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Review

Cytotoxic and Targeted Systemic Therapy in Advanced and Recurrent Cervical Cancer: Experience from Clinical Trials

Hyun-Joo Seol,[1] Roshani Ulak,[1] Kyung-Do Ki[1] and Jong-Min Lee[1]

[1]Department of Obstetrics and Gynecology, School of Medicine, Kyung Hee University, Seoul, South Korea

Cervical cancer is the third most common malignant disease of women worldwide. Despite advances in screening and treatment strategies, a significant number of patients have advanced and recurrent disease. These patients are not amenable to curative treatments, such as surgery and radiation, and have poor prognosis. Therefore, palliative treatment remains the standard of care for these patients. Several phase II/III trials have demonstrated that cisplatin is the most active single agent, and the combination of cisplatin and paclitaxel is considered a standard regimen for clinical practice and trials in these patients with improved response rates and progression-free intervals. Although other cisplatin doublet chemotherapy regimens were not superior to cisplatin plus paclitaxel, substituting topotecan or gemcitabine for paclitaxel might be helpful for some patients considering different toxicity profiles. Because the response to palliative chemotherapy is poor, several targeted agents including bevacizumab, erlotinib, pazopanib, lapatinib, sunitinib and cetuximab, each of which inhibits cell proliferation and angiogenesis, were evaluated in these patients. Of them, bevacizumab, targeting vascular endothelial growth factor, showed favorable results. Recent phase III trial showed that bevacizumab combined with chemotherapy was shown to significantly improve the response rate, progression-free interval, and overall survival compared to chemotherapy alone. These results suggest that targeted agents could significantly improve survival and affect practice guidelines in these patients showing poor prognosis. Thus, future trials using newly developed targeted agents are warranted to improve treatment strategies in these patients.

Keywords: cervical cancer; chemotherapy; metastasis; recurrence; targeted therapy
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Introduction

Cervical cancer is the third most common malignant disease in women worldwide and the seventh most common malignant disease in Korean women (Jemal et al. 2011; Seol et al. 2014). The incidence of cervical cancer in Korean women has decreased over the last two decades because of the widespread use of screening tests and early detection with proper management for pre-invasive lesions of the cervix. However, cervical cancer is detected at a locoregionally advanced stage in a significant number of women. Late detection increases the possibility of disease recurrence, resulting in a stagnant 5-year relative survival rate of between 80.0% and 81.2% over the last 15 years (Seol et al. 2014).

Conventional radical surgery and chemoradiation therapy can cure more than 85% of women with early stage disease (Lee et al. 2006). However, stage IVB, recurrent or persistent cervical cancer is not amenable to these conventional treatments and remains a major cause of cancer-related death. Therefore, chemotherapy is still the standard option for treatment with a palliative intent in patients with advanced and recurrent cervical cancer. However, cervical cancer is considered chemoresistant compared to breast and ovarian cancer, and chemotherapy has been limited to patients with metastasis and/or recurrences which are not curable (Rein and Kurbacher 2001). Fortunately, several single agents have been reported to be active for cervical cancer, with modest response rates. Additionally, combination chemotherapy has shown improved response rates and progression-free intervals, with questionable effects on overall survival.

There have been numerous reports in this field. However, cooperative groups such as the Gynecologic Oncology Group (GOG) have made the most important advances on the basis of the results of trials. This paper aims to review and summarize the history and results of the cooperative group trials that performed palliative therapy in patients with advanced and recurrent cervical cancer.

