

Chemotherapy for Advanced, Recurrent, and Metastatic Cervical Cancer

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Cervical cancer, chemotherapy, phase III trials

Abstract

When cervical cancer is beyond curative treatment with surgery or radiation therapy, the prognosis is poor and palliation is the primary objective. Early prospective studies identified cisplatin as an active drug for advanced, metastatic, or recurrent cervical cancer, and results with other platinum analogs seemed inferior to cisplatin. Several phase III trials have established the combination of cisplatin plus paclitaxel as standard therapy for comparison. Using pooled data from 3 Gynecologic Oncology Group (GOG) phase III studies, a predictive model was developed to better identify patients who are unlikely to respond to cisplatin-containing chemotherapy. The GOG is currently developing a phase III trial to investigate the impact of bevacizumab and a regimen containing topotecan instead of cisplatin in combination with paclitaxel chemotherapy and also to externally validate the predictive model. This study has the potential to radically change standard care for cervical cancer chemotherapy. Furthermore, if the predictive model is upheld, then patients with high risk factors for treatment failure may be directed to chemotherapy regimens that do not include cisplatin or to investigational trials. (*JNCCN* 2008;6:53–57)

Approximately 11,150 women will be diagnosed with invasive cervical cancer in the United States in 2007. Although most cases will be cured with treatments based on surgery or radiation therapy, an estimated 3670 deaths will still occur from this disease.¹ When cervical cancer is beyond curative treatment with surgery or radiation therapy, the prognosis is poor and palliation is the primary objective. The need to identify more effective

chemotherapy for these patients is an ongoing task. Every year, meeting abstracts and journal articles report high response rates with various agents or regimens that later prove inactive or too toxic when subjected to larger and more rigorous multi-institutional trials. Only through well-designed phase III studies will drugs or combinations be evaluated, compared, and either discarded or selected for further study. This review discusses pertinent clinical trials that define the current treatment standard.

Platinum Compounds

Because of its recognized activity against other solid tumors, the Gynecologic Oncology Group (GOG) initiated a phase II study of cisplatin 50 mg/m² at an infusion rate of 1 mg/min every 3 weeks in patients with stage IVB or recurrent cervical cancer. The response rate was 50% (3 complete responses, 8 partial responses) among the 22 patients who had not undergone prior chemotherapy, and 17% (0 complete responses, 2 partial responses) among the 12 patients who had undergone prior chemotherapy.² Although later series with larger patient numbers reported lower response rates, generally in the 20% to 30% range, the activity of cisplatin was confirmed.

To further explore the use of cisplatin in the treatment of cervical carcinoma, the GOG conducted a study of cisplatin at 3 dose schedules to determine if improved results could be achieved through increased dose intensity. Of 581 women entered into the trial, 497 were considered evaluable. Although the objective response rate increased from 21% to 31% ($P = .015$) by increasing the cisplatin dose from 50 mg/m² to 100 mg/m² every 3 weeks, no associated improvement was seen in the complete response rate, progression-free interval, or overall survival. Furthermore, higher cisplatin doses were associated with greater nephrotoxicity and myelosuppression.³ In a subsequent GOG study, 380 patients were randomized to

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receive 50 mg/m² cisplatin given as either a short infusion (1 mg/min) or over 24 hours. The overall response rate was essentially identical (18%) in each group. Although gastrointestinal toxicity (nausea and emesis) was lower in the prolonged infusion group, the incidence of other adverse effects, including nephrotoxicity, neurotoxicity, and myelosuppression, did not differ.⁴

Recognizing the activity and associated toxicity profile of cisplatin, the GOG studied other platinum analogs for the treatment of advanced, recurrent, and metastatic cervical cancer. In particular, the GOG initiated a randomized phase II study of carboplatin and iproplatin. Clinical experience indicated lesser degrees of nephrotoxicity or neurotoxicity with these drugs than with cisplatin, and either analog could be administered in an outpatient setting without prior hydration. A total of 394 patients entered this trial. The starting dose of carboplatin (400 mg/m²) was reduced to 340 mg/m² in patients who had undergone prior radiation therapy. Similarly, the starting dose of iproplatin (270 mg/m²) was reduced to 230 mg/m² doses in previously irradiated patients. Treatment cycles were repeated at 28-day intervals. The objective response rates were 15% for carboplatin and 11% for iproplatin. Although the study was not designed to compare either analog with cisplatin, these response rates were lower than those reported for cisplatin. Furthermore, after experiencing treatment failure, several patients went on to receive cisplatin. Follow-up data were available for 22 of these patients, and the secondary response rate to cisplatin (18%) was higher than the primary response rate to either analog. The GOG concluded that “this finding seems to be further evidence that cisplatin must remain the drug of choice for advanced squamous cell cancer of the cervix.”⁵

Development of Cisplatin Combinations

Given the modest activity of single-agent cisplatin and the lack of a meaningful impact on survival, clinical research focused on identifying other active drugs that could be used alone or in combination with cisplatin. After dibromodulcitol and ifosfamide had shown activity in relevant phase II studies, and subsequent phase I studies determined the feasibility of administering these agents in combination with cisplatin, the GOG initiated a phase III trial (GOG 110) comparing

cisplatin alone versus cisplatin in combination with either dibromodulcitol or ifosfamide. Compared with cisplatin alone, cisplatin plus ifosfamide showed a significantly higher response rate (33% vs. 19%) and progression-free interval (4.6 vs. 3.2 months) with no improvement in overall survival. However, adverse effects were significantly higher in the ifosfamide-containing arm. Peripheral and central neurotoxicity were more frequent and severe among patients receiving cisplatin plus ifosfamide. Central nervous system toxicity ranged from confusion to somnolence to coma or seizures. Two treatment-related deaths occurred in patients receiving cisplatin plus ifosfamide: one experienced cardiorespiratory arrest while comatose and the other developed renal failure and refused dialysis. The eligibility criteria for the study were modified to include only patients with serum albumin of 3.0 g/dL or greater and serum creatinine within normal limits for the institution. Patients with bilateral hydronephrosis were also considered ineligible. No further cases of fatal CNS toxicity occurred, but lesser degrees of encephalopathy were still observed in patients receiving cisplatin plus ifosfamide.⁶

Several studies suggest that adding bleomycin to the combination of cisplatin plus ifosfamide yields higher response rates and may also improve survival. The GOG initiated a phase III study (GOG 149) comparing the combination of cisplatin plus ifosfamide with versus without bleomycin. These regimens proved essentially identical in terms of objective response rates (approximately 32%), progression-free survival, and overall survival.⁷

GOG Protocols 169 and 179

The dichotomy of improved response rates and progression-free survival versus greater toxicity and no improvement in overall survival prompted a fundamental addition to the statistical end points of trials in patients with recurrent and metastatic cervical cancer. Patient-reported quality of life was deemed an essential end point in these study populations with poor median survival. The first randomized controlled study of palliative chemotherapy in cervical cancer to prospectively obtain quality-of-life measurements in addition to traditional clinical outcomes measures was the phase III trial (GOG 169) comparing cisplatin alone with cisplatin plus paclitaxel. Among the 264 eligible and randomized patients, the objective response

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rates were 19% (6% complete responses, 13% partial responses) for cisplatin versus 36% (15% complete responses, 21% partial responses) for cisplatin plus paclitaxel ($P = .002$). The median progression-free survival was also improved with the addition of paclitaxel, but overall survival was not improved (8.7 months for cisplatin vs. 9.7 months for cisplatin plus paclitaxel). Although toxicity, particularly myelosuppression, was more common in the group of patients receiving paclitaxel, this did not worsen quality of life.⁸

The GOG subsequently initiated a phase III trial of cisplatin compared with cisplatin plus topotecan, again with quality of life included among the outcomes measures. GOG 179 was initially activated as a 3-arm study, but the methotrexate, vinblastine, doxorubicin, and cisplatin arm was closed by the Data Safety Monitoring Board after 4 treatment-related deaths occurred among 63 patients. A total of 293 eligible patients were randomized to receive one of the cisplatin-containing regimens. Objective response rates were 13% (3% complete responses, 10% partial responses) for cisplatin versus 26% (10% complete responses, 16% partial responses) for cisplatin plus topotecan ($P = .004$). Progression-free survival was also better among patients undergoing combination chemotherapy. Median survival for patients receiving cisplatin versus cisplatin plus topotecan was 6.5 versus 9.4 months, respectively ($P = .014$). This was the first prospective trial to identify a chemotherapy drug or regimen yielding a survival advantage in this patient population.⁹ Furthermore, despite increased toxicity, the cisplatin plus topotecan combination did not significantly reduce patient-reported quality of life.¹⁰

GOG Protocol 204

Although GOG 179 resulted in a statistically significant improvement in overall survival with the cisplatin

plus topotecan combination, median survival in this study was not appreciably different than that for the 2 previous GOG phase III trials (Table 1).

This discrepancy may be caused by the increasing use of concurrent chemotherapy for patients with locally advanced cervical cancer undergoing primary radiation therapy. Acknowledging the impressive results from 5 phase III trials, the National Cancer Institute issued a Clinical Announcement in 1999 stating, "Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer."^{11,12} Patients in GOG 179 (58%) had a nearly twofold increase in the prior use of concurrent chemotherapy compared with those in GOG 169 (31%). The characteristics of patients participating in these chemotherapy trials had changed, thereby invalidating direct comparisons of results between trials.

To resolve this dilemma and further study other drugs with demonstrated activity (and possible synergy when used in combination with cisplatin), the GOG initiated a randomized phase III study (GOG 204) of cisplatin plus 1 of 4 agents—paclitaxel, topotecan, vinorelbine, or gemcitabine—in stage IVB, recurrent, or persistent carcinoma of the cervix. The GOG closed the study in April 2007. Cisplatin plus paclitaxel was designated the control arm, and whether cisplatin plus topotecan or one of the other cisplatin combinations will show superiority is currently unclear.

Carboplatin

The GOG experience with carboplatin⁵ has not deterred other groups from studying this drug. Tinker et al.¹³ reported a 40% objective response rate for carboplatin in combination with paclitaxel. Nagao et al.¹⁴

Table 1 Comparison of GOG Phase III Trials

Protocol	Regimen	N	OR	CR	PFS (mo)	OS (mo)
GOG 110	P	140	19%	6%	3.2	8.0
	P + IFX	151	31%	13%	4.6	8.3
GOG 169	P	134	19%	6%	3.0	8.9
	P + T	130	36%	15%	4.9	9.9
GOG 179	P	145	13%	3%	2.9	7.0
	P + Topo	148	26%	10%	4.6	9.2

Abbreviations: CR, complete response; GOG, Gynecologic Oncology Group; IFX, ifosfamide; N, number of patients; OR, odds ratio; OS, overall survival; P, cisplatin; PFS, progression-free survival; T, paclitaxel; Topo, topotecan.

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reported a 76% objective response rate for carboplatin in combination with docetaxel. The Japan Clinical Oncology Group is presently conducting a phase III investigation comparing paclitaxel in combination with either cisplatin or carboplatin, but the trial is not expected to complete accrual until fall 2009 (www.clinicaltrials.gov).

Future Directions

The goal of developing a highly active, curative chemotherapy for patients with advanced, recurrent, or metastatic cervical cancer has not been attained. Most patients do not experience response to chemotherapy in any meaningful way. To develop a model predictive of response to chemotherapy, data from GOG protocols 110, 169, and 179 were pooled and a multivariate analysis conducted to identify factors independently predictive of response and survival. Multivariate analysis identified 5 factors (African-American; performance status > 0; pelvic disease; prior radiosensitizer; recurrence \leq 1 year) independently predictive of poor response among patients undergoing combination chemotherapy containing cisplatin. Patients were classified into 3 risk groups based on the total number of risk factors (low risk: 0–1 factor; mid-risk: 2–3 factors; high risk: 4–5 factors). Patients with 4 to 5 risk factors were predicted to experience a treatment response of only 13% and a median progression-free and overall survival of 2.8 and 5.5 months, respectively. This subgroup of patients consists of approximately 14% of the target population in clinical trials.¹⁵ Although the predictive model was externally validated using the GOG 149 database that was not used for model development, further validation is recommended before the model can be applied to clinical trials development or clinical practice.

Cervical cancers are among the cancers with the highest overexpression of epidermal growth factor receptor (EGFR). Preclinical data implicate EGFR in the DNA repair processes after radiation and clinical trial data show that monoclonal inhibitors of EGFR are synergistic with radiation and chemotherapy.¹⁶ Thus, EGFR is an attractive therapeutic target. Evidence also shows that angiogenesis plays an important role in the progression of cervical cancer.¹⁷ Molecular inhibition of tumor angiogenesis is another potential therapeutic strategy. The GOG is currently in the final stages of developing a phase III trial to investigate the impact of bevacizumab and a regimen

containing topotecan instead of cisplatin in combination with paclitaxel chemotherapy. Overall survival is the primary end point. This study is important because it will 1) be the first prospective evaluation of a standard chemotherapy (cisplatin plus paclitaxel) plus an inhibitor of angiogenesis (bevacizumab) for the treatment of advanced, recurrent, or metastatic cervical cancer; 2) be the first phase III trial to successfully evaluate a non-platinum-containing regimen (topotecan plus paclitaxel); and 3) gather further data on the validity of the aforementioned predictive model. This study has the potential to radically change standard care for cervical cancer chemotherapy. Furthermore, if the predictive model is upheld, then patients classified as high risk should be directed to chemotherapy regimens that do not include cisplatin or to investigational trials.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Thigpen JT, Shingleton H, Homesley H, et al. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II trial of the Gynecologic Oncology Group. *Cancer* 1981;48:899–903.
3. Bonomi P, Blessing JA, Stehman FB, et al. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 1985;3:1079–1085.
4. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 1989;32:198–202.
5. McGuire WP III, Arseneau JC, Blessing JA, et al. A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 1989;7:1462–1468.
6. Omura GA, Blessing JA, Vaccarello L, et al. A randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 1997;15:165–171.
7. Bloss JD, Blessing JA, Behrens BC, et al. Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2002;20:1832–1837.
8. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2004;22:3113–3119.
9. Long HJ, Bundy BN, Grendys EC, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005;23:4626–4633.
10. Monk BJ, Huang HQ, Cella D, Long HJ. Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005;23:4617–4625.

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11. Moore DH. Combined chemotherapy and radiation therapy for cervical cancer. *J Natl Compr Canc Netw* 2004;2:631–635.
12. National Cancer Institute. Concurrent chemoradiation for cervical cancer. *Clinical Announcement*, Washington, D.C., February 22, 1999.
13. Tinker AV, Bhagat K, Swenerton KD, Hoskins PJ. Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: the British Columbia Cancer Agency experience. *Gynecol Oncol* 2005;98:54–58.
14. Nagao S, