Recent Developments in Chemoradiotherapy for Locally Advanced Cancer of the Cervix

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Patients with locally advanced cervical cancer comprise a significant proportion of the total population with cervical cancer, particularly in developing countries. The inability to control pelvic tumors is still a significant

Introduction

Radical surgery or definitive radiotherapy is effective treatment for many women with nonbulky, early-stage cervical cancer (stage IB1 to IIA). However, for women with bulky, early-stage (IB2) or late-stage disease (stage IIB to IVA), treatment results are unsatisfactory.[1,2] The patterns of failure are characterized by an increase in both local and distant metastases related to increasing tumor size. However, the main cause of failure is uncontrolled disease within the pelvis. Local failure can be reduced with higher doses of radiation, but this also causes an increase in complications.[3,4]

Our previous study[5] demonstrated that strategies to augment tumor shrinkage prior to intracavitary brachytherapy are necessary to improve local control and increase survival because of the geometric limitation of intracavitary brachytherapy. Strategies to enhance the efficacy of irradiation, such as hyperbaric oxygen,[6,7] hypoxic cell sensitization,[8] neutron therapy,[9] and hyperthermia,[10,11] have been attempted, especially in late-stage disease, but have shown little or no success in most studies. Many investigations are currently being conducted to identify more effective treatments.

Chemotherapy combined with radiation is the logical choice to improve local control as well as reduce distant failure. The use of chemotherapy with radiation therapy in locally advanced cervical cancer evolved as encouraging results were reported in trials investigating chemoradiotherapy in squamous cell cancer of the head and neck,[12] esophagus,[13] lung,[14] and anal canal.[15] The utility of cytotoxic chemotherapy in patients with advanced cervical cancer has been the subject of extensive clinical investigations, with variable results. These studies can be categorized as: (1) neoadjuvant chemotherapy administered prior to radiation; (2) concurrent chemotherapy in which both chemotherapy and radiotherapy are administered together; and (3) adjuvant chemotherapy in which radiation is followed by chemotherapy.

The rationale of combining chemotherapy and radiotherapy has been reviewed previously.[16] Despite the controversy concerning its efficacy, the use of chemotherapy with irradiation appears to be increasing rapidly.[17] Recently, the National Cancer Institute (NCI) distributed a clinical announcement to physicians recommending the use of concurrent cisplatin (Platinol)-based chemoradiotherapy for the treatment of cervical cancer. This article presents an overview of the results of phase III randomized trials of combined chemoradiotherapy in locally advanced cancer of the cervix.

Neoadjuvant (Induction) Chemotherapy With Radiotherapy

Neoadjuvant chemotherapy has been used prior to local regional radiotherapy for advanced cervical cancer. The theoretical rationale for the use of cytoreductive systemic agents prior to radiation therapy includes the following factors:

1. Access of chemotherapy to the tumor may be optimal before local treatment interferes with tumor vascularity;
2. The efficacy of radiation treatment may be improved by reduced cancer cell numbers and improved oxygenation; and
3. Distant relapse may be reduced by effects on micrometastases.

Therefore, the potential exists for neoadjuvant chemotherapy to both improve local cancer control and reduce distant metastasis.
Numerous studies of the combination of chemotherapy and radiation therapy for advanced cancer of the cervix appear in the literature, but most are uncontrolled phase II trials involving small numbers of patients. Conclusions cannot be drawn about the relative merits of these regimens without data from a large, well-designed phase III trial.

**Reports From Phase III Trials**

Ten phase III trials of neoadjuvant chemoradiotherapy in advanced cancer of the cervix have been reported (see Table 1). All were single-center trials except for those reported by Sundfør et al and Tattersall et al. Many of the trials were small, with fewer than 100 patients in each arm. Cisplatin-based chemotherapy was utilized in all these trials. In general, two or three courses were administered before radiation treatment. Complete response rates achieved with neoadjuvant chemotherapy prior to radiotherapy ranged from 0% to 26% (average, 7%). Complete response rates for radiotherapy alone and for neoadjuvant chemotherapy followed by radiation treatment ranged from 33% to 89%, and 42% to 85%, respectively. Median follow-up in these studies ranged from 1.3 years to 5.0 years.

None of these trials demonstrated a significant difference in survival with neoadjuvant chemotherapy compared to radiotherapy alone. Two studies reported a decreased survival rate and increased treatment complication rate with neoadjuvant chemotherapy. This was due partially to the death of several patients in one study from bleomycin (Blenoxane)-associated pulmonary toxicity.

