A phase I study of docetaxel as a radio-sensitizer for locally advanced squamous cell cervical cancer

Edwin A. Alvarez a,⁎, Aaron H. Wolfson b, J. Matt Pearson b, Meredith P. Crisp c, Luis E. Mendez d, Nicholas C. Lambrou e, Joseph A. Lucci III b

a University of California, San Diego School of Medicine, USA
b University of Miami, Leonard B. Miller School of Medicine, Sylvester Cancer Center, FL, USA
c University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, USA
d South Florida Gynecologic Oncology, Coral Gables, FL, USA
e Baptist Health South Florida, Division of Gynecologic Oncology, FL, USA

A B S T R A C T

Objectives. This study was designed to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of weekly docetaxel with concurrent radiotherapy (RT) for the primary treatment of locally advanced squamous cell carcinoma of the cervix.

Methods. Eligible patients included those with locally advanced squamous cell cervical cancer without para-aortic lymph node involvement. Docetaxel dose levels were 20 mg/m², 30 mg/m² and 40 mg/m² given intravenously weekly for 6 cycles. Three patients were to be treated at each dose level and 6 to receive the MTD.

Results. Fifteen patients completed 4–6 cycles of chemotherapy. One of three patients experienced 2 delayed grade 3 severe adverse events (SAE) at the 20 mg/m² dose level consisting of colonic and ureteral obstruction. At the 30 mg/m² dose level, 1/4 patients had a probable treatment-related celiotomy due to obstipation and a necrotic tumor. Of the 8 patients treated at the 40 mg/m² dose level, 1 experienced grade 3 pneumonitis, likely treatment related. Overall, 10/15 (67%) experienced grade 1 or 2 diarrhea, 6 had grade 2 hematologic toxicity, and 2 had grade 2 hypersensitivity. 10 of 16 patients (67%) had no evidence of disease with follow-up ranging from 10–33 months (average 23 months).

Conclusions. The recommended phase II dose of docetaxel administered weekly with concurrent radiotherapy for locally advanced squamous cell carcinoma of the cervix is 40 mg/m².

© 2009 Elsevier Inc. All rights reserved.

Introduction

Cervical cancer is the 3rd leading cause of cancer death for women in the world [1]. In the United States, 11,150 new cases of cervical cancer and 3670 deaths were expected in 2007. Five year survival rates by stage at diagnosis range from 92% in women with local invasion, to 55.5% with regional spread, and 14.6% with distant spread [2].

Current treatment for locally advanced cervical cancer has been defined by a series of studies showing the benefit of chemoradiation using cisplatin with a combination of external beam and brachy-therapy [3]. Combination chemoradiation has been shown to decrease cancer deaths over radiation alone by 30–50% [4].

Among these are bone marrow suppression, neurotoxicity, gastrointestinal, and renal toxicities. Many patients with locally advanced disease present with renal compromise, thus curtailing cisplatin use. Due to these toxicities options for radiation sensitization for cervical cancer are sought. Important considerations are primary anti-tumor effect, radio-sensitization, non-renal excretion, acceptable toxicity, and ease of administration.

Docetaxel acts by promoting microtubule assembly but inhibits subsequent microtubule depolymerization, thus blocking cells in the G2/M phase which is 2.5 times more sensitive to radiation than the G1/S phase [7–9]. In vitro studies have confirmed the radiation sensitizing effects [10], and the radioresistant S-phase cytotoxicity of docetaxel [11,12]. Due to biliary excretion, renal function does not affect docetaxel dosing, or toxicity [13].

Concurrent docetaxel and radiation therapy has been studied outside the context of cervical cancer treatment, and has been found to have acceptable toxicity. Weekly docetaxel administration with concurrent radiation has been evaluated in several phase I and II studies [14–20]. These studies included non-operable breast cancer, prostatic cancer, non-small cell lung carcinoma, and pancreatic cancer.
Docetaxel maximum tolerated doses ranged from 20–35 mg/m²/week typically with 60 Gy radiotherapy and 5–6 week courses. Phase II overall response rates ranged from 46–80%. Phase I and II trials of docetaxel with concomitant radiation therapy in head and neck cancers have used doses ranging from 10–25 mg/m² for 4 to 7 weekly cycles. [21–25].

Our aim was to find a maximally tolerated dose of weekly docetaxel with concurrent pelvic external beam radiation, followed by brachytherapy in a cohort of patients with locally-advanced squamous cell cervical cancer. Although not a specific endpoint, we also aimed to evaluate the clinical activity of this combination.

Materials and methods

Patient eligibility

Approval for this study was obtained from the institutional review board at the University of Miami. Patients were recruited using informed consent in the hospitals and Gynecologic Oncology clinics of the University of Miami and Jackson Memorial Hospital. All patients underwent pretreatment evaluation using International Federation of Obstetricians and Gynecologists (FIGO) standards. Evaluation included physical exam, chest x-ray, CT scan, and, optionally, cystoscopy and proctoscopy, and/or intravenous pyelogram.

Eligible patients were 18 years old or greater, had biopsy-proven and untreated squamous cell carcinoma of the cervix, stages IIB through IVA, had negative para-aortic lymph nodes as determined by lymphadenectomy, CT scan or PET scan, were scheduled for definitive chemo-radiation, had adequate bone marrow, renal and hepatic function, and a GOG Performance Status of 2 or less. Additionally, laboratory criteria for entry included white blood cell count ≥ 3000/mm³, absolute granulocyte count ≥ 1500/mm³, platelets ≥ 100,000 mm³, total bilirubin ≤ 1.5 times upper normal limit, serum creatinine ≤ 1.5 times upper normal limit, and AST or ALT ≤ 2.5 times upper normal limit. Patients with enlarged para-aortic nodes were required to have biopsy-documented negative histology before entry.

Treatment regimen

All patients were planned to receive an approximate total radiation dose of 85 Gy prescribed to point “A”. The external beam radiation therapy (EBRT) phase involved the administration of approximately 45 Gy at 1.8 Gy per fraction using at least 10 MV photons to the whole pelvis. A standard pelvic four-field “box” summated technique was used. Fields extended from the L4–5 interspace to the ischial tuberosities. Customized blocking was used to minimize irradiation of the normal surrounding tissues. After completing whole pelvic EBRT, patients then received approximately 9 Gy additional EBRT as a bilateral parametrial boost. After EBRT, patients then were candidates to have a low-dose-rate intracavitary brachytherapy implant to bring the total dose to point “A” to 85 Gy.

This was a dose-escalating study with 3 docetaxel dose levels and 3 planned patients per dose level. The maximum planned, or maximum tolerated dose (recommended phase II dose) cohort was to consist of 6 patients. The dose levels were: 20, 30, and 40 mg/m² IV weekly by standard infusion for 4–6 cycles given during radiation therapy. The total course of chemo-radiation was planned to last no more than 8–10 weeks. The use of colony stimulating factors and erythropoietin was permitted.

Weekly assessments for toxicity were performed during treatment and at 30 days after completion of chemotherapy. If no grade III/IV severe adverse effect (SAE) was observed in any of the three patients in a cohort, then dose escalation would occur for the next cohort. One SAE would prompt expansion of the cohort to 6 patients. A second SAE would prompt expansion of the prior dose-level cohort to 6 patients, and prevent further dose escalation. The recommended phase II dose would be the dose with less than 2 SAE’s per 6 patients. If no DLT was found, then the phase II recommended dose would be the maximum dose planned. If toxicity forced a treatment delay, the patient was restarted at the prior dose level. Adverse effects and performance levels were monitored serially using GOG toxicity criteria based upon CTEP v2.0 guidelines [26].

Response

Clinical responses were measured using RECIST criteria [27] or pelvic exam findings. Complete response (CR) is defined by disappearance of tumor by physical exam and/or CT imaging. Partial response (PR) is defined by more than a 30% decrease in the sum of the longest diameter (LD) of the target lesion. Progressive disease (PD) is at least a 20% increase in the sum of the LD of the target lesions, or the appearance of new lesions. Stable disease (SD) consists of neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Recurrent disease is defined by a complete response followed by reappearance of disease.

Statistical methods

Median values for continuous variables are reported. The Kaplan–Meier product limit method was used to estimate 2-year progression-free survival rates (Fig. 1) [28]. Time to progression and length of survival were measured from the completion of therapy. Those who were alive and without documented recurrence were censored for the progression-free analysis. Analysis was performed with Statistix 9 software.

**Fig. 1.** Kaplan–Meier survivorship.
Results

Table 1 shows patient characteristics. Of 25 patients screened, 10 underwent alternative treatment (such as radical hysterectomy or emergent radiation) or withdrew consent. The majority of patients were Hispanic or Haitian, which is characteristic of our patient population. Most were staged FIGO stage IIB or IIBB. Most patients had squamous histology; one had adenocarcinoma and remained disease free at 25 months, while another had carcinoma with anaplastic and clear cell features and experienced recurrence at 14 months. Although entry criteria specified squamous histology and grade IIB–IVA, 2 patients with non-squamous histology and 2 patients with less than IIB stage were inadvertently screened, consented, and treated. Because we are reporting our phase I toxicity data, we will include them in this report.

Fifteen patients completed 4–6 cycles of chemotherapy. Three patients were treated at 20 mg/m². Four were treated at 30 mg/m² and 8 patients treated at 40 mg/m². Total number of cycles was 77. Median number of chemotherapy cycles per patient was 5.1. Reasons for completing less than 5 cycles of chemotherapy were: noncompliance (2) or adverse event (1). One patient was lost to follow-up after 4 cycles. Forty percent received all 6 cycles, 33% received 5 cycles and 27% received 4. Follow-up ranged from 10–33 months at time of manuscript preparation. Median follow up was 23 months.

Of the 15 study patients, 3 did not receive brachytherapy application. Two of these had either disease persistence or progression at the culmination of external beam therapy, while the other did not tolerate external beam therapy and elected to discontinue therapy altogether after 4 cycles of chemotherapy. This latter patient is still alive and disease free at 17 months of follow up. The remaining 12 protocol patients all completed their radiation therapy within 8 total weeks and received approximately 85 Gy (+/−5%) to point “A”.

Toxicity

This treatment regimen was well tolerated. Two delayed grade 3 severe adverse events (SAE) were observed at the 20 mg/m² dose level in one patient. This patient experienced complete colonic obstruction due to radiation fibrosis 32 months after the conclusion of treatment. She also had bilateral ureteral stenosis requiring nephroureteral stents. She underwent recto-sigmoid resection and end colostomy, and was without evidence of disease. At the 30 mg/m² dose level, 1 had a treatment-related complication which presented as a colonic obstruction and pelvic abscess. She underwent celiotomy and was found to have obstruction and necrotic tumor. She received only 4 chemotherapy cycles due to surgery, but remained disease free at 26 months of follow up. At the 40 mg/m² dose level, 1 patient experienced grade-3 pneumonitis after 5 cycles of chemotherapy, likely treatment related. She also experienced disease progression, so treatment was halted.

Overall, 10/15 (67%) experienced grade I or II diarrhea, 6 had grade II hematologic toxicity (40%), 1 had grade 3 pneumonitis, 1 had grade 4 colonic obstruction and a grade 3 ureteral stricture, and 2 had grade II hypersensitivity. See Tables 2 and 3. Aside from the patient with colonic and ureteral obstruction, no other long term treatment complications such as fistulae have been observed.

Treatment response

Although this study was not designed to provide data about treatment efficacy, we will report on our experience regarding treatment response. Ten of 15 (67%) patients have no evidence of disease with follow-up ranging from 10 to 33 months and an average of 23 months. Mean time to disease recurrence was 9.7 months.

Of the patients that recurred, 1 recurred at the 20 mg/m² dose level 9 months after finishing the treatment. One patient recurred at the 30 mg/m² dose level 29 months after finishing the therapy. One patient at the 30 mg/m² dose level had persistent disease upon culmination of EBRT — this patient’s tumor had features consistent with clear cell carcinoma. One patient at the 40 mg/m² dose level experienced disease progression during treatment, while another patient at the 40 mg/m² level was diagnosed with recurrence 10 months after finishing the therapy.

There were 2 patients who did not have squamous histology in the study. One with adenocarcinoma recurred but is now without evidence of disease, while the patient with carcinoma displaying clear cell and anaplastic features had persistent disease at the culmination of chemotherapy and teletherapy. Of the patients that recurred, 1 had stage IIIB and 4 had stage IIBB disease.

No patient had disease recurrence or persistence limited to the pelvis. The patient with clear cell carcinoma had persistent cervical disease and had metastatic disease to the para-aortic lymph nodes at

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>15</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median 54.3, Range 38–73</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>White − Caucasian 0, Black (African American) 1, Black (Haitian) 3, Hispanic 10, Asian 1</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Squamous 13, Adeno 1, Clear cell 1</td>
</tr>
<tr>
<td><strong>FIGO stage</strong></td>
<td>IIB 1, IIA 1, IIB 5, IIIA 1, IIIB 7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel dose (mg/m²)</strong></td>
<td>20 30 40</td>
</tr>
<tr>
<td><strong>Number of patients treated at dose level</strong></td>
<td>3 4 8</td>
</tr>
<tr>
<td><strong>Event</strong></td>
<td>Grade</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
</tr>
<tr>
<td>Nausea</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
</tr>
<tr>
<td>Colonic obstruction</td>
<td>3</td>
</tr>
<tr>
<td><strong>General conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1–2</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>3</td>
</tr>
<tr>
<td>Cystitis</td>
<td>1–2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1–2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1–2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>6</td>
</tr>
</tbody>
</table>
the time of exploratory laparotomy. Three patients had para-aortic recurrence or progression of which one also had a peri-urethral recurrence. Of these, one had recurrent pelvic tumor and a microscopically positive para-aortic node at the time of pelvic exenteration. She underwent post-operative chemotherapy and has been free of disease for the last 2 years as of manuscript preparation. Aside from the patient who underwent pelvic exenteration, all patients with recurrence are alive with disease at the time of manuscript preparation.

**Discussion**

We conclude that docetaxel 40 mg/m² weekly in conjunction with EBRT (maximum of 85 Gy over 6 weeks) is a tolerable dose for use as a radiosensitizer for patients with locally advanced squamous cervical cancer. Furthermore, in this small number of patients, 67% have not recurred at an average 23 months of follow up.

One acute dose limiting toxicity was experienced at the final dose level of 40 mg/m². This patient underwent admission to the intensive care unit because of dyspnea, but did not require intubation. The cause of her dyspnea was determined to be pneumonitis, although no biopsy was done to confirm the diagnosis. Pneumonitis in this patient was felt to possibly be treatment related.

Pneumonitis has been noted to be a potential adverse event in treatment with docetaxel. Indeed many case reports have been published reflecting this clinical entity in tumors including non-small cell lung cancer and prostate cancer [29–33]. The incidence of greater than grade 2 pneumonitis complicating docetaxel therapy ranges in the literature from 5.6 to 8% [34,35].

One patient in the 30 mg/m² had a treatment related surgical exploration for what was felt to be bowel obstruction and pelvic abscess. The final diagnosis, however, was constipation and necrotic tumor. Although treatment related, we did not attribute treatment with docetaxel as the cause of the patient’s constipation and therefore continued with dose escalation.

One patient experienced a delayed treatment-related grade 3 toxicity which did not influence progression of dose levels. This patient had radiation fibrosis of the colon and ureters necessitating colostomy and nephro-ureteral stents. Such complications of pelvic radiation with or without chemotherapy are well known though rare. Severe urologic complications necessitating urologic intervention occur in 1.24% of patients who have undergone radiation therapy for gynecologic carcinoma [36]. Actuarial risk for severe ureteral stenosis has been reported by Eifel to range from 1.0 to 2.5% up to 20 years after therapy with radiation for cervical carcinoma [37]. Eifel also reported a 1.0 to 1.5% actuarial risk from 5 to 20 years for rectal stricture in the same group of patients. Although it is impossible to know from this small study if rectal and ureteral strictures in this patient were related to treatment with docetaxel, we feel it was most likely due to radiation therapy.

