the adjuvant setting, efficacy has been shown with radiotherapy (RT), systemic chemotherapy, or both. This is the first report describing the efficacy and toxicity of adjuvant ifosfamide or ifosfamide plus cisplatin "sandwiched" with RT in patients with surgically staged and completely resected uterine carcinosarcoma.

Methods. Women with surgically staged CS with no gross residual disease were initially administered ifosfamide (1.2 g/m^2/day × 5 days) with cisplatin (20 mg/m^2/day × 5 days) every 3 weeks for 3 cycles followed by pelvic external beam RT and brachytherapy followed by 3 additional cycles of ifosfamide (1.0 g/m2/day) with cisplatin (20 mg/m^2/day × 5 days) every 3 weeks. Similar to the GOG trial in recurrent CS (Sutton et al., 2000), the addition of cisplatin added toxicity without additional efficacy, so mid-study, the cisplatin was eliminated from the regimen. Toxicities were recorded and disease-free survival (DFS) was calculated with Kaplan–Meier statistical methods.

Results. In total, 12 patients received ifosfamide and cisplatin and 15 patients received ifosfamide alone, both 'sandwiched' with RT. The median follow up was 35.9 months (range 6–88). The 2 year DFS was similar in both the ifosfamide/cisplatin and ifosfamide groups (log-rank $p = 0.16$), so they were combined for analysis. 19 patients (70%) completed the protocol. As expected, stage 1 patients had a better 2-year DFS (18.75 ± 1.12 months; log-rank $p = 0.008$ when compared to stages 2, 3, 4). Also, in stages 2, 3 and 4 patients, the DFS was 15.81 ± 1.73 months. Grade 3/4 neutropenia, anemia and thrombocytopenia occurred in 18%, 4% and 4% of cycles, respectively.

Conclusions. Ifosfamide "sandwiched" with RT appears to be an efficacious regimen for surgically staged CS patients with no residual disease, even in patients with advanced stage. The addition of cisplatin to the regimen added toxicity without improving efficacy. Even with ifosfamide alone, the efficacy of this 'sandwich' regimen comes with a moderate but tolerable toxicity profile.

Introduction

Uterine carcinosarcoma (CS) represents approximately 4% of primary uterine malignancies and 26% of uterine cancer deaths [1,2]. It is an aggressive uterine tumor with a poor prognosis and a high recurrence rate [3]. Patterns of spread are both by hematogenous and lymphatic dissemination which explains the pelvic and extrapelvic sites of failure, with most patients developing extrapelvic disease [4]. 36% of CS patients with disease clinically confined to the uterus have nodal metastasis at the time of diagnosis and the majority of these patients will die of metastatic disease within 2 years of the diagnosis [5].

Even in patients with an early stage who receive adjuvant treatment, pelvic failure is common. Chi et al. evaluated patients with stage I or II CS who were treated with surgery versus surgery followed by whole pelvic radiation therapy. There was a trend towards fewer pelvic recurrences in the patients who received radiation therapy compared to those who did not ($p = 0.09$) [6]. Other studies showed similar statistically significant lower rates of pelvic recurrence in patients who received radiation therapy compared to those who did not (28% versus 48% ($p = 0.0002$) [7] and 3% versus 55% ($p < 0.0001$) [8]). Although pelvic radiation has been shown to decrease the rate of pelvic recurrence, it has not been shown to improve the overall survival [6,7,9–14]. This finding is likely attributable to the high

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* Corresponding author at: Division of Gynecologic Oncology, 1695 Eastchester Rd., Suite 601, Bronx, NY 10461, USA. Fax: +1 718 405 8087.
E-mail address: meinstein@montefiore.org (M.H. Einstein).

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incidence of distant metastasis known to occur at the time of CS recurrence. In a study of CS patients who received a combination of chemotherapy and radiation therapy in an adjuvant setting, there was a longer median disease specific survival ($p<0.001$) and disease free survival ($p=0.02$) [15].

Many chemotherapeutic agents that have demonstrated therapeutic efficacy in uterine CS include adriamycin, cisplatin, ifosfamide and paclitaxel [16–20]. The use of chemotherapy in the adjuvant setting has been explored as a means of attempting to impact subclinical extrauterine metastasis. The Gynecologic Oncology Group (GOG) evaluated ifosfamide and cisplatin in the adjuvant setting in patients with completely resected Stage I or II CS. At a minimum of 2 years of follow-up, 69% were progression free and 82% remained alive [21]. However, 12 out of 23 patients recurred in the pelvis. The authors concluded that this regimen, in the 4-day schedule, is tolerable and the impact on progression free and overall survival was difficult to evaluate in the absence of simultaneous controls but were better than historical controls. The high incidence of pelvic failures suggested that a combined approach with chemotherapy and radiotherapy should be evaluated. The results from this trial led to a randomized trial of ifosfamide versus ifosfamide with cisplatin in patients with advanced, persistent, recurrent CS with measurable disease after primary surgery [20]. This regimen was associated with significant toxicity necessitating a 20% dose reduction of ifosfamide with the same dose of cisplatin during the course of the trial. Results from this study identified a statistically significant progression free interval ($p=0.02$) in the ifosfamide/cisplatin group (6 months) compared to the ifosfamide alone group (4 months). However, there was no significant difference in overall survival ($p=0.07$) as well as considerable additional toxicity. In a separate GOG CS trial, chemotherapy was compared to whole abdominal irradiation (GOG 150) [22]. After adjusting for stage and age the estimated death rate was 29% lower in the chemotherapy group than the WAI group. This difference was seen despite the administration of only 3 cycles of chemotherapy. The WAI group had more abdominal recurrences and the chemotherapy group had more vaginal recurrences, but these were not statistically significant.

