Concurrent chemoradiation for locally advanced carcinoma of the cervix: where are we in 2006?

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introduction
Significant improvements in detection and treatment have continued to decrease the incidence and mortality of cervical cancer in the Western world. We are now poised to mount efforts to eliminate the disease through mass human papilloma virus (HPV) vaccination [1]. However, while improvements in cervical cancer have been common place in the Western world, large populations in Africa, Asia and South America remain unscreened and have a high disease incidence and mortality [2]. More effective treatment for cervical cancer has evolved through sophisticated imaging and the use of cisplatin-based concurrent chemotherapy and radiation therapy. This manuscript will discuss the studies that established cisplatin-based chemotherapy as the new standard of care in the United States and led to the US National Cancer Institute (NCI) Clinical Alert. Furthermore, the more recent studies and future direction on research in this area will be discussed.

the NCI clinical alert
In October of 1998, the National Cancer Institute convened a meeting to review the results of five randomized trials that evaluated the role of concurrent cisplatin-based chemotherapy with 'standard' radiation therapy in patients receiving radiation therapy for cervical cancer. These trials dealt with different clinical disease settings in a variety of cervical cancer stages. Based on the uniformity of these results a clinical alert was drafted and subsequently issued with the expedited publication of three of the five trials. Since this clinical alert, patterns of care data demonstrate increased utilization of this therapy consistent with a wide acceptance and implementation of these guidelines [3].

concurrent chemoradiation
Concurrent chemoradiation for cervical cancer had been investigated for approximately 20 years. However, when evaluated at an NCI sponsored consensus conference in April 1995 the panel concluded that there was 'no evidence that hydroxyurea or any other concomitant chemotherapy agent should be incorporated into standard practice' [4]. Only 3 years later a series of five randomized trials in a variety of cervical cancer stages conducted in the United States in the mid and late 1990s became mature [5–9]. Collectively, all five trials comparing cisplatin-based chemoradiation to radiation alone show a significant reduction in the risk of recurrence and death with cisplatin-based chemoradiation. The five randomized cervical cancer trials involved a total of 1894 women with a wide variety of disease stages of cervical cancer in which radiation therapy would be used. The five randomized trials are listed in Table 1 and described briefly below.

GOG 85
The Gynecologic Oncology Group (GOG) randomized 388 patients with stage IIB–IVA cervical cancer to receive radiation therapy with concurrent cisplatin and 5-fluorouracil (5-FU) infusion for 4 days versus hydroxyurea [5]. Patients on the cisplatin-containing treatment arm had significantly better progression-free and overall survival (survival 63% versus 47% at 5 years). With a median follow-up of 8.7 years this difference in survival has been maintained. In addition, significantly less leukopenia occurred with cisplatin and 5-FU than with hydroxyurea.

RTOG-9001
In a subsequent trial, the Radiation Therapy Oncology Group (RTOG) randomized 401 stage IB–IVA patients to chemoradiation with cisplatin and 5-FU versus extended field radiation [6]. This trial was based on a previous RTOG trial demonstrating superiority of extended field radiation in advanced cervical cancer [10]. Concurrent chemotherapy with cisplatin and 5-FU with pelvic radiation therapy was again superior resulting in an overall survival of 73% compared with 58% for radiation alone. Chemoradiation decreased both the rate of local failure and the rate of distant failure. Acute toxicity was more common with chemoradiation but rates of late complications (complications that persisted or occurred more than 60 days after treatment) were similar.

GOG120
To study further single-agent cisplatin delivered weekly and the combination of cisplatin, 5-FU and hydroxyurea, the GOG performed a three arm trial in 526 evaluable patients with stage IIB–IVA cervical cancer comparing weekly cisplatin versus cisplatin, 5-FU and hydroxyurea versus hydroxyurea alone concurrently with radiation therapy [7]. These results demonstrated superior survival rates for both concurrent
cisplatin regimens (66% and 64%, respectively) compared with concurrent hydroxyurea alone (39%). Again, local failure rates were significantly decreased in the cisplatin arms suggesting the chemotherapy was acting as a radiation sensitizer. The toxicity of treatment was least with the single-agent cisplatin regimen.

