

Chemotherapy and molecular targeting therapy for recurrent cervical cancer

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Abstract: For patients with primary stage IVB, persistent, or recurrent cervical cancer, chemotherapy remains the standard treatment, although it is neither curative nor associated with long-term disease control. In this review, we summarized the history of treatment of recurrent cervical cancer, and the current recommendation for chemotherapy and molecular targeted therapy. Eligible articles were identified by a search of the MEDLINE bibliographical database for the period up to November 30, 2014. The search strategy included the following any or all of the keywords: “uterine cervical cancer”, “chemotherapy”, and “targeted therapies”. Since cisplatin every 21 days was considered as the historical standard treatment for recurrent cervical cancer, subsequent trials have evaluated and demonstrated activity for other agents including paclitaxel, gemcitabine, topotecan and vinorelbine among others. Accordingly, promising agents were incorporated into phase III trials. To examine the best agent to combine with cisplatin, several landmark phase III clinical trials were conducted by Gynecologic Oncology Group (GOG) and Japan Clinical Oncology Group (JCOG). Through, GOG204 and JCOG0505, paclitaxel/cisplatin (TP) and paclitaxel/carboplatin (TC) are now considered to be the recommended therapies for recurrent cervical cancer patients. However, the prognosis of patients who are already resistant to chemotherapy, are very poor. Therefore new therapeutic strategies are urgently required. Molecular targeted therapy will be the most hopeful candidate of these strategies. From the results of GOG240, bevacizumab combined with TP reached its primary endpoint of improving overall survival (OS). Although, the prognosis for recurrent cervical cancer patients is still poor, the results of GOG240 shed light on the usefulness of molecular target agents to chemotherapy in cancer patients. Recurrent cervical cancer is generally considered incurable and current chemotherapy regimens offer only modest gains in OS, particularly for patients with multiple poor prognostic factors. Therefore, it is crucial to consider not only the survival benefit, but also the minimization of treatment toxicity, and maximization of quality of life (QOL).

Keywords: Cervical cancer; chemotherapy; molecular targeting therapy

Submitted Jan 29, 2015. Accepted for publication Aug 08, 2015.

doi: 10.3978/j.issn.1000-9604.2015.12.01

View this article at: <http://dx.doi.org/10.3978/j.issn.1000-9604.2015.12.01>

Introduction

Secondary to effective cervical cytology screening, cervical cancer incidence has declined by 70% over the last half-century in most developed countries (1). In Japan, cervical cancer is the most common gynecologic cancer and the second most common cause of death among these patients. 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 (2). Although early-stage and locally advanced cancers may be cured with radical surgery, chemoradiotherapy, or both, patients with metastatic cancers and those with persistent or recurrent disease after platinum-based chemoradiotherapy have limited options (3-17).

In locally advanced cervical cancer, Rose *et al.* identified prognostic factors by multivariable analysis including histology, race/ethnicity, performance status, tumor size, International Federation of Gynecology and Obstetrics stage, tumor grade, pelvic node status, and treatment with concurrent cisplatin-based chemotherapy (18). 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 (19). The prognosis for advanced or recurrent cervical carcinoma is poor, with a 1-year survival rate between 10% and 15% (20). The need for effective therapy in this clinical setting is well recognized and optimal treatment has yet to be defined.

In this review, we summarized the history of the medical treatment of recurrent cervical cancer, and the current recommendations for chemotherapy and molecular targeted therapy. Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to November 30, 2014. The search strategy included any or all of the following keywords: “uterine cervical cancer”, “chemotherapy”, and “targeted therapies”.

Single agent chemotherapy

CDDP

Cisplatin has been the primary chemotherapy for advanced cervical cancer patients. The Gynecologic Oncology Group (GOG) study included 34 patients with advanced or recurrent cervical squamous cell carcinoma treated with cisplatin 50 mg/m² every 3 weeks (21). Overall response rate (ORR) was 38%; however, three complete responses (CR) and eight partial responses (PR) were observed in 22 previously untreated patients for an ORR of 50%. Only two PR were observed in 12 patients who had received prior chemotherapy.

Based on antitumor effect, toxicity, and feasibility, a dose of 50 mg/m² every 21 days became the standard administration method for cisplatin.

Topotecan

Topotecan inhibits topoisomerase-I, an intranuclear enzyme which relieves torsional stress in DNA (22). Binding of topotecan to topoisomerase-I creates a stabilized cleavable complex leading to single-strand DNA breaks, which are converted to lethal double-strand breaks during DNA

replication. In addition to these direct effects, topotecan has been shown to potentiate the activity of cisplatin through inhibition of DNA repair (23).