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Correspondence: Jong-Min Lee, Department of Obstetrics and Gynecology, Kyung Hee University Hospital at Gangdong, 892, Dongnam-ro, Gangdong-Gu, Seoul 134-727, Korea.
e-mail: kgo02@hanmail.net

Single agent chemotherapy

Table 1 shows several single agents with modest activity for cervical cancer. Of these agents, cisplatin has been extensively studied. In GOG 26C (Thigpen et al. 1981), in which cisplatin 50 mg/m^2 was administered every 3 weeks for advanced or recurrent squamous cell carcinoma of the cervix, the overall response rate was 38% with mild to moderate toxicity: patients without prior chemotherapy had a 50% (11/22) overall response rate, while patients previously treated with chemotherapy had a 17% (2/12) overall response rate. In GOG 43 (Bonomi et al. 1985), the optimal dose and application schedule of cisplatin was determined. High-dose regimens (100 mg/m^2 every 3 weeks and 20 mg/m^2 × 5 days every 3 weeks) did not improve the progression-free interval and overall survival compared to low-dose regimens (50 mg/m^2 every 3 weeks), with higher grades of myelosuppression and nephrotoxicity being associated with the higher dose regimens. Therefore, cisplatin at 50 mg/m^2 every 3 weeks is considered to be the most efficacious regimen for cervical cancer. This result formed the basis for future clinical trials. Other platinum analogues, including carboplatin, iproplatin and oxaliplatin, do not result in improved oncologic outcomes compared to cisplatin (McGuire et al. 1989; Weiss et al. 1990; Fracasso et al. 2003). Non-platinum agents including mitomycin-C and ifosfamide were also associated with modest response rates in cervical cancer (Sutton et al. 1989; Thigpen et al. 1995).

A number of relatively newer compounds—taxanes (paclitaxel and docetaxel), camptothecin analogues (topotecan and irinotecan), gemcitabine, and vinorelbine—have been evaluated in clinical trials over the last few decades (McGuire et al. 1996; Look et al. 1998; Bookman et al. 2000; Schilder et al. 2000; Curtin et al. 2001; Muderspach et al. 2001; Muggia et al. 2004, 2005; Garcia et al. 2007; Fiorica et al. 2009). The GOG performed 2 phase II trials of paclitaxel at 170 mg/m^2 (135 mg/m^2 in cases of prior pelvic radiation) every 3 weeks, with dose escalations to 200 mg/m^2 and de-escalations to 110 mg/m^2 in patients with advanced squamous cell cervical cancer with no prior chemotherapy and in patients with non-squamous cervical cancer who failed to respond to standard chemotherapy (McGuire et al. 1996; Curtin et al. 2001). The overall response rate was 17.3% in the former group, whereas it was 31.0% in the latter patient group. The primary and dose-limiting toxicity was neutropenia. Docetaxel (100 mg/m^2 every 3 weeks) showed minimal activity in patients with previously treated squamous cell carcinoma of the cervix, with a partial response rate of 8.7% and median survival of 7 months (Garcia et al. 2007). The GOG evaluated the efficacy and toxicity of topotecan in patients with metastatic, recurrent, or persistent squamous cell carcinoma of the cervix (Muderspach et al. 2001). In patients without prior chemotherapy, topotecan administered at 1.5 mg/m^2/day for 5 days every 4 weeks showed an overall response rate of 18.6%, a median progression-free interval of 2.4 months, and a median survival of 6.4 months, with considerable hematologic toxicities. Additionally, topotecan, at the same dose every 3 weeks, showed an overall response rate of 12.5%, a median progression-free interval of 2.1 months, and a median survival of 6.6 months in patients with squamous cell carcinoma, treated with prior chemotherapy (Bookman et al. 2000). However, weekly topotecan, administered at 3.0 mg/m^2 on days 1, 8, and 15 every 4 weeks, showed minimal activity with no responders and median progression-free intervals of 2.4 months in patients with progressive disease and 6.2 months in patients with

Table 1. Active single cytotoxic agents for cervical cancer.

Drug	Regimen (mg/m^2)	(reference)	Interval (weeks)	Patients (N)	Response rate (%)	Median survival (months)
Cisplatin	50	(Thigpen et al. 1981)	3	34	38	
Carboplatin	340 or 400	(McGuire et al. 1989)	4	175	15	
Oxaliplatin	130	(Fracasso et al. 2003)	3	28	8.3	
Mitomycin-C	20	(Thigpen et al. 1995)	6	56	12	4.9
Ifosfamide	1,200, D1-5	(Sutton et al. 1989)	4	30	11.1	
Paclitaxel	170 or 135	(McGuire et al. 1996)	3	52	17.3	
Paclitaxel	170 or 135	(Curtin et al. 2001)	3	42	31.0	
Docetaxel	100	(Garcia et al. 2007)	3	27	8.7	7.0
Topotecan	1.5, D1-5	(Muderspach et al. 2001)	4	49	18.6	6.4
Topotecan	1.5, D1-5	(Bookman et al. 2000)	3	45	12.5	6.6
Topotecan	3.0, D1, 8 & 15	(Fiorica et al. 2009)	4	27	0	
Irinotecan	125, D1, 8, 15 & 22	(Look et al. 1998)	6	54	13.3	
Gemcitabine	800, D1, 8 & 15	(Schilder et al. 2000)	4	27	8	4.9
Vinorelbine	30, D1 & 8	(Muggia et al. 2004)	3	44	13.7	
Vinorelbine	30, D1 & 8	(Muggia et al. 2005)	3	30	7.1	

D, days.

stable disease (Fiorica et al. 2009). Irinotecan (125 mg/m^2/week for 4 weeks followed by a 2-week rest) showed an overall response rate of 13.3% with relatively severe toxicity for recurrent squamous cervical carcinoma (Look et al. 1998). Gemcitabine (800 mg/m^2/week for 3 weeks followed by a one-week rest period) has been reported to have limited activity, with response rates of 8% and 4.5% in patients with previously treated squamous cell carcinoma and in those with non-squamous cell carcinoma of the cervix, respectively (Schilder et al. 2000). Vinorelbine (30 mg/m^2 on days 1 and 8 every 3 weeks) showed response rates of 13.7% and 7.1% in patients with advanced or recurrent squamous cell and in those with non-squamous carcinoma who failed to respond to prior chemotherapy, respectively (Muggia et al. 2004, 2005).

Combination chemotherapy

Because of the limited efficacy of single-agent chemotherapy in cervical cancer, various clinical trials have been conducted to evaluate the efficacy and toxicity of combination chemotherapy regimens based on cisplatin, the most active single agent for cervical cancer.

Phase II trials

Several cisplatin-based combination phase II trials were evaluated by the GOG (Table 2). In GOG 76G (Bonomi et al. 1989), cisplatin 50 mg/m^2 on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1-5 were administered every 3 weeks in patients with advanced squamous cell carcinoma of the cervix. The overall response rate was 21.8%, and the median survival was 6.4 months. These results reflect no significant survival advantage for the combination regimen over cisplatin alone.

Burnett et al. reported a favorable response rate for cisplatin (50 mg/m^2) and gemcitabine (1,250 mg/m^2 on days 1 and 8) administered every 3 weeks in patients with advanced, recurrent, or persistent squamous cell carcinoma of the cervix (Burnett et al. 2000). However, the GOG reported disappointing results for the administration of cisplatin (30 mg/m^2) and gemcitabine (800 mg/m^2 on days 1 and 8) every 4 weeks in patients with previously treated squamous cell carcinoma of the cervix (Brewer et al. 2006). A partial response was observed in 21.9% of patients, and the median progression-free interval was 3.5 months.

Fiorica et al. evaluated the efficacy and toxicity of cisplatin (50 mg/m^2) and topotecan (0.75 mg/m^2 on days 1-3) administered every 3 weeks in patients with recurrent or persistent squamous and non-squamous cervical cancer (Fiorica et al. 2002). Favorable results, including an overall response rate of 28% and a median overall survival of 10 months, were observed, with tolerable toxicities.

The GOG performed a phase II trial of paclitaxel (135 mg/m^2 with dose escalation to 170 mg/m^2) and cisplatin (75 mg/m^2) administered every 3 weeks, as first-line therapy in patients with recurrent or advanced squamous cell carcinoma of the cervix (Rose et al. 1999). Although 90.9% of patients received prior radiation therapy, the overall response rate was 46.3%, and median overall survival was 10 months. However, there were 2 mortality cases due to neutropenic sepsis.