The other toxicities in this study were mainly grade 1 or 2 diarrhea and nausea/vomiting. These were easily managed, and did not cause delay of therapy. These did not seem to have a clear relation to dose level. Fatigue was evident in review of our patient’s progress, but aside from global functioning scales, we did not capture the full extent experienced by our patients undergoing pelvic radiation and docetaxel chemotherapy.

Although recurrence-free survival was not an endpoint of the study, it is useful to report our experience. This study had a 67% recurrence-free rate at an average follow-up of 23 months in patients with mainly squamous cervical cancers ranging in stage from IB2 to IIIB. All those who have recurred are alive with disease at the time of manuscript submission. Of note, the patients without squamous histology recurred or persisted. The recurrences were all in stage IIIB (adenocarcinoma, 1 patient) or stage IIIB (4 patients). Given that 13/15 patients were stage IIB to IIIB, this recurrence rate compares favorably to the Gynecologic Oncology Group trial numbers 85 and 120 which had 55% and 67% percent survival rates at more than 5 years, respectively [38,39]. Each of these trials included a similar population as is found in this study. However, follow up was longer in each of the trials, 30 months and 8.7 years, respectively.

None of the patients in this study had a recurrence limited to the pelvis. In comparison, GOG 85 reported a 25% pelvic-only recurrence rate in patients treated with radiation, cisplatin and 5-FU. This may reflect an improved radiation sensitizing effect with docetaxel, or it may be that we have insufficient follow-up to fully demonstrate the recurrence patterns in this sample.

Cisplatin is known to be effective as an anti-cervical cancer cytotoxic in-vitro, in-vivo, and in clinical trials [40,41]. However, its efficacy as a radiation sensitizing has not been fully established in preclinical models of cervical cancer. Indeed, cisplatin failed to demonstrate synergy with radiation in 15/19 cervical cancer cell lines in one study [42]. It is quite possible that the survival advantage due to chemo-radiation with cisplatin for cervical cancer is due to additive cytotoxic effect, not via synergistic radio-sensitization. Docetaxel has been shown to be a potent cytotoxic against human cervical carcinoma cells in cell culture and in xenograft mouse models [43]. Furthermore, docetaxel has been shown to be at least a moderate radiosensitizer for human cervical cancer cells [44].

Clinically, cisplatin as a single agent seems to have an advantage over docetaxel. The overall response rate for neoadjuvant single-agent docetaxel chemotherapy for locally advanced cervical cancer was 34% in a phase II study [45]. This contrasts with the response rates for neoadjuvant single-agent cisplatin of 85% overall response and 28% complete response in locally advanced cervical carcinoma [46].

Although our study demonstrates a feasible dose of docetaxel for further clinical study as a radiation sensitizer for locally advanced cervical cancer, perhaps the radiosensitizing effect of docetaxel might be best combined with the superior cervical cancer cytotoxic, cisplatin. One can argue that while docetaxel might be better at reducing pelvic recurrence in combination with radiation, it may be useful to add a platinum agent to capitalize on the ability to decrease distant recurrence. This question deserves further study. Docetaxel has been added to platinum agents in the treatment of head and neck cancers, without significant increases in toxicity [47]. Phase III trials comparing chemoradiation with docetaxel vs a platinum agent with or without docetaxel have not been done.

Because advanced cervical cancer patients can present with obstructive or intrinsic uropathies where platinum agents would be contraindicated [6], docetaxel radio-sensitization may be an acceptable alternative. This study did not allow entry of patients with uncorrected obstructive uropathy, but does demonstrate the fea-
sibility of combining docetaxel with pelvic radiation. Further study of this subgroup will likely need the support of a cooperative group.

With observed efficacy and with an acceptable amount of toxicity at the highest dose, the recommended phase II dose of docetaxel is 40 mg/m² administered weekly with concurrent radiotheraphy at a total dose of 85 Gy over 6 weeks for locally advanced cervical carcinoma. Hematologic and gastrointestinal toxicities are minimal or manageable.

Conflict of interest statement

Aaron H. Wolfson, M.D. declares a commercial licensing agreement with BioNucleonics, Inc and a paid consulting agreement with Soft, Inc. The other authors of this study have no conflicts of interest to disclose.

Acknowledgment

The authors would like to thank Fanchette August, RN for her contributions to this study including patient care coordination and data management.

References