Original Articles

Radiation therapy with concomitant and adjuvant cisplatin and paclitaxel in high-risk cervical cancer: long-term follow-up

P.A. Argenta[1], *M.D.*; **R. Ghebre**[1], *M.D.*; **K.E. Dusenbery**[2], *M.D.*; **M.D. Chen**[1], *M.D.*; **P.L. Judson**[1], *M.D.*; **L.S. Downs Jr.**[1], *M.D.*; **L.F. Carson**[1], *M.D.*

[1]*Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Women's Health*
[2]*Department of Therapeutic Radiation, University of Minnesota, Minneapolis, MN (USA)*

Summary

Introduction: Chemo-potentiation of radiation improves survival in women with cervical cancer. Our group has previously demonstrated the tolerability of weekly paclitaxel combined with cisplatin during radiation therapy. We sought to determine the efficacy of this regimen in patients with "high risk" cervical cancer, and to determine the short- and long-term toxicity of this approach.

Methods: We prospectively enrolled surgically staged patients with positive peritoneal cytology, resectable nodal metastases, or primary tumor > 6 cm. Patients were treated using external beam radiation with concomitant cisplatin (50 mg/m^2) during weeks 1, 4, and 7, and weekly paclitaxel (50 mg/m^2), followed by four courses of adjuvant cisplatin (50 mg/m^2) and paclitaxel (135 mg/m^2). Toxicity, overall, and disease-free survival were evaluated.

Results: Twenty-three patients were enrolled, and 21 were evaluable. Patient allotment by FIGO stage was: IB_1 - seven, IB_2 - five, IIA - two, IIB - four, IIIB - two, IV - three. Twenty patients (95%) completed radiation treatment (median dose to point A was 8278 cGy). Seventeen patients (81%) completed all chemotherapy. At a median follow-up of 58 months the overall survival was 68%. Overall survival for patients with clinical Stage I and II disease was 82% at a median of 64 months. Hematologic toxicity was common but rarely resulted in treatment delays. Late complications requiring intervention (obstruction, fistula, significant lymphocyst) occurred in 11 patients (52%).

Conclusion: The combination of paclitaxel and cisplatin appears efficacious in "high-risk" cervical cancer patients. Hematologic toxicity was common but tolerable. Long-term survival was common in these patients, however late toxicity was significant. This regimen should be investigated in collaborative phase III trials.

Introduction

Cervical cancer ranks among the most common cancers in women despite a steadily falling incidence in the developed world. Even in the United States, where screening has been widely available for decades, approximately 10,520 new cases are anticipated yearly, with 40% presenting in advance of Stage I [1].

The benefit of potentiating radiation through the concomitant use of sensitizing chemotherapy in the treatment of advanced cervical cancer was initially demonstrated by Hreshchyshyn *et al.* in a study of the Gynecological Oncology Group that showed a near doubling of the median survival with the addition of hydroxyurea to radiation [2]. Recently, multiple well-designed, prospective, multicenter studies have demonstrated unequivocally the importance of chemotherapy-induced radiosensitization of cervical cancers [3-7]. Among these Whitney *et al.* observed that the combination of cisplatin and 5-fluorouracil was superior to hydroxyurea, demonstrating that radiosensitizing agents are not inherently equally efficacious [3]. Conversely, when cisplatin was used, outcomes were significantly improved across a variety of treatment schedules. Rose *et al.* demonstrated nearly equal efficacy of potentiation with weekly cisplatin at 40 mg/m^2 versus a combination of cisplatin (50 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day for 96 hours) given monthly during treatment [6]. Morris *et al.* observed similar benefits in survival using an every third week regimen of cisplatin and 5-fluorouracil. These results have led to efforts by our group and others to optimize the dosing and agents in chemo-radiation strategies.

The mild increase in acute toxicities, predominantly hematologic, from cisplatin-based chemo-potentiation appears tolerable, especially given the survival advantages demonstrated [3-7]. Delayed grade 3 and 4 complications resulting from combination therapy, such as fistulas, bowel obstruction, marked lymphedema, or lymphocyst formation are reported irregularly however, and "complication-specific" incidences in retrospective studies vary widely, ranging as high as 75% in long-term survivors [8-11]. The differences reported may reflect length of follow-up, intensity of surveillance and/or whether complications were felt attributable primarily to therapy.

Our group has previously reported data from a phase I study demonstrating the tolerability of combining intravenous paclitaxel (50 mg/m^2) with cisplatin (50 mg/m^2) during and after radiation therapy for advanced or high-risk cervical cancer [12]. Concomitantly, multiple phase

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II trials demonstrated potential benefits to adjuvant chemotherapy following chemotherapy-potentiated radiation [13]. The aim of this study was to determine the efficacy and toxicity of this regimen in patients with locally advanced, or high-risk cervical cancer.