The GOG evaluated the activity and toxicity of topotecan in a multicenter Phase II study for patients with previously treated squamous cell carcinoma of the uterine cervix (24). Topotecan was administered at 1.5 mg/m² per day for 5 consecutive days, on a 21 days cycle. Forty patients were evaluated and the ORR was 12.5% with stable disease (SD) in an additional 37.5%. Median progression free survival (PFS) was 2.1 months. As a single agent topotecan shows modest antitumor activity in patients with previously treated squamous cell carcinoma of the cervix. These results led the GOG to include the combination of topotecan and cisplatin in phase III trials.

Paclitaxel

A phase II trial of paclitaxel was initiated in advanced non-squamous carcinoma of the cervix to determine its activity in patients who had failed standard chemotherapy (25). The starting dose of paclitaxel was 170 mg/m² (135 mg/m² for patients with prior pelvic radiation) given as a 24-hour continuous intravenous infusion with courses repeated every 3 weeks. In this trial, 42 assessable patients were initially entered onto the study, and 13 responses were seen; 4 patients had a complete response, and 9 patients had a partial response. The ORR was 31%. The primary and dose-limiting toxicity was neutropenia.

The authors concluded that paclitaxel was effective in non-squamous carcinoma of the cervix.

Nab-Paclitaxel

Nab-paclitaxel is a nanoparticle formulation of albumin-bound paclitaxel (26). No premedication is required as the risk of hypersensitivity (27).

GOG conducted a phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer (28).

Nab-paclitaxel was administered at 125 mg/m² i.v. over 30 min on day 1, 8 and 15, of each 28-day cycle, to 37 women with metastatic or recurrent cervix cancer that had progressed or relapsed following first-line cytotoxic drug treatment. Thirty-five eligible patients were evaluated for response and tolerability. All of the eligible patients had one prior chemotherapy regimen and 27 of them had prior radiation therapy with concomitant cisplatin. The median numbers of nab-paclitaxel cycles were 4 (range, 1–15). Ten

Table 1 Overall response rate (ORR) to cervical cancer (single agent chemotherapy)

Agent	ORR (%)
Cisplatin (21,33)	20–30
Carboplatin (34)	15
Nedaplatin (35,36)	34–41
Ifosphamide (33)	14–40
Paclitaxel (37)	17
Irinotecan (38)	24
Topotecan (25)	19
5-fluorouracil (39,40)	4–9
Bleomycin (41)	10
Gemcitabine (31)	8
Vinorelbine (42)	17
Docetaxel (43)	9
Liposomal doxorubicin (29)	11

This table is partially modified from ref (44).

[28.6%; 95% confidence interval (CI), 14.6–46.3%] of the 35 patients had a PR and another 15 patients (42.9%) had SD. The median PFS and overall survival (OS) were 5.0 and 9.4 months, respectively. In fact, the 28.6% ORR in the 35 eligible patients is the highest ever recorded in the GOG for a single-agent against drug refractory, platinum resistant disease (29–32). Thus, nab-paclitaxel may be considered a leading candidate for future studies of combinations of agents in both adjuvant and advanced disease settings, especially evaluating weekly dosing schedules.

Table 1 shows the results of ORR of single agent chemotherapy.

Combination chemotherapy: phase II clinical trials

In trials of combination chemotherapy, other active agents were selected with cisplatin. Therefore, several agents, which showed modest to good response, were used to test the activity in phase II trial combined with cisplatin. Also, cisplatin analogues (CBDCA, nedaplatin) were examined to have response substitution for cisplatin for decreasing the adverse effects of cisplatin.

Topotecan/CDDP

Fiorica and colleagues conducted a phase II trial evaluating

cisplatin/topotecan in persistent or recurrent cervical cancer patients (45).

A 50 mg/m² of cisplatin on day 1 and 0.75 mg/m² of topotecan on day 1, 2, and 3 of a 21-day cycle were given for 6 cycles or until disease progression.

Thirty-two of the 35 enrolled patients were evaluated for toxicity and tumor response. All but two evaluable patients had received previous radiotherapy. No patient received prior chemotherapy. The most common toxicity was hematologic, with grade 3 and 4 neutropenia and thrombocytopenia reported in 30% and 10% of cycles, respectively. The ORR was 28% (9/32), with 3 CR and 6 PR. Nine (28%) patients had SD. The antitumor response in non-irradiated fields (30%) was similar to the response observed in previously irradiated fields (33%), suggesting good drug penetration. Median duration of response was 5 months (range, 2 to 15+ months). An additional 9 (28%) patients achieved SD. The median OS was 10 months. The authors concluded that cisplatin/topotecan is safe, well tolerated, and active in cervical cancer patients.

