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Review

Chemotherapy for advanced and recurrent cervical carcinoma: Results from cooperative group trials

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HIGHLIGHTS

- Platinum based doublets are the standard of care for patients with recurrent cervical cancer, although clinical benefit is limited.
- Clinical trial participation should be encouraged in order to determine potentially more efficacious regimens.

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ABSTRACT

Objective. To review the clinical trial experience with chemotherapy for patients with primary Stage IVB, persistent and recurrent cervical cancer.

Methods. PubMed and cooperative group website search was performed and included clinical trials until September 2012. Emphasis was placed on the phase II and III clinical trial experience of the Gynecologic Oncology Group.

Results. Experience and trial results with single agents and combination agents in phase II settings are reviewed. Cisplatin has been considered as the most effective agent for metastatic cervical cancer. Most patients who develop metastatic disease have received cisplatin with concurrent radiation and may no longer be sensitive to single-agent therapy. Therefore, cisplatin-based combination chemotherapy regimens have been extensively studied and eight sentinel phase III trials are discussed in this review.

Conclusion. Based on phase III results, the combination of cisplatin and paclitaxel remains the standard of care; however, alternative combination therapies including cisplatin/topotecan and cisplatin/gemcitabine may be acceptable considerations for patients when considering potential toxicities. Further research is necessary to determine the optimal therapy for this group of patients. Final data from GOG 240 and JCOG 0505 will likely contribute to the design of future clinical trials in this disease setting.

Contents

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Introduction

Secondary to effective cervical cytology screening, cervical cancer incidence has declined by 70% over the last half-century in most developed countries [1]. Additionally, HPV vaccination appears to be highly efficacious for the prevention of infection with high-risk HPV subtypes, the obligate cause of most cervical cancers [2–6]. While cervical cancer is only the 12th most common malignancy of women in the United States, it still accounts for 12,200 cases and 5000 deaths annually and is the second leading cause of cancer death in women aged 20–39 [7]. Moreover, cervical cancer is the third most common cancer worldwide with an annual incidence of 530,000 cases; 250,000 deaths are expected from this largely preventable disease [8].

For patients with primary Stage IVB, persistent, or recurrent cervical cancer, chemotherapy remains the standard treatment, although this is neither curative nor associated with long-term disease control [9]. Best supportive care and clinical trials are reasonable alternatives. The majority of the research in this area is based on the experience of the Gynecologic Oncology Group (GOG), especially phase II and III clinical trials. The GOG has utilized two separate queues of phase II trials, GOG 76 and GOG 127, where patients with metastatic cervical cancer had received no prior chemotherapy or one prior treatment, respectively. Active regimens from phase II trials were utilized in phase III trials either alone or in combination with cisplatin. Although several randomized trials have reported outcomes since the last review of this topic in *Gynecologic Oncology* in 2007, little excitement in cytotoxic agents has been generated from these trials [10]. Finally, a recent review of targeted therapy is recommended to review these important alternatives for cervical cancer treatment [11].

Although 80% of cervical cancers are squamous in origin, protocols have been variable about their inclusion or exclusion of non-squamous lesions. Secondary to the under representation of non-squamous histology, less is known about the optimal treatment of these histologic variants of cervical cancer. The purpose of the current review is to summarize the historical background of clinical trials, which have evaluated chemotherapy in the setting of primary Stage IVB, persistent or recurrent cervical cancer.

Methods

A PubMed query utilized the following; “recurrent cervical cancer”; “chemotherapy”; “advanced cervical cancer”; “stage IVB cervical cancer” with a search performed from 1966 until September 2012. Non-English publications were excluded. Cooperative Group websites including the GOG, Southwest Oncology Group (SWOG), and Japanese Clinical Oncology Group (JCOG) were evaluated for potential articles of interest. In addition, manuscripts were reviewed for other potential studies to include. Trials utilizing a biologic or non-cytotoxic agent were excluded.

Single agent chemotherapy

Historically, cisplatin has been the primary chemotherapy for advanced cervical cancer patients. An early GOG study included 34 patients with advanced or recurrent cervical squamous cell carcinoma treated with cisplatin 50 mg/m^2 every three weeks [12]. Overall response rate was 38%; however, three complete and eight partial responses were observed in 22 previously untreated patients for a response rate of 50%. Only two partial responses were observed in 12 patients who had received prior chemotherapy. Responses were observed in patients with both pelvic and extrapelvic disease. The most common adverse effects included nausea/vomiting, azotemia, thrombocytopenia, and leukopenia. These trial results determined that cisplatin would be the standard drug in the treatment of cervical cancer.