Methods

Eligibility

Patients were eligible for enrollment if they had "high-risk cervical cancer" defined as histologically confirmed cervical cancer that was considered either unsuitable for curative treatment with surgery alone, or at high risk for recurrent or persistent disease following surgical staging. The former group included patients with unresected pelvic and/or paraaortic lymph node metastases, gross peritoneal disease, or Stage IV disease. The latter group included patients with resected gross disease who had positive peritoneal cytology, resected pelvic or paraaortic lymph node metastases, or a primary tumor greater than 6 cm in diameter. Patients with Stage IVB were eligible if all known tumor was within the radiation field.

All FIGO stages and all cell types, except small cell carcinoma, were eligible. All patients had a baseline GOG performance status of 0, 1, or 2 prior to enrollment, and had recovered from the surgical staging. Adequate bone marrow (white blood cell count > 3,000/μl, platelet count > 100,000/μl, and granulocyte count > 1,500/μl), renal function (creatinine < 2.0 mg%), and hepatic function (bilrubin < 1.5 institutional normal, SGOT, and alkaline phosphatase < 3 times the institutional normal) were required before entry.

Patients were excluded if they had previously been diagnosed with cancer, excluding non-melanoma skin cancer, or had received prior chemotherapy or therapeutic radiation. The University of Minnesota institutional review board approved this trial, and all patients gave informed consent prior to enrollment.

Pretreatment evaluation included medical history, physical examination, chest X-ray, abdomino-pelvic computed tomography, EKG, audiology examination, complete blood count, and serum assessment of liver and renal function.

Surgery

Prior to enrollment all patients underwent a staging procedure that included examination under anesthesia, cystoscopy, and proctoscopy, and pelvic and paraaortic lymphadenectomy with or without radical hysterectomy. Lymphadenectomy was performed using the extraperitoneal approach in most cases, but this approach was not mandatory for inclusion. Inguinal lymph node removal was allowed when clinically indicated.

Radiation

Radiotherapy was administered at fraction sizes of 175 cGy/day five days per week and was tailored to the operative findings. The superior treatment margin was designed to include one nodal group above the highest level of pathologically proven disease. Treatment fields included the pelvis and entire paraaortic node (PAN) field (top of the field at T9-10 interspace) in 11 patients, the pelvis and "low" paraaortic nodes (top of the field at L2-L3 interspace) in nine patients, and the pelvis and inguinal nodes in one patient. Radiation to the PANs was delivered using AP-PA opposed fields. The pelvis was treated with 4-field technique (AP PA and right and left lateral fields). Intracavitary, low dose rate radiation was also allowed in women with an intact uterus at the discretion of the radiation oncologist employing Fletcher suit after-loading tandem and ovoids in two applications.

The entire PAN nodes received between 4025 and 5075cGy (median 4725 cGy), the "low" PAN nodes between 4025 and 4900 cGy (median 4725 cGy, and the whole pelvis doses ranged from 3500 to 5175 cGy (median 4025 cGy) with additional parametrial boosts bringing the pelvic external beam doses up to a median of 4900cGy (range 4500 to 5175 cGy). Point "A" doses following brachytherapy ranged from 7254 to 9045 cGy (median 8277 cGy) and Point "B" doses from 5922 to 6064 cGy (median 6006 cGy).

Chemotherapy

During radiation treatments, chemotherapy was infused as follows: cisplatin (50 mg/m^2) delivered over one hour intravenously in weeks 1, 4, and 7 with standard hydration. Cisplatin was omitted in the latter weeks if creatinine clearance fell below 50 ml/min or serum creatinine rose above 2.0 mg/dl. Paclitaxel (50 mg/m^2) was delivered weekly as an intravenous infusion over three hours. All patients were premedicated with dexamethasone, diphenhydramine, and cimetidine.

Four additional courses of chemotherapy were administered every three weeks as follows: cisplatin (50 mg/m^2) and paclitaxel (135 mg/m^2) beginning three to four weeks after the completion of radiation therapy, provided that progressive or recurrent disease was not observed.

Follow-up and Assessment

During treatment patients had a complete blood cell count twice weekly, and physical examinations, serum electrolyte analysis and liver function tests every third week. Surveillance examinations began three weeks after treatment, and continued every three months thereafter. Patients underwent physical examination, review of medical history, tumor measurement (by CT scan or physical examination), chest X-ray, and complete blood cell count.