SWOG-8797/GOG-109

Following radical hysterectomy, patients with nodal metastasis, parametrial extension or involved margins of resection are considered at high risk for recurrence. A trial by the Southwest Oncology Group (SWOG) and the GOG accrued patients with clinical stage IA₂, IB, and IIA disease with nodal metastasis, parametrial extension or involved margins of resection to radiation therapy with or without cisplatin-based chemotherapy. Two hundred and sixty-eight patients were randomized postoperatively to radiation therapy with cisplatin and 5-FU or radiation alone [8]. This trial differed from the other four trials in that chemotherapy was given both concurrently during radiation therapy for two cycle and for two cycles after radiation completion. Survival favored the chemoradiation arm (81%) versus radiation alone (63%).

GOG-123

Tumor size has long been recognized as a prognostic risk factor for stage IB cervical cancer [11]. Recognizing this the International Federation of Gynecology and Obstetrics (FIGO) revised their staging system to subdivide IB cervical tumors into IB₁ (tumors ≤4 cm) and IB₂ (tumors >4 cm). In a retrospective review, Finan et al. reported that patients treated with primary radical hysterectomy for stage IB₂ tumors significantly more often received postoperative radiation therapy and had a significantly poorer survival than patients with IB₁ tumors [12]. The role of adjuvant hysterectomy for bulky stage IB cervical cancer has also been evaluated by numerous phase II studies. The GOG performed a randomized trial of radiation versus radiation and adjuvant hysterectomy [13]. Preliminary results suggested a lower relapse in the pelvis with immature survival results. Therefore, in the subsequent trial, radiation and adjuvant hysterectomy became the standard against which concurrent weekly cisplatin, radiation and adjuvant hysterectomy was compared [9]. In this trial, pathologic examination of the hysterectomy specimens demonstrated a significant decrease in persistent disease with chemoradiation. Significant differences in progression-free survival and survival also favored the chemoradiation arm. Estimated survivals at 48 months were 82% and 68%, respectively, for chemoradiation versus radiation therapy alone followed by hysterectomy. More leukopenia and gastrointestinal toxicity was seen with chemoradiation but this was transient.

These studies demonstrated a remarkable symmetry in the reduction of relative risk of relapse or death by 30%–50%. This consistency of results presents compelling evidence for the inclusion of cisplatin with radiation in the treatment of patients with cervical cancer who require radiation. Based on the results of these five trials, the National Cancer Institute released a clinical announcement stating that ‘strong consideration’ should be given to the incorporation of concurrent chemotherapy with radiation for patients who require radiation therapy for the management of cervical cancer [14].

costs

Since incremental costs that are associated with chemoradiation are of interest particularly for poorer countries with a high incidence of the disease, a cost analysis was performed [15]. Incremental costs for cisplatin-based chemoradiation therapy treatment per year of life gained varied from $2408 to $27 882 based on published survival and $311 to $3598 based on estimated survival. The variations in regimen cost were largely dependent on treatment setting, i.e. outpatient or inpatient. Incremental cost per year of life gained (IC/YLG)
based on published survival ranging from $2408 to $6120 in the outpatient setting and $9178 to $27 882 in the inpatient setting. Based on estimated survival, IC/YLG ranged from $311 to $644 in the outpatient setting and $1184 to $3598 in the inpatient setting. Since IC/LYG ratios of $40 000–$75 000 or more have been considered acceptable, cisplatin-based chemoradiation has an acceptable pharmacoeconomic profile.

the NCIC trial

Following the dissemination of the clinical alert a sixth large randomized trial comparing cisplatin-based chemotherapy to radiation therapy alone for locally advanced cervical cancer was reported from the NCI Canada [16]. Despite the fact that this trial utilized similar doses of cisplatin delivered weekly, a statistical benefit was not seen in the chemoradiation arm. The strengths of the study included that it was multi-institutional and used appropriate doses of cisplatin and radiation. The radiation therapy schedule in this sixth trial was more optimal and this raised the concern that cisplatin-based chemoradiation was only of benefit to patients who received suboptimal radiation therapy. However, the study’s weaknesses included its relative small sample size, inclusion of patients with involved para-aortic nodes and failure to treat severe anemia, which was more common in the chemotherapy-treated patients. Despite these conflicting results the pooled analysis of all six trials demonstrated a survival benefit with improved local control (Figure 1, Table 2) [17].

other chemotherapy agents evaluated in randomized trials

In addition to cisplatin-based regimens other concurrent chemotherapy regimens have been compared to radiation therapy alone in randomized trials in cervical cancer.

