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Original Research Article

Docetaxel, carboplatin and 5-fluorouracil (TCF) chemotherapy in patients with unresectable metastatic carcinoma of cervix

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ABSTRACT

Objectives. This retrospective study evaluates the efficacy and safety of chemotherapy with docetaxel, carboplatin and 5-FU (TCF) in patients with metastatic cervical carcinoma.

Methods. Between January 2006 and April 2007, 23 patients with metastatic cervical carcinoma were included in the study. Patients fulfilling the following criteria were enrolled: histologically confirmed metastatic cervical carcinoma; documented progressive disease (PD) after cisplatinum-based treatment if applicable; an Eastern Cooperative Oncology Group (ECOG) performance scale of 0–2; not candidates for local therapy; measurable metastatic lesions as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST); and adequate hematologic, hepatic, and renal functions. Treatment consisted of intravenous docetaxel at 60 mg/m^2 diluted in 500 ml 5% glucose administered over 1 h on day1, followed by carboplatin (AUC of 5 or 6) given as a 1-h intravenous infusion delivered on day 2, followed by 5-FU at 500 mg/m^2 diluted in 500 ml normal saline continuously infusion for 24 h for 2 days on day 2. Chemotherapy was repeated every 21 days, and a total of 1–5 courses were performed.

Results. There were 3 (13%) complete responses; 4(17%) partial responses; 6 (26%) with stable disease, and 10 (43%) with disease progression. The overall response rate was 56%. After a median follow-up of 16 months, the median overall survival was 12 months. Neutropenia was the most severe toxicity.

Conclusions. The combination of docetaxel, carboplatin and 5-fluorouracil (TCF) appears to have activity in metastatic cervical carcinoma with acceptable toxicity profile.

Introduction

Carcinoma of the cervix is considered a relatively chemotherapy-resistant disease. The incidence of failure at various sites in carcinoma of the uterine cervix is closely correlated to the disease stage. Surgery, irradiation, and chemotherapy have been combined in various settings in an effort to improve disease control and survival rates of patients with cervical cancer. Despite aggressive local therapy with excellent local control, the incidence of distant metastases in patients with invasive carcinoma of the uterine cervix is high and the majority of recurrence occurs within 2 years of initial treatment [1].

Several single chemotherapy agents and combination regimens are active in patients with metastatic disease or recurrences that are not amenable to local therapy. Based upon an overview, the most active single agents (with response rate) are cisplatin (19%) [2], ifosfamide (20%) [3], paclitaxel (17%) [4], vinorelbine (RR 14%) [5] and topotecan (17%) [6]. In addition, comparing to single agent cisplatin, combined therapy with cisplatin and ifosfamide was associated with a significantly better response rate (31 vs. 18%) and median time to progression (4.6 vs. 3.2 months), with similar median overall survival (8.3 vs. 8.0 months). The chemotherapy side effects of leukopenia, renal toxicity, as well as central and peripheral neuropathy were worse with the combination regimen. Another trial compared cisplatin alone to the combination of cisplatin plus paclitaxel in patients with stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix [7]. The combination of cisplatin plus paclitaxel was associated with a higher RR (36 vs. 19%), and median PFS (4.8 vs. 2.8 months), but survival was similar in both arms. In addition, the randomized trial that shows a survival benefit with multiagent therapy was the comparison of cisplatin to cisplatin plus topotecan [8]. The study showed that the topotecan/cisplatin arm had a higher response (27% vs. 13%), a higher progression-free survival (4.6 vs. 2.9 months), and median survival (9.4 vs. 6.5 months), but was associated with significant toxicity (70% vs. 1% grade 3 or 4 neutropenia). To differentiate between these established doublets, a randomized trial was performed to compare cisplatin/vinorelbine, cisplatin/gemcitabine, and cisplatin/topotecan to the cisplatin/paclitaxel arm [9]. It was found that the three experimental cisplatin

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doublets did not show any benefit compared to the reference arm, cispatin/paclitaxel. However, there was a trend favoring the treatment with cisplatin/paclitaxel for response rate, progression-free survival, and overall survival.

Because paclitaxel plays an important role in the treatment of cervical cancer, it is possible to use docetaxel as an alternative to paclitaxel to increase the response rate. In fact, docetaxel and paclitaxel have the same mechanism of action and represent a unique class of cancer chemotherapeutic drugs. Both agents promote tubulin assembly in microtubules, stabilize microtubules, and inhibit depolymerization to free tubulin, thus blocking cells in M phase, the most radiosensitive phase the of cell cycle [10].

Recently, Watanable et al. [11] reported that the combination use of docetaxel and nedaplatin achieved 40% of partial response rate in 20 patients with recurrent squamous cell cervical carcinoma, even in patients previously treated by cisplatin concurrent chemoradiotherapy. In a Phase 1 study of docetaxel as a radio-sensitizer for locally advanced squamous-cell cervical cancer, 67% of patients had no evidence of disease with follow-up ranging from 10 to 33 months [12]. Garcia et al. [13] reported the effectiveness of docetaxel in a Phase 2 trial of refractory squamous-cell carcinoma of the cervix. The median time to progression was 3.8 months, whereas the median survival time was 7 months. The most frequently reported adverse events were neutropenia, infection, gastrointestinal, and constitutional.

