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Review Article

Chemotherapy for advanced or recurrent cervical cancer

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Abstract

The primary treatment options for cervical cancer are surgery and radiation for more than a century. However, over the last 40 years chemotherapy has been building up its reputation in the management of cervical cancer in various forms such as chemoradiation, neoadjuvant chemotherapy, and palliative chemotherapy for advanced or recurrent disease. Among these, in this review, chemotherapy for advanced or recurrent cervical cancer will be discussed.

Keywords: advanced or recurrent cervical cancer; chemotherapy; palliative therapy

Introduction

According to the GLOBOCAN report in 2008, cervical cancer was the third most common type of cancer in women worldwide, following breast and colorectal cancer. In 2008 alone, 530,232 women were diagnosed with cervical cancer. It was also the fourth most common cause of female mortality, responsible for 275,008 deaths [1]. Although the incidence of cervical cancer has declined in developed countries, in Japan approximately 12,000 women were estimated to be affected by invasive cervical cancer, with 3,500 deaths reported in 2008.

Cervical cancer has been treated with surgery or radiotherapy, or both, for a long time; but, over the last 40 years, a number of cases have been treated with a third method, namely, chemotherapy. However, because a large number of patients with recurrent disease develop tumors in previously irradiated areas, malignant tumor cells are surrounded by fibrotic and avascular tissue. As a result, the concentration of chemotherapeutic agent in the tumor is not enough to achieve a high clinical outcome. Therefore, chemotherapy has been used only on patients with refractory cervical cancer or as an ordinary treatment option, as a palliative measure.

Chemotherapy for recurrent or advanced cervical cancer

For the treatment of recurrent and advanced cervical cancers, chemotherapy has proven to be palliative. The activity of single agents against recurrent or advanced squamous cell carcinoma of the cervix reported before 1976 is listed in Table 1 [2]. When used individually, these agents have shown only relatively low efficacy. However, in the late 1970s, several multidrug regimens were tested, as part of a Phase II study, hoping for signs of increased antitumor effectiveness [3–8]. However, each of these trials enrolled only a small number of patients, and no regimens were tested as randomized trials on a large scale. In the 1980s many newly developed antitumor agents emerged and were tested in Phase II studies (Table 2). Among these studies of single-use chemotherapeutic agents, cisplatin showed a higher response rate (RR) than other agents in many Phase II trials [9].

Based on the results obtained in these studies, cisplatin became the key drug for advanced or recurrent cervical cancer. The next logical step was to find the appropriate dose and administration schedule of cisplatin, and therefore, the Gynecologic Oncology Group (GOG) conducted a randomized

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Table 1
Single-agent chemotherapy for cervical cancer before 1976.

Drug		Objective response (%)
Cyclophosphamide	29/188	15
Chlorambucil	11/44	25
Melphalan	4/20	20
5-Fluorouracil	29/140	21
Methotrexate	12/77	16
Vincristine	10/44	23
Bleomycin	17/172	10
Adriamycin	5/28	18
Mitomycin C	4/18	22

prospective trial comparing various doses and administration schedule of 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 [19]. Four hundred ninety-seven patients participated in this study and the RRs were 20.7%, 31.4%, and 25.0%, for regimens 1, 2, and 3, respectively; the complete remission rates were 10.0%, 12.7%, and 8.6% for regimens 1, 2, and 3, respectively. The median duration of response ranged from 3.9 to 4.8 months, the median progression-free interval from 3.7 to 4.6 months, and the median survival time from 6.1 to 7.1 months. The difference in RRs for regimens 1 and 2 is statistically significant ($p = 0.015$), but less than the magnitude originally considered clinically significant. The differences in complete remission rates, response duration, progression-free interval, and survival times are not statistically significant. The regimen consisting of a single dose of 100 mg/m^2 cisplatin produced a statistically significant higher RR than the 50 mg/m^2 regimen, while producing no appreciable differences in complete remission rate, response duration, progression-free interval, or survival. In addition, the higher dose regimen was associated with greater myelosuppression and nephrotoxicity. Based on the antitumor effect, toxicity, and feasibility, a dose of 50 mg/m^2 every 21 days became the standard administration method for cisplatin.