"Sandwich" sequencing allows for treatment of systemic disease with chemotherapy while controlling micrometastatic disease in the pelvis with radiation therapy. In addition, this treatment allows for the maximum therapeutic dosing for both chemotherapy and radiation therapy while limiting the overall toxicity. Our group has had experience with combining sequential radiation therapy sandwiched with paclitaxel and carboplatin chemotherapy in uterine papillary serous carcinoma (UPSC) [23,24]. Patients with stages I–IV UPSC, without evidence of gross residual disease received adjuvant paclitaxel/platinum for three cycles, followed by external beam radiotherapy (EBRT) and brachytherapy and then three more cycles of paclitaxel/platinum. In this trial, the 3-year % survival probability for stage I/II patients was 84% and stage III/IV patients was 50%. The vast majority of the patients completed the prescribed protocol and most of the toxicities were self-limiting. Grade 3 hematologic toxicities occurred in 14% of cycles and grade 4 hematologic toxicities occurred in 13% of cycles. This regimen was considered highly efficacious and well tolerated in patients with completely resected stage I–IV UPSC. The objective of this study was to evaluate the toxicity and efficacy of pelvic radiation "sandwiched" between cycles of ifosfamide alone or ifosfamide and cisplatin in patients with CS, including defining patterns of recurrence.

Patients and methods

After IRB approval, eligible patients with surgically staged I–IV CS without evidence of gross residual disease after primary surgery were recruited from 1999 to 2009 to this registered phase II trial (clinicaltrials.gov identifier: NCT00231842). Eligible patients underwent surgical staging comprised of total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, lymph node sampling, and omental biopsy, when clinically indicated. All eligible patients were ≥18 years of age, had an ECOG performance status of 0 or 1, adequate hematologic function (hematocrit ≥30%, WBC ≥300/mm^3, platelet count ≥100,000/mm^3), BUN ≤25 mg%, creatinine ≤2 mg%, total bilirubin ≤1.5 mg/dl, aminotransferases ≤2.5 times the institutional upper limit of normal. Patients with concurrent medical conditions limiting their life expectancy to ≤3 months or those who received prior chemotherapy and/or RT for pelvic malignancy were excluded.

Pre-treatment evaluation and follow up

At screening, all patients had protocol-required lab testing, including tumor markers, EKG, chest X-ray, and CT scan of the chest, abdomen, and pelvis. In addition to a physical examination, complete blood counts, serum electrolytes, and markers were performed prior to each cycle of chemotherapy, after completion of chemotherapy, every 3 months for 24 months, and then every 6 months thereafter. Imaging was repeated after treatment and during follow-up as clinically indicated. Adverse events were monitored for each cycle during therapy and during follow-up and graded using the National Cancer Institute Common Toxicity Criteria (CTC) version 3.0 as this trial was initiated in 1999, prior to instituting NCI CTC v4.0.

Treatment plan

Chemotherapy

At initiation of this protocol, cisplatin at 20 mg/m^2/day with ifosfamide 1.2 g/m^2/day for 5 days was administered. Similar to what was found in the GOG trial in recurrent CS [20], in the initial phase of this trial's two-stage design, the addition of cisplatin added toxicity without additional efficacy, so cisplatin was dropped in the remainder of the recruited patients [25]. The ifosfamide and RT dosing remained the same. Ifosfamide 1.2 g/m^2/day was administered parenterally for 5 days every 21 days for 3 cycles prior to RT and 1.0 g/m^2/day for 5 days every 21 days for 3 cycles after RT. EBRT generally lasted for 5 weeks, depending on the treatment fields and boosts, when appropriate. This was followed by brachytherapy in all patients. To avoid chemotherapy delay, the fourth cycle of chemotherapy was initiated the same week as the last brachytherapy insertion. Standard premedications for nausea were given. Mesna 400 mg IV bolus followed by 1200 mg IV divided into 3 L/day × 5 days for cycles 1 through 3, and 333 mg IV bolus followed by 1000 mg IV divided into 3 L/day × 5 days for cycles 4 through 6 was administered sequentially with ifosfamide.

Prior to each subsequent cycle of chemotherapy, patients were required to have recovered to an ANC ≥1500/mm^3 or WBC ≥3000/mm^3, platelets ≥100,000/mm^3 and renal and hepatic parameters the same as for screening. Treatment modifications for hematologic toxicities included cycle delay until recovery with subsequent dose reduction, in addition to G-CSF and/or erythropoietin, when clinically appropriate. All toxicities, dose delays, and dose reductions were recorded.

Radiation

EBRT was delivered after the 3rd cycle of chemotherapy. The total dose of EBRT was 45 Gy over 5 weeks. Patients were treated once a day, 5 days a week, with a daily fraction of 1.8 Gy. Four-field technique (AP-PA opposed and lateral opposed fields) was used with a megavoltage beam of ≥ 6 MV. Extended field radiation to the para-aortic nodes was administered in the case of two or more positive pelvic nodes or documented para-aortic lymph node metastasis.

High dose radiation (HDR) brachytherapy was prescribed to the proximal 2/3 of the vagina using the nucleotron microselectron