Kosmas et al. [14] evaluated the paclitaxel/ifosfamide/cisplatin (TIP) combination in relapsed and/or metastatic cervical cancer. Overall response rate (RR) was 62%, complete response (CR) was 26%, and partial response (PR) was 36%. Responses according to the relapse site were overall RR: 32% within previously irradiated pelvis vs. 75% in extra-pelvic sites. Median time to progression (TTP) was 7 months and median overall survival (OS) was 16.5 months. Toxicities included grade 3–4 neutropenia, 83% (21% febrile neutropenia), grade 3–4 thrombocytopenia, 9%, no grade 3 neuropathy (35% grade 2), grade 2 asthenia/fatigue, 15%, and no treatment-related deaths.

In addition, carboplatin/paclitaxel was also found to be an active combination in advanced and recurrent cervical cancer, with a median overall survival (OS) of 21 months [15]. Interestingly, Nagao reported that the combination of docetaxel and carboplatin is an effective and safe treatment for advanced or recurrent cervical carcinoma, with the overall response rate of 76% [16]. Recently, docetaxel, cisplatin and fluorouracil (TPF) chemotherapy regimen was found to be effective in a randomized Phase 3 trial of the treatment of squamous-cell carcinoma of the head and neck. The study compared induction chemotherapy with docetaxel plus cisplatin and fluorouracil (TPF) with cisplatin and fluorouracil (PF), followed by chemoradiotherapy [17]. Five hundred one patients (all of whom had Stage III or IV disease with no distant metastases and tumors considered to be unresectable or were candidates for organ preservation) received either TPF or PF induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin therapy and radiotherapy for 5 days per week. Estimates of overall survival at 3 years were 62% in the TPF group and 48% in the PF group; the median overall survival was 71 months and 30 months, respectively. Rates of neutropenia and febrile neutropenia were higher in the TPF group. Patients with squamous-cell carcinoma of the head and neck who received docetaxel plus cisplatin and fluorouracil induction chemotherapy plus chemoradiotherapy appeared to have a significantly longer survival than did patients who received cisplatin and fluorouracil induction chemotherapy plus chemoradiotherapy.

Before the initiation of the TCF regimen in our institution, chemotherapy with doublets combination was used with various results. Because patients' tolerance to these doublets was very low due to toxicity, we therefore set out to use the TPF-like regimen in treating the metastatic carcinoma of the cervix. To reduce the toxicity and to be in line with patient's compliance, we substituted cisplatin with carboplatin. So far, there was no information available regarding the use of docetaxel, carboplatin and 5-fluorouracil (TCF) regimen in the treatment of metastatic carcinoma of the cervix. Therefore, we conducted a retrospective study to assess the efficacy and safety of combination chemotherapy with TCF regimen in previously-treated patients with metastatic cervical carcinoma.

Methods

Patients

Between January 2006 and April 2007, 23 patients with metastatic cervical carcinoma were included in the study. Patients fulfilling the following criteria were enrolled: histologically confirmed metastatic cervical carcinoma; documented (PD) after cisplatin-based treatment; an Eastern Cooperative Oncology Group (ECOG) performance scale of 0–2; not candidates for local therapy; measurable metastatic lesions as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST); and adequate hematologic, hepatic, and renal functions. The disease was staged according to American Joint Committee on Cancer (AJCC). Exclusion criteria included: >80 years of age, any small cell carcinoma component, an Eastern Cooperative Oncology Group (EGOC) performance status >3, a neutrophil count of $<1\times10^9$/l, or prior cytotoxic therapy (except when used for radiosensitization). All patients gave written consent before the initiation of any treatment.

Treatment

The chemotherapy regimen was modified from TPF regimen, with carboplatin replacing cisplatin on day 2, while reducing 5-FU infusion from 4 to 2 days. This is to reduce the severe toxicity of TPF regimen. The treatment consisted of intravenous docetaxel at 60 mg/m^2 diluted in 500 ml 5% glucose administered over 1 h on day1, followed by carboplatin (AUC of 5 or 6) given as a 1-h intravenous infusion delivered on day 2, followed by 5-FU at 500 mg/m^2 diluted in 500 ml normal saline continuously infusion for 24 h for 2 days on days 2 and 3. Chemotherapy was repeated every 21 days, and a total of 1–5 courses were performed. Dose adjustment should be done when grade 4 hematological or grade 3, 4 nonhematological toxicities appeared, a dose reduction was of 25% in subsequent cycles. Antiemetic therapy with granisetron and dexamethasone was administered to all patients. However, chemotherapy was immediately interrupted if there was evidence of progressive disease (PD) and/or severe toxicity. Prophylactic granulocyte colony-stimulating factor was permitted only if a patient had febrile neutropenia or infection, a delay in recovery of the absolute neutrophil count at day 14, or grade 4 neutropenia persisting for 5 days or more.

Evaluation of response and toxicity

For each patient, baseline evaluations included a complete physical examination, computed tomography and/or magnetic resonance imaging of the target lesion, blood-cell count, serum chemistries. Before receiving each dose of docetaxel, patients underwent a complete blood-cell count. Blood chemistry studies were repeated before each treatment cycle. Radiologic assessments were performed only after two treatment cycles unless required earlier because of clinical situation. Response criteria were based on the Response Evaluation Criteria in Solid Tumor (RECIST) Committee. If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after 4 weeks. Toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria (CTC, version 3.0). Treatment was delayed when granulocyte count was under 1500/mm^3 or the platelet count was less than 100,000/mm^3. Dose reductions were