5-Fluorouracil

The role of 5-FU as a radiosensitizer is well established in anal carcinoma and has been evaluated in two randomized trials in cervical cancer. Comparing radiation therapy with 5-FU to radiation therapy alone, Thomas et al. [18] demonstrated a benefit in survival for patients with stage IB2-IIIB with unilateral parametrial involvement but not for patients with more advanced disease. For unknown reasons this benefit was seen for patients who received daily radiation therapy but not twice daily radiation therapy. Recently, the Gynecologic Oncology Group completed a trial comparing radiation with weekly cisplatin versus radiation with continuous 5-FU infusion [19]. This trial was closed when it was felt that the 5-FU was unlikely to be superior.

epirubicin

Wong et al. [20] randomized 220 patients with locally advanced cervical cancer to treatment with concurrent epirubicin for six courses with the first course of therapy initiated with the first day of pelvic radiation therapy. Improvement in both progression-free and overall survival were seen among the epirubicin-treated patients. Whether the benefit of epirubicin is due to its concurrent or adjuvant administration or both is uncertain.

mitomycin C and 5-FU

Lorvidhaya et al. [21] reported on a four-arm, randomized trial comparing radiation, radiation with adjuvant chemotherapy, radiation with concurrent chemotherapy, and radiation with concurrent and adjuvant chemotherapy. The concurrent chemotherapy was mitomycin-C on days 1 and 29 and oral 5-FU on days 1–14 and 29–42. Adjuvant chemotherapy consisted of three courses of oral 5-FU for 4 weeks, with a 2-week break. The concurrent chemotherapy arms had significantly improved rates of local control and survival.

Although other agents, including mitomycin-C and epirubicin, have demonstrated activity with concurrent radiation, their efficacy relative to platinum compounds has not been evaluated. In addition, mitomycin-C was previously abandoned as a radiation sensitizer in North American studies because of a three-fold increase in late intestinal complications [22].

Table 2. Pelvis as site of first failure

<table>
<thead>
<tr>
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<th>Cisplatin-based therapy</th>
<th>Non-cisplatin control</th>
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<tr>
<td></td>
<td>Total number</td>
<td>No. with pelvic failure</td>
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<tr>
<td>GOG 85</td>
<td>177</td>
<td>44</td>
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<td>GOG 120</td>
<td>176</td>
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<tr>
<td>GOG 120</td>
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<td>11</td>
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<tr>
<td>NCIC</td>
<td>126</td>
<td>34</td>
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<tr>
<td>Total</td>
<td>1155</td>
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gemcitabine

Gemcitabine has demonstrated radiosensitization of HeLa cervical cancer cells, and the synergy of cisplatin and gemcitabine makes the combination attractive as a possible radiosensitizing regimen [23, 24]. Pattaranutaporn et al. [25] studied the use of pelvic radiation therapy with gemcitabine 300 mg/m² weekly, reporting a 90% response rate. A phase II trial with cisplatin 40 mg/m² weekly and gemcitabine 125 mg/m² weekly in patients with locally advanced disease IIIA–IIIB demonstrated a 90% complete response rate with acceptable toxicity [26]. In contrast a study from the Puget Sound Consortium found significant activity with this regimen but unacceptable toxicity [27]. A randomized trial comparing this dose of weekly cisplatin with weekly cisplatin/gemcitabine before radical hysterectomy demonstrated a higher pathologic response rate in patients treated with the cisplatin/gemcitabine combination [28]. A large randomized trial comparing weekly cisplatin and gemcitabine versus weekly cisplatin with concurrent radiation therapy has recently completed accrual and should be mature soon.

potential chemoradiation agents

A number of newer chemotherapy agents including carboplatin, paclitaxel, tirapazamine, topotecan and vinorelbine are candidates for study as concurrent chemotherapy agents with radiation therapy in cervical cancer. For some of these agents, combination with cisplatin is tolerated and in some cases of metastatic disease it is more active with improvement in response rate, progression-free and overall survival. Therefore, since local disease control remains an issue in patients with locally advanced advanced cervical cancer there is a potential for improvement with these newer combinations.

carboplatin

Carboplatin, which is a less nephrotoxic, neurotoxic and emetogenic platinum analog than cisplatin, has also been studied as a radiosensitizing agent in cervical cancer. Regimens have utilized carboplatin daily continuous [29], twice weekly [30], weekly [31–33] and every 3 weeks [34]. Previous phase II studies of single agent carboplatin in advanced and recurrent cervical cancer have demonstrated a lower response than seen with cisplatin in some [35, 36] but not all studies [37]. Therefore, while cisplatin and carboplatin are often used interchangeably for systemic treatment it cannot be assumed that carboplatin-based regimens will be as effective a cisplatin-based regimen in concurrent chemoradiation treatment of cervical cancer.