The GOG performed a phase II trial of cisplatin (75 mg/m^2) and vinorelbine (30 mg/m^2 weekly) administered every 4 weeks, in patients with advanced or recurrent squamous cell carcinoma of the cervix (Morris et al. 2004). The overall response rate was 30%, and the overall median response duration was 5.5 months.

Phase III trials

Based on the phase II trials, the GOG performed several phase III trials to compare cisplatin doublet chemotherapy to cisplatin alone (Table 3). In GOG 110 (Omura et al. 1997), cisplatin doublet chemotherapy (50 mg/m^2) plus mitolactol (180 mg/m^2 orally on days 2-6) and cisplatin (50 mg/m^2) plus ifosfamide (5 g/m^2) were compared to cisplatin (50 mg/m^2) alone. Cisplatin plus ifosfamide showed an improved response rate compared to cisplatin alone (31% vs. 18%, p = 0.004), as well as increased progression-free interval (4.6 vs. 3.2 months, p = 0.003). However there was also greater toxicity, and no improvement in overall survival in patients treated with cisplatin and ifosfamide compared to cisplatin alone (8.3 vs. 8.0 months, p = NS). Cisplatin plus mitolactol showed no significant improvement in any of these parameters compared to cisplatin alone.

Table 2. Phase II trials of cisplatin-based combination chemotherapy in advanced and recurrent cervical cancer.

Drug & regimen (mg/m^2)	(reference)	Interval (weeks)	Patients (N)	Response rate (%)	Median survival (months)
Cisplatin 50 + 5-FU 1000, D 1-5	(Bonomi et al. 1989)	3	55	22	6.4
Cisplatin 50 + Gemcitabine 1250, D 1 & 8	(Burnett et al. 2000)	3	19	41	12 for responder 7 for nonresponders
Cisplatin 30 + Gemcitabine 800, D 1 & 8	(Brewer et al. 2006)	4	32	22	3.5 (PFI)
Cisplatin 50 + Topotecan 0.75, D 1-3	(Fiorica et al. 2002)	3	35	28	10
Cisplatin 75 + Paclitaxel 135	(Rose et al. 1999)	3	47	46	10
Cisplatin 75 + Vinorelbine 30 weekly	(Morris et al. 2004)	4	73	30	5.5 (median response duration)

5-FU, 5-fluorouracil; D, days; PFI, progression-free interval.

Table 3. Phase III trials by the GOG for advanced and recurrent cervical cancer.

Trial (reference)	Drug & regimen	Interval (weeks)	Patients (N)	Response rate (%)	Progression-free interval (months)	Overall survival (months)
GOG 110 (Omura et al. 1997)	C vs. C+IFO	3	140/151	18/31 ($p = 0.004$)	3.2/4.6 ($p = 0.003$)	8.0/8.3 (NS)
GOG 149 (Bloss et al. 2002)	C+IFO vs. C+IFO+B	3	146/141	32/31 (NS)	4.6/5.1 (NS)	8.5/8.4 (NS)
GOG 169 (Moore et al. 2004)	C vs. C+P[a]	3	134/130	19/36 ($p = 0.002$)	2.8/4.8 ($p < 0.001$)	8.8/9.7 (NS)
GOG 179 (Long et al. 2005)	C vs. C+Topo	3	146/147	13/27 ($p = 0.004$)	2.9/4.6 ($p = 0.014$)	6.5/9.4 ($p = 0.017$)
GOG 204 (Monk et al. 2009b)	C+P[a] vs.C+V/C+G/ C+Topo	3	103/108/112/111	29/26/22/23 (NS)	5.8/4.0/4.7/4.6 ($p = -/0.06/0.04/0.19$)	12.9/10.0/10.3/10.3 (NS)
GOG 240 (Tewari et al. 2014)	C+P[b] vs. Topo+P[c]	3	229/223	38/29 (NS)		15/12.5 (NS)

C, cisplatin 50 mg/m^2; IFO, ifosfamide 5 g/m^2; B, bleomycin 30 units; Topo, topotecan 0.75 mg/m^2 on days 1-3; V, vinorelbine 30 mg/m^2 on days 1 and 8; G, gemcitabine 1,000 mg/m^2 on days 1 and 8; NS, not significant.

