Combined Chemotherapy and Radiation Therapy for Cervical Cancer

David H. Moore, MD, Indianapolis, Indiana

Key Words
Cervical cancer; radiation; chemotherapy; phase III trials

Abstract
More than 50% of patients with newly diagnosed cervical cancer will undergo radiation therapy as a primary treatment modality. Results from five phase III trials conducted by National Cancer Institute (NCI)-sponsored cooperative groups showed significant survival advantages from the addition of cisplatin-based chemotherapy to primary radiation therapy, changing the standard of care for patients with bulky or locally advanced cervical carcinoma. The majority of patients for whom treatment fails, however, have persistent pelvic disease. Other agents (alone or in combination with cisplatin) with potential synergy with radiation therapy should be studied. Future trials should investigate potential interrelationships between anemia, tumor hypoxia, angiogenesis, and the effectiveness of radiation therapy. Therapies specific to tumor hypoxia (tirapazamine) or strategies to maintain higher nadir hemoglobin levels during treatment (aggressive transfusion policies; erythropoietin) should also be studied. (JNCCN 2004;2:631–635)

In 2003, approximately 12,200 new cases and 4,100 deaths from cervical cancer occurred in the United States.1 Approximately 50% of patients will require either postoperative radiation therapy on the basis of surgical-pathologic high risk factors or radiation-based therapy on the basis of locally advanced disease that is not amenable to surgical extirpation. The majority of women for whom primary radiation therapy fails develop recurrent disease in the previous radiation treatment field. The purpose of this review is to highlight the clinical development of concurrent chemotherapy and radiation therapy for cervical carcinoma from preclinical rationale to phase III trials to standard of care.

Rationale for Concurrent Chemotherapy
If administered in combination with radiation therapy, chemotherapy theoretically could reduce local (via drug-radiation interactions) and distant relapse (via cytotoxic effects), and thus improve overall survival. Putative drug-radiation interactions include inhibition of sublethal damage repair; inhibition of recovery from potentially lethal damage; alterations in cellular kinetics; and decreases in tumor bulk leading to improved blood supply, tissue oxygenation, and increased radiosensitivity.2

Hydroxyurea
Hydroxyurea was one of the first drugs to be combined with radiation therapy. Hydroxyurea preferentially kills cells in the S-phase, resulting in an accumulation of cells at the G1−S interphase—a relatively radiosensitive phase of the cell cycle.3 It was later shown that hydroxyurea also prevents sublethal damage repair.4 In a randomized controlled trial of 40 patients with stage IIB cervical carcinoma, Piver et al.5 reported 5-year survival of 94% for radiation therapy plus hydroxyurea versus 53% for radiation therapy plus placebo. Although only one patient treated with hydroxyurea died of cervical carcinoma, four died of treatment-related complications. The Gynecologic Oncology Group (GOG) conducted a trial of hydroxyurea versus placebo concomitant to radiation therapy in patients with stage IIIB-IV cervical cancer. The protocol did not require pretreatment evaluation of the aortic lymph nodes. Among the 190 women entered in this study, only 104 were evaluable for toxicity and only 97
were evaluable for survival. The incidence of leukopenia in the hydroxyurea-treated group was significant, with 27 of 57 (47%) patients having nadir grade 2 to 4 leukopenia. The estimated median survival was improved with hydroxyurea versus placebo (19.5 vs. 10.7 months, respectively). Despite its apparent impact on survival, the majority of the oncology community did not adopt hydroxyurea as a treatment standard.

5-Fluorouracil and Mitomycin C

5-Fluorouracil (5-FU) has minimal activity against cervical cancer. However, considerable in vitro data indicate that 5-FU functions as a radiosensitizer. Byfield et al. showed that 5-FU drug-radiation synergy depended on drug concentration and was achieved only with prolonged drug exposures after irradiation. Consequently, most chemoradiation schemes with 5-FU have specified infusion rather than bolus therapy. Mitomycin C is an antitumor antibiotic that is preferentially activated by hypoxic cells. No evidence is available to suggest that mitomycin C functions as a radiosensitizer; therefore, the effects when it is given in combination with radiation therapy are additive and not synergistic. Thomas et al. published a large comparative study of radiation therapy plus 5-FU with or without mitomycin C, which did not yield improvements in either pelvic failure rate or overall survival with the addition of mitomycin C. The use of mitomycin C was associated with severe late bowel toxicity.

Nitroimidazoles

More than 20 years ago, researchers began to study compounds with high electron affinity resembling the effects of molecular oxygen as possible “hypoxic cell sensitizers.” The nitroimidazoles have been the most studied of these compounds. Misonidazole was the first of the nitroimidazoles to be combined with radiation therapy for the treatment of cervical cancer. Preclinical research had suggested that misonidazole was superior to metronidazole as a hypoxic cell sensitizer.

The Gynecologic Oncology Group conducted a randomized trial of misonidazole versus hydroxyurea in combination with radiation therapy in patients with stage IIIB to IVA cervical cancer and negative aortic lymph nodes based on pretreatment surgical staging. Among 296 evaluable patients, the median progression-free interval was 42.9 months for the hydroxyurea group versus 40.4 months for the misonidazole group. The initial report of this trial did not detect a survival difference between the two arms, although the pelvic failure rate was higher in the misonidazole group (23.6%) versus hydroxyurea group (18.0%) and the overall recurrence rate was higher in the misonidazole group versus the hydroxyurea group (43.9% vs. 36.7%, respectively).

A later report was issued after an extended follow-up that detected both a progression-free and survival advantage in the hydroxyurea arm. Consistent with adverse effects witnessed in phase I studies, central and peripheral neurologic toxicities were more common among patients taking misonidazole. More recent data suggest that nitroimidazoles may actually inhibit rather than augment the effectiveness of radiation therapy.

Pimonidazole is a misonidazole analogue with less neurotoxicity than the parent compound. In a randomized controlled trial of pimonidazole plus radiation therapy versus radiation therapy alone in locally advanced cervical cancer, there was a lower complete response rate, pelvic control rate, disease-free rate, and overall survival rate in the pimonidazole group. The Radiation Therapy Oncology Group reported their results in patients with stage IIIB to IVA cervical cancer of radiation therapy with or without misonidazole and found that misonidazole plus radiation was no better than radiation therapy alone.

Phase III Trials: Cisplatin

Cisplatin is one of the most active cytotoxic agents in the treatment of cervical cancer and has often been studied—either alone or in combination—as a “radiation sensitizer.” Researchers generally believe that cisplatin inhibits sublethal damage repair and may also function as a hypoxic cell sensitizer. Several uncontrolled studies of single-agent cisplatin concurrent to radiation therapy reported high clinical response rates. Considering the high clinical response rates achieved with radiotherapy alone, the effectiveness of cisplatin cannot be ascertained from these phase II studies. Choo et al. reported results from a randomized trial of radiation therapy, with or without cisplatin, in patients with locally advanced cervical cancer. Unfortunately, a disproportionate number of patients with stage IIIB disease were randomized to the radiation therapy-only arm. Recurrent cervical...
cancer occurred in 20% of the cisplatin group versus 28% of the radiation therapy-only group.

Until recently, there were too few prospective randomized trials of radiation plus chemotherapy to determine whether the addition of drug in fact yielded improved results over those achievable with optimal radiation therapy alone. In 1999, Whitney et al. published results from a Gynecologic Oncology Group (GOG 85) trial of cisplatin plus 5-FU plus radiation versus hydroxyurea plus radiation therapy for the treatment of locally advanced cervical carcinoma. All 363 eligible patients had locally advanced (stage IIB-IVA) cervical carcinoma and underwent pretreatment surgical staging to confirm negative common iliac and aortic lymph nodes. Median follow-up time among surviving patients was 8.7 years. Progression-free survival was significantly better in the cisplatin plus 5-FU arm \((P = 0.033)\). Disease progression occurred in 43% of patients randomized to cisplatin plus 5-FU versus 53% of patients randomized to hydroxyurea. Overall survival was also significantly better in the cisplatin plus 5-FU arm \((P = 0.018)\). The 3-year survival rate for women who received cisplatin plus 5-FU versus hydroxyurea was 67% versus 57%, respectively. Progression-free and overall survival differences were a result of reduced pelvic and lung recurrences with no difference in distant sites of progression. Severe or life-threatening leukopenia occurred in only 6 patients who received cisplatin plus 5-FU versus 46 patients who received hydroxyurea.\(^{22}\)

Morris et al.\(^{23}\) reported results from a Radiation Therapy Oncology Group (RTOG 9001) trial of radiation therapy plus concurrent cisplatin plus 5-FU chemotherapy versus pelvic plus aortic radiation therapy. Eligible patients had stage IB2 to IVA cervical carcinoma, or stage IB disease with positive pelvic lymph nodes. In that study, 403 patients were eligible, with median follow-up 43 months. Estimated 5-year survival rates were 73% versus 58%, respectively, for patients treated with chemotherapy versus radiation therapy alone \((P = 0.004)\). The addition of chemotherapy to radiation therapy was effective in reducing both the frequency of local recurrences and distant metastasis.