The primary and secondary endpoints were progression-free and overall survival, respectively. Tumor response could not be reliably assessed because a majority of patients had little or no clinically or radiologically-detectable residual after surgical staging. Progression-free interval was defined as the period from study entry to disease progression or recurrence, or to the date of last contact. Toxicities were graded according to the Gynecologic Oncology Group Common Toxicity manual.

Results

Patients accrued to the phase II portion of this study from February, 1996 until September, 1999. Twenty-three patients enrolled of which 21 were considered evaluable. Two patients who completed therapy at other institutions had inadequate documentation of follow-up, and were excluded from analysis. Patient characteristics are listed in Table 1.

Compliance

Twenty patients (95%) completed radiation with chemotherapy potentiation. No patients required a dose reduction of chemotherapy during radiation potentiation. Seventeen patients (81%) completed all four scheduled doses of consolidation chemotherapy. Two patients (9%), both Stage IV, demonstrated progressive disease during treatment and did not receive additional adjuvant chemotherapy. One patient discontinued treatment after three courses because of grade 3 nausea. One additional

Table 1. — *Patient characteristics (n = 21).*

Age (years)	
Median (range)	49 (25-80)
Previous pelvic surgery	9 (43%)
Tobacco abuse	10 (48%)
Stage I	
IB1	6 (29%)
IB2	4 (19%)
Stage II	
IIA	2 (10%)
IIB	4 (19%)
Stage III	
IIIA	0
IIB	2 (10%)
Stage IV	
IVA	1 (5%)
IVB	2 (10%)
Surgical intervention	
Lymphadenectomy only	14 (67%)
With radical hysterectomy	3 (14%)
With salpingo-oophorectomy	2 (10%)
Cystoscopy/proctoscopy only	1 (5%)
Inguinal lymph-node sampling	1 (5%)
Histology: incidence (%)	
Squamous	14 (67%)
Adenocarcinoma	3 (14%)
Adenosquamous	4 (18%)
Grade	
2	6 (29%)
3	8 (38%)

patient withdrew from the study without overt toxicity after one cycle of consolidation chemotherapy. Patients were analyzed on an intention to treat basis, and all evaluable patients were included.

Toxicity

Acute toxicities are summarized in Table 2. Grade 3 and 4 hematologic toxicities were common (71% of patients), however treatment delay (either chemotherapy or radiation) was required in nine cases (43%), and only two cases (10%) required extension of radiation therapy beyond 49 days. Grade 3 or 4 neuropathy was uncommon.

Delayed complications were observed in 11 patients (52%) (Table 2). The incidence of individual delayed complications was insufficient to draw conclusions regarding the specific impact of surgical staging, chemotherapy, radiation, or pre-existing medical liabilities.

Table 2. — *Complications and toxicity rates (grade 3 or 4).*

Hematologic	N (%)
Neutropenia	15 (71)
Anemia	2 (10)
Thrombocytopenia	0
Lymphocyst (symptomatic)	6 (29)
Requiring surgical drainage	5 (24)
Lymphedema	8 (38)
Neuropathy	2 (10)*
Radiation toxicity	
Skin	2 (10)
Diarrhea	2 (10)
Fistula formation	3 (14)**
Small bowel obstruction	1 (5)

* One patient had moderate diabetic neuropathy prior to treatment which progressed.

** Two patients experience vesico-vaginal fistulas (Stages IIIB and IVB), and one had both vesico- and recto-vaginal fistulas (Stage IVA).

Response

At a median follow-up of 58 months (range 7-102 months) the overall survival was 68%. The overall survival for patients with clinical Stage I and II disease was 82% at a median of 64 months of follow-up, and 20% for patients with clinical Stage III and IV disease with median follow-up and survival equal to 15 months. Disease-free and overall survival were identical after 26 months (Figure 1). Disease progression during treatment was observed in one patient (5%), and one patient died of intercurrent ailments prior to evaluation for response.

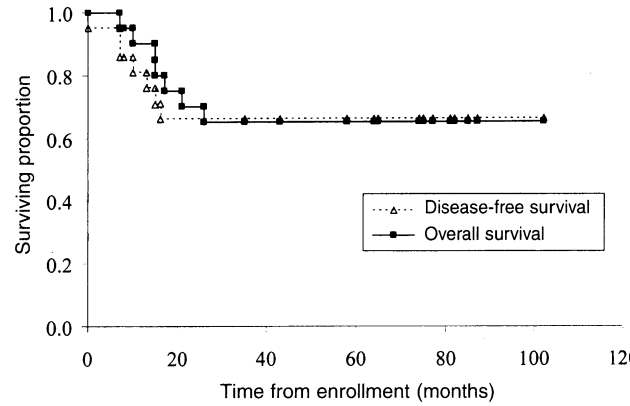

Figure 1. — Disease-free and overall survival.

Discussion

The results of this trial demonstrate that the addition of paclitaxel to cisplatin during and following radiation therapy for "high-risk" cervical cancer is feasible and efficacious, but is associated with high overall toxicity. We observed a significant number of grade 3 and 4 delayed toxicities, but also a long disease-free and overall survival. Relapse following treatment was attended by a grim prognosis, with most patients who recurred expiring from their disease.

Recent well-designed prospective trials have demonstrated a clear and consistent benefit from the addition of cisplatin-containing chemotherapy to standard radiation in the setting of clinically advanced disease and selected patients with low-stage disease [3-7]. While the benefit of radiation potentiation appears to be validated, the optimal patient population, dose and/or combination of chemotherapy has not been determined [14]. Pathologic risk factors that portend recurrence, such as lymph node metastasis and positive surgical margins, have been described but were used as eligibility criteria in only one of the above-mentioned collaborative trials, most of which did not include a primary surgical intervention [7]. The improving accuracy of modern radiology techniques,

and increasing use of primary surgical management of Stage IB2 cervical cancers, will likely increase the number of patients requiring postoperative radiation or falling de novo into the "high-risk" low-stage category, highlighting the need for additional study in this population.

Efforts to optimize chemo-sensitization strategies have included combining established sensitizing agents with novel cytotoxic and bioreductive agents into first-line therapy. This combination of cisplatin and paclitaxel was adopted to take advantage of the established efficacy of cisplatin and the potentially synergistic effect of paclitaxel, which stabilizes mictrotubule assembly trapping cells in the radiosensitive G_2/M portion of the cell cycle [12]. Paclitaxel as a single agent has been shown to have significant activity both in vivo and in the clinical setting of advanced or recurrent squamous cervical cancer [15-22]. Further, the combination of paclitaxel and cisplatin has been shown to be more efficacious than cisplatin alone in the setting of recurrent cervical cancer [23]. The dosing schedule used in this study was previously demonstrated to be tolerable in a phase I evaluation [12].

The treatment efficacy observed here compares favorably to regimens in current usage. The five-year disease-free and overall survival were comparable to those obtained by Morris *et al.* using radiation combined with cisplatin and 5-fluorouracil, and likewise similar to those reported by Peters *et al.*, despite their exclusion of patients with progressive disease during treatment from the final analysis [5, 7]. We observed grade 3 and 4 granulocytopenia rates that were almost twice as high as those reported for patients receiving potentiation with weekly cisplatin alone (68% vs 35%), however significant treatment delays were rare and the overall tolerability is reflected in the high percentage of patients completing treatment [3]. By comparison, we observed significant grade 3 and 4 long-term toxicity potentially attributable to therapy. Unfortunately, expected rates of delayed toxicity are ill defined. Peters *et al.*, in the only other prospective study to incorporate surgical staging prior to radiation, did not report their incidence of lymphedema, lymphocyst formation, or fistula formation, but these were common in our trial. The increased complication rate may be attributable, in part, to the inclusion of patients with advanced stage disease, who were excluded by Peters *et al.* Additionally, our study had a longer median follow-up (58 vs 42 months), though most delayed toxicity was apparent in the first year following treatment. In analyzing the patients who met criteria for inclusion in SWOG 87-97 we observed only one recurrence in 12 patients with a median follow-up of 70 months.

The role of surgical staging in the development of postoperative complications remains unresolved, and potential risks and benefits must be weighed judiciously [24]. Hasenburg *et al.* have demonstrated that surgical staging affects radiation field size in almost 45% of patients [25]. Cosin *et al.* further demonstrated a therapeutic benefit in progression-free survival of surgical staging attributed to the removal of bulky nodal metastases. This strategy was attended by a high incidence of lymphocyst formation (20%), lymphedema (18.4%), and an 11% risk of grade 4 RTOG gastrointestinal and genitourinary complications [26]. Most studies examining the potential hazards of surgical staging in cervical carcinoma are uncontrolled and include heterogeneous patient populations and varied adjuvant therapies, making the contribution of staging difficult to assess [27, 28].

In summary, the combination of cisplatin and paclitaxel appears effective in potentiating radiation in the treatment of cervical carcinoma. While acute toxicity was tolerable, long term toxicity however common and excessive, limiting the utility of this regimen in patients at low risk for persistence/recurrence. In more advanced cases however, toxicity must be weighed against the guarded short-term prognosis, and aggressive treatment may be warranted.

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Address reprint requests to:
P.A. ARGENTA
MMC 395
420 Delaware St. SE
Minneapolis, MN 55455 (USA)