[a]paclitaxel 135 mg/m^2, [b]paclitaxel 135 or 175 mg/m^2, [c]paclitaxel 175 mg/m^2.

A randomized phase III trial of cisplatin (50 mg/m^2) plus ifosfamide (5 g/m^2) versus bleomycin (30 units on day 1) followed by cisplatin plus ifosfamide (same dose as above) was performed in patients with advanced, recurrent or persistent squamous cell carcinoma of the cervix (Bloss et al. 2002). There were no significant differences between the two arms with respect to the response rate, progression-free interval, overall survival and toxicity incidence, with the exception of pulmonary toxicity.

GOG 169 was a randomized phase III trial of cisplatin (50 mg/m^2) with or without paclitaxel (135 mg/m^2) every 3 weeks for 6 cycles, in patients with stage IVB, recurrent or persistent squamous cell carcinoma of the cervix (Moore et al. 2004). Cisplatin doublet chemotherapy was superior to cisplatin alone with respect to response rate (36% vs. 19%, $p = 0.002$) and progression-free interval (4.8 vs. 2.8 months, $p < 0.001$), with a sustained quality of life. Similar to other studies, however, there was no significant improvement in overall survival between the two study arms (9.7 vs. 8.8 months, p = NS).

GOG 179 was a randomized, three-armed study that compared cisplatin (50 mg/m^2) alone versus cisplatin plus topotecan (0.75 mg/m^{2}on days 1-3) versus methotrexate, vinblastine, and doxorubicin plus cisplatin (MVAC) in patients with advanced, recurrent or persistent cervical cancer (Long et al. 2005). The MVAC arm was prematurely closed by the Data Safety Monitoring Board after the occurrence of 4 treatment-related deaths. Cisplatin plus topotecan showed a statistically improved overall survival (9.4 vs. 6.5 months, $p = 0.017$) as well as improved response rate (27% vs. 13%, $p = 0.004$) and progression-free interval (4.6 vs. 2.9 months, $p = 0.014$) compared to cisplatin alone. However, grade 3 to 4 hematologic toxicities were more common in patients treated with cisplatin doublet chemotherapy than in patients with cisplatin alone, with no significant difference in patient-reported quality of life. This was the first phase III trial to demonstrate a survival advantage for combination chemotherapy over cisplatin alone in cervical cancer patients.

Even though combination chemotherapy with cisplatin plus topotecan showed a statistically significant improvement in overall survival compared to cisplatin alone, the median overall survival in GOG 179 was not much better than previous trials. When the results of GOG 169 are compared to those of GOG 179, it is important to note that 56.2% of the patients in the control arm in GOG 179 had received prior chemoradiation, whereas only 29.9% of those in GOG 169 had received prior chemoradiation. This difference could explain the inferior survival of control arm in GOG 179 compared to historical controls, as well as the survival advantage seen in patients with cisplatin plus topotecan compared to cisplatin alone in this study. To resolve this discrepancy, GOG 204 assessed the efficacy and toxicity of 4 cisplatin doublet combinations (paclitaxel vs. vinorelbine, gemcitabine, or topotecan) in advanced or recurrent cervical cancer (Monk et al. 2009b). Before the interim analysis recommended early closure, a total of 513 patients were enrolled in this study, and approximately 70% of these patients had received prior chemoradiation. The 3 cisplatin doublet chemotherapy regimens, including vinorelbine, gemcitabine or topotecan, did not elicit a superior response rate, progression-free interval, or overall survival compared to paclitaxel doublet chemotherapy. The incidence of severe neutropenia was lower in the gemcitabine doublet chemotherapy group, whereas the incidence of grade 2 alopecia was higher in the paclitaxel doublet chemotherapy group. However, paclitaxel doublet chemotherapy has become the standard regimen for future trials because of a favorable trend in the response rate, progression-free interval, and overall survival seen in patients treated with paclitaxel doublet chemotherapy.

In the era of cisplatin-based chemoradiation for high-risk early stage, and locoregionally advanced stage cervical cancer, many patients with recurrent disease had prior cispl-

atin-based chemoradiation and, therefore show a decreased response rate and survival compared to cisplatin-treated patients in previous studies. Therefore, GOG 240 compared non-platinum doublet therapy consisting of paclitaxel plus topotecan to cisplatin plus paclitaxel at the standard dose in recurrent, persistent or advanced cervical cancer (Tewari et al. 2014). About 75% of the patients had received prior platinum chemotherapy. Compared with cisplatin doublet chemotherapy, non-platinum doublet chemotherapy showed a significantly higher risk of disease progression (hazard ratio 1.39; 95% CI, 1.09-1.77; two-sided p = 0.008), nor did it significantly affect overall survival (hazard ratio 1.20; 99% CI, 0.82-1.76; one-sided p = 0.88). These results indicate that substituting topotecan for cisplatin did not improve survival outcomes with respect to the progression-free interval and overall survival. A study performed by a Japanese group showed that carboplatin plus paclitaxel elicited a similar response in terms of overall survival, with different toxicities compared to the standard cisplatin plus paclitaxel regimen (17.5 vs. 18.3 months) (Kitagawa et al. 2012). Therefore, if different toxicity profiles are considered, carboplatin plus paclitaxel may be considered as another standard regimen in future trials for patients with recurrent cervical cancer.

Targeted therapy

Platinum-based combination chemotherapy remains the standard treatment for advanced and recurrent cervical cancer. However, the response to palliative chemotherapy is poor and warrants the development of new therapeutic agents with novel mechanisms of action. A number of targeted agents that modulate different signal transduction pathways are actively being evaluated for many solid tumors. In this review, we mainly focus on the results of prospective trials in a palliative setting for cervical cancer (Table 4).

Phase II trials

Vascular endothelial growth factor (VEGF) plays an important role in the control of angiogenesis, tumor growth, and metastasis. Overexpression of VEGF has been reported to be associated with tumor progression and poor prognosis in several types of solid tumors. Bevacizumab, a recombinant humanized monoclonal antibody, targets all major isoforms of VEGF and inhibits cell proliferation and angiogenesis (Zagouri et al. 2012). Bevacizumab has been tested and used in several solid tumors with favorable results. The GOG performed a phase II trial to evaluate the efficacy and toxicity of bevacizumab (15 mg/kg every 3 weeks until disease progression or prohibitive toxicity) in persistent or recurrent squamous cell carcinoma of the cervix (Monk et al. 2009a). Compared to historical control data from 6 GOG trials in this disease setting, bevacizumab showed remarkable activity. Of the 46 patients enrolled in the study, all had been previously treated with 1 or 2 cytotoxic chemotherapy regimens, and 38 patients had received prior radiation. Five patients showed partial responses. The median progression-free interval and overall survival were 3.4 months and 7.3 months, respectively. Although bevacizumab was well tolerated, several grade 3 or 4 adverse events including hypertension, thromboembolism, anemia, vaginal bleeding, neutropenia and fistula did occur. Among all the targeted agents that were tested, only bevacizumab was deemed worthy of further investigation in several phase II trials and was incorporated in a phase III trial (GOG 240).

Pazopanib is an oral multi-targeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and c-Kit. Lapatinib is an oral dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2)/neu. Monk et al. performed a phase II trial comparing pazopanib (800 mg/day) or lapatinib (1,500 mg/day)

Table 4. Phase II/III trials of targeted agents for advanced and recurrent cervical cancer.