Two other GOG trials showed improved results with concurrent cisplatin therapy. Rose et al.\(^{24}\) reported a three-arm study (GOG 120) of pelvic radiation therapy plus concurrent chemotheray: cisplatin alone versus cisplatin plus 5-FU plus hydroxyurea versus hydroxyurea alone. All patients had stage IIB to IVA cervical cancer with surgically confirmed negative common iliac and aortic lymph nodes. The final analysis included 526 women with median follow-up duration of 35 months. Patients randomized to either cisplatin-containing arm showed significant improvements in progression-free and overall survival over patients who received hydroxyurea. Cisplatin-containing chemotherapy was effective in reducing the frequency of both pelvic and lung cancer relapses. Grade 3 to 4 leukopenia was more common in the three-drug combination than in either single-drug regimen. Because treatment with cisplatin alone was equally effective and less toxic than treatment with the three-drug combination, the authors recommended weekly cisplatin as the standard drug for chemoradiation therapy of cervical cancer.\(^{24}\)

Keys et al.\(^{25}\) reported results of a prospective trial (GOG 123) of weekly cisplatin plus radiation therapy versus radiation therapy alone in patients with bulky stage IB2 cervical cancer. All patients had pretreatment computed tomography, lymphangiography, or surgical staging showing negative aortic lymph nodes. Extrafascial hysterectomy was performed 3 to 6 weeks after the conclusion of radiation-based treatment. The rates of progression-free and overall survival were significantly higher in the cisplatin arm, as were the rates of transient hematologic and gastrointestinal side effects. Improved outcome in this trial was due to improved local control.\(^{25}\)

Peters et al.\(^{26}\) reported results from a phase III trial (Intergroup protocol 0107) conducted by the Southwest Oncology Group, Gynecologic Oncology Group, and Radiation Therapy Oncology Group to determine if radiation therapy and concurrent cisplatin plus 5-fluorouracil chemotherapy is superior to radiation therapy alone in patients with positive surgical margins, positive parametrial disease, or pelvic lymph node metastases. Eligible patients underwent radical hysterectomy for stage IA2 to IIA carcinoma of the cervix and were found to have the aforementioned high-risk factors (with negative aortic lymph nodes). Patients with common iliac lymph node metastasis received extended-field radiation therapy to include the aortic lymph nodes. The study included 268 patients, and median follow-up was 42 months. The concurrent administration of cisplatin plus 5-fluorouracil chemotherapy resulted in improved progression-free and overall survival, and both pelvic and extrapelvic recurrences were less frequent.\(^{26}\)
The relative risk of death in these five phase III trials was reduced by 30% to 50% with the addition of cisplatin or cisplatin-based chemotherapy to radiation therapy (Figure 1). The National Cancer Institute issued a clinical announcement stating, “Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.”

Future Directions
Despite these substantial gains, the majority of patients for whom cisplatin-based chemoradiation therapy fails have uncontrolled pelvic disease. Thus, the search for the ideal “radiation sensitizer” has not ended. A number of agents have been identified as having possible synergy versus additive effects when combined with radiation therapy, including but not limited to paclitaxel, gemcitabine, and topotecan. These drugs should be studied, either alone or in combination with cisplatin, in relevant clinical trials. The GOG conducted a phase III trial of radiation therapy plus weekly cisplatin versus prolonged venous infusion 5-FU for the treatment of stage IIB to IVA cervical carcinoma. This trial was closed when an interim analysis determined that the experimental arm (5-FU) did not prove superior to weekly cisplatin.28 Cisplatin did, however, result in a substantial decrease in hemoglobin level during treatment.28 Retrospective trials have shown that low hemoglobin levels during treatment translate into lower pelvic control and survival rates.29 In vitro and translational studies have suggested that tumor hypoxia and (increased) angiogenesis within cervical tumors may render radiation therapy less effective. Future trials should investigate potential interrelationships among anemia, tumor hypoxia, angiogenesis, and the effectiveness of radiation therapy. Furthermore, therapies specific to tumor hypoxia (tirapazamine) or strategies to maintain higher nadir hemoglobin levels during treatment (aggressive transfusion policies; erythropoietin) should be studied.

References