Thereafter, various drugs were tested in combination with cisplatin in a Phase III setting, in order to obtain better survival rates (Table 3). Because ifosfamide achieved a high RR next to cisplatin, ifosfamide plus cisplatin (IP) was compared with cisplatin only [20]. The results showed that the IP regimen had a significantly higher RR and longer progression-free survival (PFS); however, the overall survival (OS) rate was almost the same. Moreover, toxicity of the IP regimen was more severe than cisplatin alone, and therefore, IP was not widely accepted. The addition of bleomycin to IP did not yield any additional therapeutic gain [21]. Paclitaxel showed only a 17% RR when used alone [10]; however, when used in combination with cisplatin, it achieved a RR of 46%, despite the fact that 91% of the treated patients were previously given radiation [22]. In a randomized Phase III study of cisplatin with and without paclitaxel, cisplatin with paclitaxel (TP) showed significantly better RR and PFS. Regarding OS, PC tended to show better results than cisplatin alone, and the increase in toxicity of TP was mild [23]. Thereafter, PC seemed to be the standard regimen in advanced and recurrent cervical cancer. Treatment method consisting of a combination of topotecan and cisplatin (TopoP) showed significantly better results than cisplatin alone in terms of RR, PFS, and OS [24]; however, TopoP showed high hematological toxicity, and between the two treatment groups, there was a bias in the time from initial diagnosis to study entry, which influenced the OS rate. At the same time, the GOG reported two Phase II studies on cisplatin plus vinorelbine, and cisplatin plus gemcitabine [25,26]. Because both combinations were promising, the GOG conducted a four-arm Phase III study comparing TP (reference arm) with the three other combinations. In this study, there were no significant differences in RR, median PFS, or OS among the four regimens [27]. As a result, TP was considered as the standard regimen for recurrent and advanced cervical cancer.

Table 2
Chemotherapeutic agents introduced to Phase II trial.

Drug		Objective response (%)
Cisplatin [9]	190/815	23
Carboplatin [10]	27/175	15
Ifosfamide [9]	35/157	14–40
Paclitaxel [11]	9/52	17
Irinotecan [12]	13/55	24
Topotecan [13]	8/43	19
Gemcitabine [14]	2/25	8
Vinorelbine [15]	6/42	15
Docetaxel [16]	2/23	9
Doxorubicin (Doxil) [17]	3/26	11
Mitolactol [18]	16/55	29

Patients with recurrent or advanced cervical cancer, however, often have problems in the urinary tract, which can induce renal dysfunction. For such patients, administration of cisplatin was difficult owing to its renal toxic effects. Carboplatin, despite being a derivative of cisplatin, was gaining attention because of its low renal toxic effect and there is no need of hydration. Thus, carboplatin was tested in a Phase II study, but it achieved a RR of only 15%, which was lower than expected [11]. A Phase II study suggested that carboplatin plus paclitaxel (TC) could be superior to TP in terms of RR and OS [28]. Thus, the Japan Clinical Oncology Group conducted a randomized Phase III study to evaluate the clinical benefit of TC compared with TP for patients with advanced or recurrent disease. The objective response was 60% for TP and 62% for TC. The median OS and PFS were 18.3 and 6.9 months for TP and 17.5 and 6.2 months for TC. Thus, TC proved comparable with TP in terms of its antitumor activity. The TC was also less toxic than TP in inducing febrile neutropenia, creatinine elevation, and nausea/vomiting. This Phase III study therefore drew the conclusion that TC could be recommended as the new standard treatment for advanced and recurrent cervical cancer [29].

Second-line chemotherapy

Thigpen et al studied 34 patients with advanced or recurrent disease who were treated with cisplatin (intravenously

Table 3
Phase III studies for advanced and recurrent cervical cancer.