Drug & Regimen	Reference	Interval	Patients (N)	Response rate (%)	Progression-free interval (months)	Median survival (months)
Bevacizumab 15 mg/kg	(Monk et al. 2009a)	3 weeks	46	11	3.4	7.3
Pazopanib 800 mg vs Lapatinib 1,500 mg	(Monk et al. 2010; Monk and Pandite 2011)	Daily/daily	74/78	9/5	4.5/4.3 (p < 0.013)	12.4/11.0 (p = 0.407)
Sunitinib 50 mg/daily for 4 weeks	(Mackay et al. 2010)	6 weeks	19	0	3.5	
Cetuximab 400 mg/m^2 followed by 250 mg/m^2	(Santin et al. 2011)	Weekly	35	0	2.0	6.7
Cisplatin 30 mg/m^2, D 1 & 8 + Cetuximab 400 mg/m^2 followed by 250 mg/m^2 D 1, 8 & 15	(Farley et al. 2011)	3 weeks	69	12	3.9	8.8
Erlotinib 150 mg	(Schilder et al. 2009)	Daily	28	0	1.9	5.0
Chemo[a] vs Chemo[a] + bevacizumab 15 mg/kg	(Tewari et al. 2014)	3 weeks	225/227	36/48 (p = 0.008)	5.9/8.2 (p = 0.002)	13.3/17 (p = 0.004)

D, days.

[a]Cisplatin 50 mg/m^2 + paclitaxel 135-175 mg/m^2 or paclitaxel 175 mg/m^2 + topotecan 0.75 mg/m^2 on days 1-3.

monotherapy with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer (Monk et al. 2010; Monk and Pandite 2011). In this trial, the combination therapy arm was prematurely discontinued because of a crossed futility boundary and imbalanced toxicity compared to the monotherapy arm. Pazopanib improved the progression-free interval compared to lapatinib (4.5 months vs. 4.3 months, $p < 0.013$), but did not improve overall survival (12.4 months vs. 11.0 months, $p = 0.407$).

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor of VEGFR, PDGFR and c-Kit. Mackay et al. performed a phase II trial of sunitinib (50 mg/day orally for 4 weeks followed by a 2-week rest period) in patients with locally advanced or metastatic cervical carcinoma (Mackay et al. 2010). Sunitinib showed insufficient activity with no objective responses, a median time to progression of 3.5 months and a higher rate of fistula formation (26.3%).

Cetuximab is a monoclonal antibody that binds to the extracellular portion of EGFR and inhibits tyrosine kinase activation. The GOG performed a phase II trial to assess the efficacy and tolerability of cetuximab (loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly until disease progression or prohibitive toxicity) in persistent or recurrent squamous or non-squamous cell carcinoma of the cervix (Santin et al. 2011). Of the 35 patients evaluated, 31 had received prior radiation and all had previously been treated with 1 or 2 chemotherapy agents. No clinical responses were observed. The median progression-free interval and overall survival were 2.0 and 6.7 months, respectively. Farley et al. also performed a phase II trial of cisplatin (30 mg/m^2 on days 1 and 8) plus cetuximab (a loading dose of 400 mg/m^2 followed by 250 mg/m^2 on days 1, 8, and 15 in a 21-day cycle) in advanced, recurrent, or persistent cervical cancer (Farley et al. 2011). The estimated response rate was 11.6%. The median progression-free interval and overall survival were 3.9 months and 8.8 months, respectively. Based on these results, cetuximab did not provide a survival advantage over cisplatin. The French trial of cetuximab (initial dose of 400 mg/m^2 followed by subsequent weekly dose of 250 mg/m^2) with cisplatin (50 mg/m^2) plus topotecan (0.75 mg/m^2 on days 1-3 every 3 weeks) in advanced cervical cancer was prematurely terminated due to serious toxicities and high mortality (28%) (Kurtz et al. 2009).

Erlotinib is an oral drug that binds to EGFR tyrosine kinase and blocks EGFR phosphorylation. Schilder et al. performed a phase II trial of erlotinib (150 mg orally daily) in recurrent squamous cell carcinoma of the cervix (Schilder et al. 2009). Although erlotinib showed a higher response rate in a definitive setting with cisplatin-based concurrent chemoradiation (Nogueira-Rodrigues et al. 2008), erlotinib monotherapy was inactive in recurrent cervical cancer. No objective responses were observed. The median progression-free survival and overall survival were only 1.9 months and 5.0 months, respectively.

Phase III trials

Recently, the National Cancer Institute, USA, released a report stating that bevacizumab significantly improves survival for patients with recurrent and metastatic cervical cancer (NCI Press Release 2013). GOG 240 was designed to compare cisplatin plus paclitaxel with or without bevacizumab versus non-platinum doublet chemotherapy of topotecan plus paclitaxel with or without bevacizumab in patients with advanced, recurrent or persistent carcinoma of the cervix. As mentioned previously, non-platinum doublet (topotecan plus paclitaxel) chemotherapy was not superior to platinum doublet (cisplatin plus paclitaxel) chemotherapy with respect to response rate and overall survival. In GOG 240 (Tewari et al. 2014), however, bevacizumab (15 mg/kg) was administered with chemotherapy every 3 weeks and showed a significantly improved response rate (48% vs. 36%, $p = 0.008$) and progression-free interval (8.2 vs. 5.9 months; hazard ratio 0.67; 95% CI, 0.54-0.82; two-sided $p = 0.002$) compared to the study arm not treated with bevacizumab. Furthermore, the hazard ratio of death was 0.71 for patients who received chemotherapy with bevacizumab compared to those who did not receive bevacizumab (98%, CI 0.54-0.95; one-sided $p = 0.004$). Patients who received bevacizumab had a median survival time 3.7 months longer than that of patients who did not receive bevacizumab (17 months vs. 13.3 months) and also had an improved progression-free interval (8.2 months vs. 5.9 months). However, adverse events such as hypertension, neutropenia and thromboembolism were more common in patients who received bevacizumab than in those who did not. Additionally, there was no significant difference in the quality of life reported by patients. GOG 240 is the first report to suggest that targeted agents can significantly improve survival in advanced, recurrent or persistent cervical cancer.

Summary

Patients with advanced and recurrent cervical cancer have been treated with cisplatin alone or cisplatin doublet chemotherapy. However, only approximately one-third of these patients have been reported to respond to chemotherapy, with median response duration of 3-6 months and a median overall survival of 5-9 months. In GOG 204 (Monk et al. 2009b), paclitaxel plus cisplatin showed a favorable trend with respect to the response rate, progression-free interval and overall survival. However, the difference was not significant compared to the other cisplatin doublet chemotherapy regimens including vinorelbine, gemcitabine, and topotecan. Furthermore, non-platinum doublet chemotherapy with topotecan plus paclitaxel was not superior to cisplatin plus paclitaxel. Therefore, cisplatin plus paclitaxel is the standard regimen in palliative chemotherapy for these patients. However, substituting non-platinum agents such as topotecan or gemcitabine might be helpful for some patients because they have different toxicity profiles compared to paclitaxel.

Although various targeted agents, which have been

theoretically considered to be efficacious, have been evaluated in these patients, most of them showed disappointing results in phase II trials. Recently, however, bevacizumab combined with chemotherapy led to a significant improvement in survival outcomes in GOG 240 (Tewari et al. 2014). This is the first report of an anti-angiogenic targeted agent that could be helpful for these patients. Therefore, this result could affect practice guidelines and future clinical trials. However, because of the high cost of bevacizumab, cost-effectiveness analyses should be undertaken. Furthermore, future trials using newly developed targeted agents are warranted to improve oncologic outcomes in patients with metastatic, recurrent, or persistent cervical cancer.

Conflict of Interest

The authors declare no conflict of interest.

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