Paclitaxel + CDDP

On the basis of activity of paclitaxel as a single agent in chemotherapy for naive squamous cell carcinoma of the cervix in a prior GOG trial, a phase II study of paclitaxel and cisplatin, as first-line therapy, was conducted by the GOG (46).

Patients received paclitaxel 135 mg/m² over 24 h followed by cisplatin 75 mg/m² every 21 days. A total of 41 patients were evaluable for response. Forty (90.9%) had received prior radiation therapy. Of the 41 assessable patients, 5 (12.2%) had CR and 14 (34.1%) had PR for an ORR of 46.3%. The median PFS was 5.4 months with a median OS of 10.0 months (range, 0.9–22.2 months). Response was more frequent in patients with disease in non-irradiated sites (70% vs. 23%, P=0.008).

The authors concluded that this regimen seemed highly active and those results led to the development of GOG169 in a phase III randomized study, comparing combinations of paclitaxel/cisplatin with cisplatin alone.

Paclitaxel + CBDCA

Patients with advanced or recurrent carcinoma of the cervix were treated with carboplatin/paclitaxel every 28 days (47). Starting doses of carboplatin/paclitaxel were: AUC 5–6 and 155–175 mg/m².

Twenty-five women treated with this combination were identified. Twenty-three women (92%) had prior treatment with pelvic radiotherapy and 14 (56%) had concurrent radio-sensitizing cisplatin. There was a 20% PR and a 20% CR rate (10/25). The median PFS for the entire group was 3 months.

The median OS was 21 months. The authors concluded that carboplatin/paclitaxel was an active combination in advance and recurrent cervical cancer.

Paclitaxel + nedaplatin

Nedaplatin (cis-diammine glycolato platinum) is a cisplatin analogue which was developed as a less nephrotoxic agent in Japan in 1995.

A multicenter phase II trial was conducted to evaluate activity and toxicity of paclitaxel/nedaplatin in patients with advanced/recurrent uterine cervical cancer. Treatments consisted of paclitaxel 175 mg/m² over 3 h and nedaplatin 80 mg/m² intravenously over 1 h on day 1 every 28 days until progressive disease or adverse effects prohibited further therapy.

A total of 45 patients were eligible for assessment of response to treatment; 31 patients (62%) received prior radiotherapy and 23 patients (46%) received prior chemotherapy. The ORR was 44.4% (11 CR and 8 PR) with 22.2% of patients having SD. Non-hematologic toxicity was generally not serious and without dominant pattern. The median PFS was 7.5 months and OS was 15.7 months. Neurotoxicity is one of the main toxicities of cisplatin and paclitaxel. Papadimitriou *et al.* reported in their phase II study with PC therapy (48), 53% of their patients developed some degree of neurotoxicity, including grade 3 neurotoxicity in 9% (8). In this study, grade 3 or 4 neurotoxicity occurred in only one patient (2.0%). The authors concluded that paclitaxel/nedaplatin demonstrated easy administration, favorable anti-tumor activity, and the toxicity profile of this regimen could be decreased with cisplatin containing combinations.

Combination chemotherapy: phase III clinical trials

As noted 50 mg/m² cisplatin every 21 days was considered the historical standard treatment for recurrent cervical cancer (21). Subsequent trials evaluated and demonstrated activity for other agents including mitolactol, ifosfamide, paclitaxel, gemcitabine, topotecan and vinorelbine among others (37,49-55). Accordingly, promising agents were

incorporated into phase III trials. In this section, we summarized landmark phase III clinical trials conducted by GOG and Japan Clinical Oncology Group (JCOG). *Table 2* shows the results of representative phase III clinical trials.

GOG169

Since previous GOG phase II trials demonstrated paclitaxel/cisplatin combination seemed highly active in cervical cancer, a phase III trial compared paclitaxel/cisplatin with cisplatin alone (14).

Among 264 eligible patients, 134 received cisplatin and 130 received cisplatin/paclitaxel. The majority of all patients had prior radiation therapy (cisplatin, 92%; cisplatin/paclitaxel, 91%). ORR was 19% (6% CR plus 13% PR) of patients receiving cisplatin *vs.* 36% (15% CR plus 21% PR) receiving cisplatin/paclitaxel (P=0.002). The median PFS was 2.8 and 4.8 months, respectively, for cisplatin *vs.* cisplatin/paclitaxel (P<0.001). There was no difference in median OS (8.8 *vs.* 9.7 months). Importantly, this trial prospectively collected quality of life (QOL) assessment data before each treatment cycle. Although the QOL scores were similar for both groups, the dropout rate, as determined by completion of the survey, was higher in the cisplatin group, suggesting stable QOL rather than worsening QOL for patients receiving combination therapy. The authors concluded cisplatin/paclitaxel is superior to cisplatin alone with respect to response rate and PFS with sustained QOL.

GOG179

Following GOG169 closure, a replacement trial compared single agent cisplatin to other active regimens from previous phase II trials. Patients were randomized into one of three treatment arms: (I) cisplatin (II) cisplatin/topotecan and (III) methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) (15). The MVAC arm was closed by the Data Safety Monitoring Board after four treatment-related deaths occurred among 63 patients, and was not included in this analysis. Among cisplatin *vs.* cisplatin/topotecan, improvements in ORR (27% *vs.* 13%; P=0.004), and PFS (4.6 *vs.* 2.9 months; P=0.014) favored cisplatin/topotecan regimens. OS was higher for the combination regimen compared to single agent cisplatin (9.4 *vs.* 6.5 months; P=0.017). This was the first randomized phase III trial to demonstrate a survival advantage for combination chemotherapy over cisplatin alone, in advanced cervix cancer. The ORR of single agent cisplatin was only 13%. Compared with

Table 2 Phase III clinical trials for stage IVB and recurrent cervical cancers

Author	Regimen	OS (months)	PFS (months)	ORR (%)
GOG43 Omura (9)	CDDP 50 mg/m ² vs. CDDP 100 mg/m ² vs. CDDP 20 mg/m ² ×5 days	7.1 vs. 7.0 vs. 6.1 (NS)	3.7 vs. 4.6 vs. 3.9 (NS)	21.0 vs. 31.0 vs. 25.0 (P<0.05)
GOG110, Omura (12)	CDDP 50 mg/m ² vs. CDDP 50 mg/m ² + IFM 5 g/m ²	8.0 vs. 8.3 (NS)	3.2 vs. 4.6 (P<0.01)	18.0 vs. 31.0 (P<0.01)
GOG149, Moore (13)	CDDP 50 mg/m ² + IFM 5 g/m ² vs. CDDP 50 mg/m ² + IFM 5 g/m ² + BLM 30 U	8.5 vs. 8.4 (NS)	4.6 vs. 5.1 (NS)	32.0 vs. 31.0 (NS)
GOG169 Moore (14)	CDDP 50 mg/m ² vs. CDDP 50 mg/m ² + PTX 135 mg/m ²	8.8 vs. 9.7 (NS)	2.8 vs. 4.8 (P<0.01)	19.0 vs. 36.0 (P<0.01)
GOG179, Long (15)	CDDP 50 mg/m ² vs. CDDP 50 mg/m ² + TOP 0.75 mg/m ²	7.0 vs. 9.2 (P<0.05)	2.9 vs. 4.6 (P<0.01)	13.0 vs. 26.0 (P<0.01)
GOG204, Monk (5)	CDDP 50 mg/m ² + PTX 135 mg/m ² vs. CDDP 50 mg/m ² + TOP 0.75 mg/m ² vs. CDDP 50 mg/m ² + GEM 1,000 mg/m ² vs. CDDP 50 mg/m ² + VNR 30 mg/m ²	12.9 vs. 10.3 vs. 10.3 vs. 10.0 (NS)	5.8 vs. 4.6 vs. 4.7 vs. 4.0 (NS)	29.1 vs. 23.4 vs. 22.3 vs. 25.9 (NS)
GOG240, Tewari (56)	CDDP 50 mg/m ² + PTX 135 mg/m ² with or without Bev 15 mg/kg vs. CDDP 50 mg/m ² + TOP 0.75 mg/m ² with or without Bev 15 mg/kg	Bev+: 17.5 or Bev-: 14.3 (P<0.05) vs. Bev+: 16.2 or Bev-: 12.7 (NS)		50.0 or 45.0 (NS) vs. 47.0 or 27.0 (P<0.05)
JCOG0505, Kitagawa (57)	CDDP 50 mg/m ² + PTX 135 mg/m ² vs. CBDCA AUC5 + PTX 175 mg/m ²	18.3 vs. 17.5 (NS)	6.9 vs. 6.2 (NS)	58.8 vs. 62.6 (NS)

OS, overall survival; PFS, progression free survival; CDDP, cisplatin; IFM, ifosfamide; BLM, bleomycin; PTX, paclitaxel; TOP, topotecan; GEM, gemcitabine; VNR, vinorelbine; Bev, bevacizumab; CBDCA, carboplatin; NS, not significant. This table is partially modified from ref (58).

GOG169, where 30% of patients received chemoradiation on the cisplatin alone control arm, 56% of patients on the control arm in GOG179 had been treated with prior chemoradiation therapy, potentially explaining the benefit seen for the experimental arm. Encouraging results for combinations including topotecan and cisplatin improved OS, leading to its addition to GOG204.

GOG204

GOG204 incorporated the winning cisplatin doublets from the two preceding trials, cisplatin/paclitaxel (GOG169) and cisplatin/topotecan (GOG179). Two other combination regimens with gemcitabine/cisplatin and vinorelbine/cisplatin were evaluated in this very important phase III trial (5). A total of 513 patients were enrolled prior to a planned interim analysis: 70% of patients had been treated with prior cisplatin chemoradiation. The trial was closed early after the analysis showed that the three control arms were not superior to cisplatin/paclitaxel. The ORR was statistically similar for each of the four arms, ranging from 22.3% for gemcitabine/cisplatin to 29.1% for paclitaxel/cisplatin. While

PFS (4–5.8 months) and OS (10–12.9 months) were similar between arms, paclitaxel was noted to have the highest response rate at 29.1% and OS of 12.9 months.

Vinorelbine/cisplatin, gemcitabine/cisplatin, and topotecan/cisplatin are not superior to paclitaxel/cisplatin in terms of OS. However, the trends in ORR, PFS, and OS favor paclitaxel/cisplatin as standard care. This GOG204 represented a significant step forward in defining optional therapy, however, low ORR (29.1%) and relatively short OS (12.9 months) were disappointing. The OS was significantly worse for patients who had undergone previous concurrent chemoradiotherapy (CCRT) than for those who had undergone radiotherapy alone [hazard ratio (HR) =1.148; 95% CI, 0.90–1.47]. These results suggest that although CCRT contributes to improve prognosis of advanced cervical cancer, treating recurrent disease after CCRT is still difficult because both chemotherapy and radiation therapy have already been administered.

JCOG0505

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 renal toxic effects. Carboplatin, despite being a derivative of cisplatin, was gaining attention because of its low renal toxic effect and no need for hydration.

JCOG conducted a randomized phase III study to evaluate clinical benefits of carboplatin/paclitaxel compared with cisplatin/paclitaxel for patients with advanced or recurrent disease.

Of 253 enrolled patients, 246 were evaluable, including 201 with disease assessable for response (57). The ORR was 60% for cisplatin/paclitaxel and 62% for carboplatin/paclitaxel. The median OS and PFS were 18.3 and 6.9 months for cisplatin/paclitaxel, and 17.5 and 6.2 months for carboplatin/paclitaxel. Thus, carboplatin/paclitaxel proved comparable with cisplatin/paclitaxel in terms of antitumor activity. Carboplatin/paclitaxel was also less toxic than cisplatin/paclitaxel in inducing febrile neutropenia, creatinine elevation, and nausea/vomiting. Most importantly, interim analysis demonstrated that substitution of carboplatin for cisplatin did not result in inferior outcome. Observed toxicities were similar in severity and frequency based on previous experiences with these compounds.

Interestingly, in secondary analysis of 117 patients who hadn't received prior platinum, cisplatin/paclitaxel doublet appeared to be superior to carboplatin/paclitaxel with median OS of 23.2 *vs.* 13.0 months (HR =1.57; 95% CI, 1.06–2.32).

Without evidence of inferiority, carboplatin and paclitaxel may become the new standard for patients with recurrent disease, unless they have not received prior chemoradiation therapy, where they may benefit from cisplatin and paclitaxel.

Molecular targeted therapy

Prognosis of patients who recurred after prior chemotherapy are very poor, therefore new therapeutic strategies are urgently required. Molecular targeted therapy will be the most hopeful candidate for these strategies. Compared with other cancer, there are few clinical trials of molecularly targeted agents. However, the results of bevacizumab in therapeutic trials for cervical cancer have shown that targeting the vascular endothelial growth factor (VEGF) pathway is an attractive therapeutic strategy.

In this section, we summarized several molecularly

targeted agents, correlating with activated pathways in cervical cancer, like VEGF, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR).

VEGF pathway

Angiogenesis, the process leading to the formation of new blood vessels from a preexisting vascular network, is necessary for tumor growth, invasion, and metastasis. Angiogenesis is critical in tumor growth and survival and has been generally considered a very attractive target for cancer therapy. VEGF plays a pivotal role in the control of angiogenesis, tumor growth and metastasis (59-61). The binding of VEGF to its receptors activates a signaling cascade that ultimately produces increased endothelial cell survival, proliferation, vascular permeability, migration and invasion (62). Cervical cancer is heavily dependent on angiogenesis, perhaps even more than most solid tumors, because human papillomavirus infection and ongoing hypoxia (associated with increased expression of hypoxia-inducible factor-1 alpha) are associated with increased levels of VEGF, a common target for anti-angiogenesis therapy. Overexpression of VEGF has been associated with tumor progression and poor prognosis in several tumors, including cervical cancer (63). Cytosol protein level of VEGF has been shown to be increased in cervical cancer compared to normal cervical tissue (64-67). Monoclonal antibodies, like bevacizumab and small-molecule tyrosine kinase inhibitors (TKIs), like pazopanib are hopeful candidates in specific treatments against VEGF.

Bevacizumab

Bevacizumab (Avastin[®], Genentech) is a humanized antibody that recognizes and neutralizes all major isoforms of VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation (68). Bevacizumab was the first FDA-approved therapy designed to inhibit angiogenesis in patients with advanced colorectal and later non-small lung cancer and renal cancer (69). Bevacizumab targets VEGF-A, which seems increased in malignant cervical cancer cells, as well as correlated with advanced stage of cervical cancer (70). A phase II multicenter trial reported a supposedly better PFS (24% probability to survive more than 6 months; 90% CI, 14–37%), median OS (7.29 months; 95% CI, 6.11–10.41 months), and ORR (10.9%; 90% CI, 4.4–21.5%) (32).

GOG240

In GOG240, a phase 3, randomized trial performed in the United States and Spain through GOG and Spanish Research Group for Ovarian Cancer, they investigated the incorporation of bevacizumab and the use of non-platinum combination chemotherapy in the treatment of advanced cervical cancer (56). They randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg/kg. Chemotherapy consisted of cisplatin at a dose of 50 mg/m², plus paclitaxel at a dose of 135 or 175 mg/m² or topotecan at a dose of 0.75 mg/m² on days 1 to 3, plus paclitaxel at a dose of 175 mg/m² on day 1. Cycles were repeated every 21 days until disease progression. The majority of patients (72%) had recurrent disease, and 11% had persistent disease. More than 70% in each group had previously received platinum-based chemoradiotherapy.

Topotecan/paclitaxel wasn't superior to cisplatin/paclitaxel (HR for death =1.20). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased OS (17.0 *vs.* 13.3 months; HR for death =0.71; 98% CI, 0.54–0.95; P=0.004 in a one-sided test) and higher ORR (48% *vs.* 36%, P=0.008). Among patients who received bevacizumab, 28 had CR, and among those who received chemotherapy alone, 14 had CR (P=0.03). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of grade 2 hypertension or higher (25% *vs.* 2%; P<0.001), grade 3 or higher thromboembolic event (8% *vs.* 1%; P=0.001), and grade 3 or higher gastrointestinal fistulas (6% *vs.* 0%; P=0.002). Bevacizumab-containing regimens were associated with reduced hazard of disease progression and increased probability of response. Even when target lesions were located in the previously irradiated pelvis, it appears bevacizumab-containing therapy was effective. The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median OS. GOG240 is a landmark trial because it is the first time a targeted agent has reached its primary endpoint of improving OS in gynecologic cancer.

The National Comprehensive Cancer Network (NCCN) updated their practice guidelines for cervical cancer treatment to include the cisplatin-paclitaxel-bevacizumab triplet as a recommended therapy in recurrent and metastatic disease (category 2A).

Anti-VEGF tyrosine kinase inhibitors (TKIs)

Pazopanib

Pazopanib is a potent and selective multi-targeted receptor TKIs of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α [®], and c-kit that blocks tumor growth and inhibits angiogenesis. Pazopanib is under clinical development for treatment of multiple tumor types and has been approved for renal cell carcinoma by the FDA (71).

A phase II study of pazopanib and lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer, has demonstrated the benefits of pazopanib (72). Patients with measurable stage IVB persistent/recurrent cervical carcinoma not amenable to curative therapy and at least one prior regimen in the metastatic setting were randomly assigned in a ratio of 1:1:1 to pazopanib at 800 mg once daily, lapatinib at 1,500 mg once daily, or lapatinib plus pazopanib combination therapy (lapatinib at 1,000 mg plus pazopanib at 400 mg once daily or lapatinib at 1,500 mg plus pazopanib at 800 mg once daily).

The futility boundary was crossed at the planned interim analysis for combination therapy compared with lapatinib therapy, and the combination was discontinued.

Pazopanib improved PFS (HR =0.66; 90% CI, 0.48–0.91; P=0.013). Median OS was 49.7 and 44.1 weeks (HR =0.96; 90% CI, 0.71–1.30; P=0.407) and ORR were 9% and 5% for pazopanib and lapatinib, respectively (73). The only grade 3 adverse effects >10% was diarrhea (11% pazopanib and 13% lapatinib). Grade 4 adverse effects were reported at 9% (lapatinib) and 12% (pazopanib). This study confirmed the activity of anti-angiogenesis agents in advanced and recurrent cervical cancer and demonstrates the benefits of pazopanib based on the prolonged PFS and favorable toxicity profile.

EGFR pathway

Anti-EGFR tyrosine kinase inhibitors (TKIs)

EGFR is composed of an extra cellular ligand-binding domain, a transmembrane lipophilic segment, and an intracellular protein kinase domain with a regulatory carboxyl terminal segment. On binding of ligand, EGFR dimerization occurs, resulting in high-affinity ligand binding, activation of the intrinsic protein tyrosine kinase activity, and tyrosine auto-phosphorylation. The EGFR

was the first identified of a family of receptors known as the EGFR family or ErbB tyrosine kinase receptors. This receptor family is comprised of four homologue receptors; EGFR itself (ErbB1/EGFR/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). The rationale for targeting the EGFR family for cancer therapy is compelling. These receptors are frequently overexpressed in human tumors, correlating with a more aggressive clinical course (74).

TKIs are a class of orally available and small molecules that inhibit ATP binding within the TK domain, leading to compare inhibition of EGFR auto-phosphorylation and signal transduction (75). Gefitinib is TKIs against EGFR, which have been evaluated as single agents in patients with cervical cancer.

Gefitinib

Gefitinib (ZD1839, Iressa[®], AstraZeneca Pharmaceuticals) has been approved by the FDA for treatment of platinum- and docetaxel- refractory non-small-cell lung cancer (76).

A multicenter phase II trial evaluated the clinical outcomes of 28 recurrent cervical cancers treated with 500 mg/day gefitinib. The exploratory objective was to investigate the correlation of baseline EGFR expression with tumor response and disease control.

Although there were no objective responses, 6 (20%) patients experienced SD with a median duration of 111.5 days. Median time to progression was 37 days and median OS was 107 days. Disease control did not appear to correlate with levels of EGFR expression. Gefitinib was well tolerated, with the most common drug-related adverse events being skin and gastrointestinal toxicities. Gefitinib has only minimal monotherapy activity. However, the observation that 20% of patients treated with gefitinib had SD may warrant further investigation (77).

mTOR pathway

The mTOR is a key protein kinase controlling signal transduction from various growth factors and upstream proteins to the level of mRNA and ribosome with regulatory effect on cell cycle progression, cellular proliferation and growth. In various diseases and mainly in cancer this balance is lost due to mutations or over-activation of upstream pathways leading to persistent proliferation and tumor growth. What makes mTOR attractive to researchers seems to be its key position which is at the crossroads of

various signal pathways (Ras, PI3K/Akt, TSC, NF- κ B) towards mRNA, ribosome, protein synthesis and translation of significant molecules, the uncontrolled production of which may lead to tumor proliferation and growth. Inhibition of mTOR by rapamycin (a natural product) or its analogs aims to prevent deleterious effects of abnormal signaling, regardless of which point of the signal pathway the abnormality has launched (78,79). The mTOR pathway is activated in cervical carcinomas. Temsirolimus is the sole mTOR inhibitor to be evaluated in patients with cervical cancer.

Temsirolimus

The phase II study assessed the activity of the mTOR inhibitor, temsirolimus, in patients with measurable metastatic and/or locally advanced, recurrent carcinoma of the cervix. Temsirolimus 25 mg i.v. was administered weekly in 4-week cycles (80).

Thirty-eight patients were enrolled. Thirty-seven patients were evaluable for toxicity and 33 for response. One patient experienced a PR (3.0%). Nineteen patients had SD (57.6%) [median duration 6.5 months (range, 2.4–12.0 months)]. The 6-month PFS rate was 28% (95% CI, 14–43%). The median PFS was 3.52 months (95% CI, 1.81–4.70). Assessment of PTEN and PIK3CA by IHC, copy number analyses and PTEN promoter methylation status did not reveal subsets associated with disease stability.