paclitaxel

Paclitaxel arrests cells in the radiosensitive G₂M phase of the cell cycle and has been shown to be a radiosensitizer [38]. Paclitaxel must be given before radiation to achieve G₂M blockage and maximum efficacy. Four of seven cervical cancer cell lines reported have demonstrated radiosensitization with paclitaxel [39]. A phase I trial of paclitaxel with pelvic radiation in patients with cervical cancer reached a maximum tolerated dose of 50 mg/m² given as a weekly 3-h infusion [40]. The combination of weekly cisplatin and weekly paclitaxel during localized pelvic radiation has been studied in patients with cervical cancer by the GOG with the maximally tolerated dose being 40 mg/m² of each agent weekly [41].

tirapazamine

Tirapazamine (3amino-1,2,4-benezotriazine 1,4-dioxide), a new cytotoxic agent which is selectively activated in hypoxic tissue, has demonstrated additive effects with radiation in hypoxic conditions [42]. Since hypoxia limits the effectiveness of radiation for cervical cancer, tirapazamine is a promising agent in this disease [43]. In addition, tirapazamine has a schedule-dependent synergy with cisplatin, which is greatest when tirapazamine precedes cisplatin [44]. A phase I trial of tirapazamine in combination with cisplatin with radiation for cervical cancer was conducted [45]. The maximally tolerated dose of tirapazamine was 290 mg/m² on days 1, 15, 29 and 220 mg/m² on days 8, 10, 12 and 22, 24, 26 with cisplatin 75 mg/m² on days 1, 15 and 29 of radiation therapy.

topotecan

Topotecan has demonstrated radiosensitizing effects [46]. As a single agent topotecan 1 mg/m² on days 1–5 and 22–26 was well tolerated with pelvic radiation therapy [47]. A phase I trial of weekly cisplatin 20 mg/m² and continuous infusion topotecan 0.15 mg/m²/day daily ×5 weekly during radiation therapy was well tolerated and clinically active with complete responses seen in all but one patient with stage IB₂–IVA disease [48]. The GOG plans to study weekly cisplatin 40 mg/m² and weekly topotecan due to topotecan’s modest hematologic toxicity with this schedule.

vinorelbine

Vinorelbine in combination with cisplatin is active in advanced and recurrent cervical cancer [49]. This combination has been studied with concurrent pelvic radiation with a maximally tolerated dose of vinorelbine 15 mg/m² in combination with cisplatin 40 mg/m² weekly [50].

conclusions

As new trials mature the optimal concurrent chemotherapy regimen remains controversial. From the currently completed randomized trials in locally advanced cervical cancer, it can be concluded that cisplatin, either alone or with 5-FU, is superior to hydroxyurea [5, 7]; that cisplatin alone is less toxic than cisplatin/5-FU/hydroxyurea [7]; and that cisplatin is superior to infusional 5-FU [19]. A randomized trial comparing cisplatin 40 mg/m² weekly ×6 with cisplatin 75 mg/m² every 3 weeks ×4, demonstrated twice as many delays of therapy with the higher, less frequent cisplatin administration [51]. Weekly cisplatin meets certain goals as the ideal chemotherapy regimen, including high antitumor activity, acceptable tolerance with concurrent radiation, lower cost and demonstration of a survival benefit in randomized trials. In a meta-analysis evaluating randomized trials of chemoradiation, a statistically significant improvement in the hazard ratio was seen only in platinum-containing
chemotherapy regimens but was not statistically significant for the non-platinum containing chemotherapy regimen subgroup [52]. The Gynecologic Oncology Group is beginning a study comparing radiation with cisplatin versus cisplatin and tirapazamine (GOG 219).

references

5. Whitney CW, Sause W, Bundy BN et al. A randomized comparison of fluorouracil plus cisplatin versus fluorouracil alone chemotherapy regimens but was not statistically significant for the non-platinum containing chemotherapy regimen subgroup [52]. The Gynecologic Oncology Group is beginning a study comparing radiation with cisplatin versus cisplatin and tirapazamine (GOG 219).