The failure of neoadjuvant chemotherapy to improve local control indicates that partial regression after neoadjuvant chemotherapy was not translated into better local control by subsequent radiotherapy. The possibility of cross-resistance between cisplatin-based drugs and radiation has also been proposed, but requires further exploration. Accelerated repopulation of clonogenic cells in the tumor may provide another possible explanation for the failure of neoadjuvant chemotherapy. As ineffective chemotherapy may prejudice response to radiotherapy simply by delaying its initiation, neoadjuvant therapy is potentially risky. Until regimens are developed that produce a high complete response rate, neoadjuvant chemotherapy is unlikely to be beneficial.

**Concurrent (Concomitant) Chemoradiotherapy**

Using chemotherapy during radiation treatment as a radiation sensitizer is an attractive approach. With this strategy, the entire treatment course is not prolonged and, thus, the effects of tumor proliferation are minimized. Unfortunately, these same mechanisms apply to normal tissue and result in greater toxicity.

We analyzed nine phase III trials of concurrent chemoradiotherapy for cervical cancer (Table 2). Seven of the nine trials were primarily radiotherapy trials, with or without concurrent chemotherapy, for late-stage disease. Two other trials utilized surgery as the primary approach for the treatment of patients with early-stage disease; one employed preoperative chemoradiotherapy for bulky stage IB disease, and the other employed postoperative chemoradiotherapy in patients with high-risk factors.

**Radiation With Concurrent Hydroxyurea**

Of the seven trials using primary radiation therapy, the first two evaluated the concurrent use of hydroxyurea. Hydroxyurea was advocated as a radiation sensitizer in earlier studies by Piver et al. In 1979, the Gynecologic Oncology Group (GOG) published the results of a randomized, prospective trial favoring concurrent hydroxyurea over radiation therapy alone. However, hydroxyurea has not been incorporated into general use because of its greater hematologic toxicity and uncertainty about its real benefit. Moreover, half of the patients in the 1979 GOG trial were ineligible due to protocol violations. The 3-year disease-free survival in this trial was only 13% in the control arm and 26% in the hydroxyurea arm.

Nevertheless, on the basis of these data, three subsequent GOG trials of concurrent chemoradiotherapy used hydroxyurea as a control arm (Table 3). First, Stehman et al compared hydroxyurea with misonidazole and reported no survival advantage for misonidazole. Next, Whitney et al compared hydroxyurea with cisplatin-based combination chemotherapy and showed survival benefits for the cisplatin combination. When Rose et al were designing their trial, the results of the hydroxyurea vs cisplatin-based combined chemotherapy trial were not available. Therefore, in a three-armed study, they compared treatment with radiation plus hydroxyurea, radiation plus weekly cisplatin, and radiation plus hydroxyurea, cisplatin, and fluorouracil (5-FU). These investigators found that the relapse-free survival rate was significantly higher in both regimens containing cisplatin. In addition, patients...
treated with hydroxyurea had significant hematologic toxicity: Grade III or IV neutropenia occurred in 24.5% of patients receiving hydroxyurea and 3.6% of patients receiving cisplatin/5-FU. Concurrent weekly cisplatin alone was a more effective, less toxic regimen than radiation plus hydroxyurea.[42,43]

**Radiation With Concurrent Cisplatin or 5-FU**
The next four trials compared concurrent cisplatin-based chemotherapy plus radiation with radiotherapy alone. The first three trials were small, single-center trials that had fewer than 100 patients in each arm. In one of three trials, the complete response rate was better with concurrent chemotherapy. However, the overall survival rates were not improved in any of these trials.[34-36] The most recent trial of concurrent cisplatin-based chemotherapy involved 388 patients with advanced disease ranging from bulky stage IB2 through stage IVA. In this Radiation Therapy Oncology Group (RTOG) trial conducted by Morris et al[38], extended-field (pelvis and para-aortic) external-beam radiation alone was the standard arm. The experimental arm consisted of standard field (pelvis) external-beam radiation with concurrent 5-FU and cisplatin. This phase III randomized trial used a higher dose of radiation (85 Gy vs 80 Gy at point A) than the GOG trials.[2,41,42,43] These investigators reported that both the 5-year disease-free survival (67% vs 40%) and overall survival (73% vs 58%) improved with concurrent cisplatin over radiation therapy alone.[38] The rates of both distant metastases and locoregional recurrences were significantly lower among patients treated with the combined approaches.

Thomas et al[37] reported that their trial of concurrent 5-FU chemotherapy and radiotherapy, as well as an altered radiation fractionation, demonstrated no survival benefit for these approaches over standard radiotherapy alone. However, a subset analysis showed a significant improvement in survival for patients with bulky IB and medial IIB disease who received standard radiotherapy and concurrent 5-FU.

**Surgery and Concurrent Chemoradiotherapy**
Two trials of primary surgery in locally advanced cervical cancer involved concurrent cisplatin-based chemoradiotherapy. Key et al[39] compared preoperative chemoradiotherapy with concurrent radiotherapy alone in bulky (> 4.0 cm) stage IB disease. Preoperative radiotherapy, identical for both arms, entailed the delivery of 45 Gy to the pelvis followed by 30 Gy to point A via one or two intracavitary brachytherapies. In both arms, radiotherapy was followed by extrafascial hysterectomy. The investigators reported that the survival rate for women treated with concurrent cisplatin chemotherapy was 83%, compared to 74% for those treated with radiotherapy alone.

The other surgical trial, conducted by Peters et al,[40] consisted of postoperative radiotherapy with or without chemotherapy in patients with stage IA2, IB, and IIA disease, who also had high-risk factors such as positive lymph nodes, a positive margin, or positive parametrial involvement. The majority of patients had positive pelvic lymph nodes. All patients had undergone radical hysterectomy. Patients with metastatic disease in the high common iliac nodes also received 45 Gy to the para-aortic field. These researchers reported that the 3-year survival rate for women treated with cisplatin was 87% compared to 77% for those treated with radiotherapy alone.

Both surgical trials demonstrated survival benefits with chemoradiotherapy.[39,40] Even though these two trials did not involve definitive radiation therapy, their results support the use of concurrent chemoradiotherapy in women with advanced cervical cancer. The National Cancer Institute of Canada recently completed a phase III trial to determine whether concurrent cisplatin plus radiotherapy is better than radiotherapy alone in this setting. The results are pending.

**The Chemotherapy/Radiotherapy Advantage**
Taken together, the recent large multi-institutional randomized trials discussed above[38-40,42,43] have provided what may be the most important breakthrough in the treatment of cervical cancer in 50 years. These five studies compared combinations of cisplatin-containing chemotherapy with concurrent radiotherapy and demonstrated a consistent advantage for the chemotherapy/radiotherapy combinations. When it became apparent in late 1998 that these studies pointed to a major improvement in treatment, the National Cancer Institute issued a rare clinical alert on the subject recommending concurrent cisplatin-based chemotherapy plus radiotherapy. However, none of the previous randomized trials were able to conclude which cisplatin-based regimen was optimal, cisplatin alone, combined with 5-FU, or in some other combination.

It should be noted that more aggressive chemotherapy is not necessarily better treatment for cancer of the cervix. Physicians must not prolong radiation therapy unnecessarily because of aggressive chemotherapy.
Extended-Field vs Standard-Field Irradiation With Concurrent Chemotherapy

In a previous RTOG trial,[44] extended-field irradiation (ie, prophylactic irradiation to the para-aortic nodes) proved more effective than pelvic-field irradiation. However, the role of the extended-field strategy needs to be clarified in light of the success seen with standard-field (pelvis only) irradiation with concurrent chemotherapy in the more recent RTOG trial.[38] Although moderate doses of extended-field irradiation can generally be administered safely, concurrent chemotherapy undoubtedly adds to the acute and possibly late morbidity of this radiotherapeutic technique.

Another RTOG trial assessed the same regimen as that used by Morris et al.[38] cisplatin, 75 mg/m², plus 5-FU[ with concurrent twice-a-day (1 Gy/fraction) extended-field irradiation in patients with positive para-aortic nodes.[45] The acute and late gastrointestinal morbidity associated with this regimen was very high. A GOG trial of a combination of extended-field radiotherapy (1.5 Gy/fraction) and chemotherapy (cisplatin, 50 mg/m², plus 5-FU) was better tolerated, but the dose of cisplatin used in this study was conservative.[46]

Need for Clinical Trials

A Patient Care Evaluation Study by the Commission on Cancer of the American College of Surgeons[17] showed that only 20% of patients receiving chemotherapy are known to have been entered into local or national investigational protocols. Patients and physicians should be strongly encouraged to participate in properly designed clinical trials.

Conclusions

The data from randomized trials clearly do not support the use of neoadjuvant chemotherapy prior to radiation. However, the results of trials of concurrent cisplatin-based chemoradiotherapy are highly promising for locally advanced cancer of the uterine cervix. Until further data become available, it is reasonable to consider the use of concurrent cisplatin-based chemoradiotherapy for locally advanced cancer of the cervix. Although these studies appear to provide convincing evidence of benefit with concurrent cisplatin-based chemotherapy, a number of important questions—for example, concerning the best schedule of cisplatin—remain unanswered.

To decrease the risk of distant metastasis and improve survival, we need to continue to search for more effective drugs and drug combinations. The efficacy of various chemotherapeutic drugs, such as the taxanes, gemcitabine (Gemzar), carboplatin (Paraplatin), and 5-FU, alone or combined with other chemotherapeutic agents and radiotherapy, needs further investigation in controlled clinical trials. The GOG is currently comparing concurrent radiotherapy and weekly cisplatin with radiotherapy plus infusional 5-FU. New drugs and biological agents, coupled with a better understanding of the biology of this disease, offer the promise of more effective and less toxic treatment options in the future.

References:


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