In this study, one patient experienced a PR and 58% had SD as the best response. The median duration of SD (6.5 months) is comparable to that seen with anti-angiogenic agents such as bevacizumab (3.5 months) in similar patients' population. They conclude that single agent temsirolimus has modest activity in cervical carcinoma in about 2/3 of patients exhibiting SD.

Supportive care based treatment strategies

In the last section, we analyzed the effectiveness, cost, and QOL associated with both current and novel treatment strategies for patients with recurrent cancer.

Despite the poor response of recurrent cervical cancer to chemotherapy, treatment usually consists of aggressive chemotherapy regimens with substantial toxicity and decreased QOL, raising the question of whether or not this strategy is cost-effective (81,82).

Moore and colleagues analyzed data from three separate GOG trials evaluating cisplatin-based chemotherapy

regimens for recurrent cervical cancer and identified five poor prognostic factors significantly and independently associated with reduced OS (GOG performance status 1 or 2, pelvic recurrence, prior radio-sensitizing chemotherapy, African American race, and first recurrence within 1 year of diagnosis) (82). When four or more of these poor prognostic factors exist together, patients are at the highest risk for treatment failure (16% of patients in the analysis by Moore and colleagues) and have the poorest prognosis with OS of less than 6 months, even with aggressive combination cisplatin-based chemotherapy.

Recurrent cervical cancer is generally considered incurable and current chemotherapy regimens offer only modest gains in OS, particularly for patients with multiple poor prognostic factors.

Phippen *et al.* explored using decision analysis of effectiveness, cost, and QOL associated with both current and novel treatment strategies for patients with recurrent cancer (83).

Their model is designed to identify both the most effective and cost-effective among four modeled strategies for managing recurrent cervical cancer: (I) standard (cisplatin-containing) doublet chemotherapy for all patients; (II) selective chemotherapy (home hospice with no chemotherapy for poorest prognosis patients with remainder receiving standard doublet chemotherapy); (III) single agent chemotherapy with home hospice; and (IV) home hospice care for all patients (no chemotherapy).

Survival in selective chemotherapy strategy was 8.7 months overall, which is an incidence-based representation of the estimated survival rates of the arms of two subgroups, according to the Moore *et al.* study: the poorest prognosis patients (16%) receiving home hospice (OS, 3.3 months) with the remainder (84%) receiving standard doublet chemotherapy (OS, 9.7 months) (84).

Standard doublet chemotherapy for all is not cost-effective compared to selective chemotherapy with an incremental cost-effectiveness ratio (ICER) of \$276,000 per quality-adjusted life-year (QALY). Sensitivity analysis predicted that a 90% improvement in survival is required before standard doublet chemotherapy is cost-effective in poorest prognosis patients.

Selective chemotherapy is the most cost-effective strategy compared to single-agent chemotherapy with home hospice with an ICER of \$78,000/QALY. Chemotherapy containing regimens become cost-prohibitive with small decrease in QOL.

GOG240 reported a 4-month (22%) improvement in

OS when bevacizumab is added to platinum-based doublet chemotherapy (56). However, the costs associated with bevacizumab are substantial and the gains seen with the addition of bevacizumab in other cancer types have yet to prove cost-effective (83-86). Supportive care based treatment strategies are potentially more cost-effective than the current standard of doublet chemotherapy for all patients with recurrent cervical cancer and warrant prospective evaluation.

Conclusions

Since cisplatin was considered as the historical standard treatment for recurrent cervical cancer, subsequent trials have evaluated and demonstrated activity with other agents. The results of GOG204 paclitaxel/cisplatin is considered to be the current recommended regimen for recurrent cervical cancer patients. Also, JCOG0505 in a secondary analysis revealed that for patients who had not received prior platinum, the cisplatin/paclitaxel appeared to be superior to carboplatin/paclitaxel with median OS. Without evidence of inferiority, carboplatin/paclitaxel may become the new standard for patients with recurrent disease, unless they have not received prior chemoradiation therapy, where they may benefit from cisplatin/paclitaxel. Although, the prognosis for recurrent cervical cancer patients is still poor, the results of GOG240 shed light on the usefulness of molecular target agents to chemotherapy in cancer patients. Recurrent cervical cancer is generally considered incurable and current chemotherapy regimens offer only modest gains in OS, particularly for patients with multiple poor prognostic factors. Therefore, it is crucial to consider not only the survival benefit, but also the minimization of treatment toxicity, and maximization of QOL.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Tsuda N, Watari H, Ushijima K. Chemotherapy and molecular targeting therapy for recurrent cervical cancer. *Chin J Cancer Res* 2015. doi: 10.3978/j.issn.1000-9604.2015.12.01