	No. of pts	Histology	Regimen	RR (%)	Median PFS (Mo)	Median OS (Mo)
Omura GA et al. [20]	454	SCC	Cisplatin 50 mg/m^2 vs	18	3.2	6.1
			Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2	31*	4.6*	7.1
Bloss JD et al. [21]	303	SCC	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 vs	32	4.6	8.5
			Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 + bleomycin 30 U	31	5.1	8.4
Moore DH, et al. [23]	280	SCC	Cisplatin 50 mg/m^2 vs	19	2.8	8.8
			Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2 (24 hr)	36*	4.8*	9.7
Long HG, et al. [24]	293		Cisplatin 50 mg/m^2 vs	13	2.9	6.5
			Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2/day, d1-3	27*	4.6*	9.4*
Monk BJ, et al. [27]	513	SCC, AC	Cisplatin 50mg/m^2 + paclitaxel 135 mg/m^2 (24 hr)	29	Hazard ratio to TP	
			Cisplatin 50 mg/m^2 + vinorelbine30 mg/m^2/day, d1,8	26	1.36	1.15
			Cisplatin 50 mg/m^2 + gemcitabine1000 mg/m^2/day, d1, 8	22	1.39	1.32
			Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2/day, d1-3	23	1.27	1.26
Kitagawa R, et al. [29]	253	SCC, AC	Cisplatin 50 mg/m^2 + paclitaxel135 mg/m^2 (24 hr)	123	6.9	18.3
			Carboplatin AUC5 + paclitaxel 175 mg/m^2 (3 hr)	121	6.2	17.5

*$p < 0{,}05$ RR: overall response rate, PFS: progression-free interval, OS: overall survival, TP:Cisplatin50 mg/m^2 + paclitaxel135 mg/m^2(24 hr).

administered) at a dose rate of 50 mg/m^2 every 3 weeks in the GOG [30]. The overall frequency of response was 52.94% (18/34). Of the 22 patients who received no prior chemotherapy, three complete and eight partial responses were observed (RR 50%), whereas only two partial responses were observed among the 12 patients receiving prior chemotherapy (RR 17%). The observed RR was significantly higher, albeit marginally, among those with no prior chemotherapy ($p = 0.059$). Thus, prior chemotherapy was thought to diminish the effect of second-line chemotherapy. Because chemoradiation with cisplatin has become popular as a primary treatment, recurrent disease will be less sensitive to chemotherapy.

Chemotherapy for adenocarcinoma of the cervix

Regarding advanced or recurrent adenocarcinoma of the cervix, a standard regimen is yet to be established. A majority of studies have so far focused only on the most common histological type, that is, squamous cell carcinoma. Cisplatin achieved four partial responses among 20 patients (20%) [31]. The GOG performed a Phase II study on paclitaxel for advanced adenocarcinoma of the cervix [32]. A total of 42 assessable patients were initially recruited into the study and 13 responses were seen (four patients had a complete response, and nine patients had a partial response). The overall RR was 31%. Kitagawa et al reported that TC therapy achieved 40% partial response (4/10) but no complete response [29]. Recently, the incidence of adenocarcinoma has increased and the recurrence rate of adenocarcinoma is higher than squamous cell carcinoma. Therefore, a large-scale clinical study is necessary.

Perspective on chemotherapy for advanced or recurrent cervical cancer

The incidence of cervical cancer is decreasing in developing countries. However, because chemotherapy has been introduced as a primary treatment, chemotherapy for recurrent disease is considered a second-line treatment. In general, second-line treatment could be less effective than first-line, probably due to drug resistance. Radiation induces fibrosis around the cancer cells and so concentrations of chemotherapeutic agents cannot reach the cytocidal level in tumors. To break such conditions in recurrent cervical cancer, a molecular targeting agent might be one solution. The GOG recently conducted a Phase III study of chemotherapy (topotecan and paclitaxel) with and without bevacizumab [33]. The results will be presented at the American Society of Clinical Oncology 2013 Annual Meeting. Along with molecular targeting agents, new strategies are expected to emerge.

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