In order to determine the optimal dose and schedule of cisplatin, the GOG compared cisplatin 50 mg/m^2 every 21 days, 100 mg/m^2 every 21 days, and 20 mg/m^2 for 5 consecutive days repeated every 21 days [13]. In 497 evaluable patients, the response rates were 20.7%, 31.4%, and 25.0%, respectively. The complete remission rates were 10.0%, 12.7%, and 8.6%, respectively. The median progression-free survival (PFS) was 3.7 to 4.6 months, and the median overall survival (OS) was 6.1 to 7.1 months. The differences in complete remission, PFS, and OS were not statistically significant. The higher dose regimen was associated with greater myelosuppression and nephrotoxicity. This study established 50 mg/m^2 as the dose for future comparisons.

The GOG studied alternative platinum agents in hopes of finding a drug with fewer side effects. 394 patients with advanced squamous carcinoma and no prior chemotherapy were randomized to either carboplatin or iproplatin, of which 361 were evaluable [14]. Both platinum analogs were given every 28 days with starting doses of 400 mg/m^2 for carboplatin and 270 mg/m^2 for iproplatin with dose reductions in patients with prior radiation. Hematologic toxicity was dose-limiting and thrombocytopenia was more common than leukopenia. Gastrointestinal toxicity was common with both; however, iproplatin was significantly more toxic than carboplatin ($p<0.001$). Similar response rates, 15% for carboplatin and 11% for iproplatin, were noted. The authors concluded that both drugs were inferior to cisplatin suggesting that cisplatin was the preferred agent in cervical cancer.

Oxaliplatin was also evaluated in previously treated cervical squamous cell carcinoma [15]. Eligible patients had measurable disease without more than one prior chemotherapy regimen. Oxaliplatin 130 mg/m^2 was administered every 21 days until disease progression. 24 patients were evaluable for response; 23 had had prior platinum therapy. There were two (8.3%) responses. One patient achieved a complete response of 2.2 months, and a second patient attained a partial response of 3.2 months. Nine (37.5%) patients had stable disease. The most frequently reported drug-related toxicities were anemia, nausea/vomiting, and neurotoxicity. Oxaliplatin has limited activity in patients with persistent or recurrent squamous cell carcinoma of the cervix and was not incorporated into combination regimens.

Fifty-six chemotherapy naïve patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix received 20 mg/m^2 of mitomycin C every six weeks [16]. In 52 evaluable patients, the overall response rate was 12% (3 complete and 3 partial) with a median duration of response of 7.3 months. The median PFS was 3.0 months, and the median OS was 4.9 months. The most frequent and severe adverse effects were due to myelosuppression. Based on the modest activity, no further studies of mitomycin C in cervical squamous cell carcinoma were conducted by the GOG.

Thirty patients with advanced squamous carcinoma of the cervix who were refractory to first-line chemotherapy were treated with ifosfamide [17]. Patients were treated with ifosfamide 1.2 g/m^2 daily for 5 days every four weeks with concomitant Mesna. 27 patients were evaluable for response. Partial responses were observed in three patients (11.1%). Severe (grade 3 or 4) leukopenia and anemia were seen in nine and seven patients, respectively. Because of such a low response rate, ifosfamide rarely is used for patients with recurrent disease.

The GOG evaluated irinotecan in patients with recurrent cervical squamous carcinoma [18]. Four weeks of irinotecan at 125 mg/m^2, were followed with a two-week rest, repeated until disease progression or unacceptable toxicity. 45 patients were evaluable for response. The incidence of grade 4 neutropenia and anemia was 6.1 and 4.1%, respectively. Nineteen patients (38.8%) developed grade 3 and 4 gastrointestinal toxicity; there was one patient death from gastrointestinal toxicity. The overall response rate was 13.3%, one complete response of 8.8 months duration and five partial responses. The authors concluded that irinotecan exhibited modest activity with moderate toxicity; the GOG did not include irinotecan in any subsequent studies due to the toxicity.

Single agent gemcitabine has been evaluated by the GOG in patients with previously treated squamous and non-squamous cell

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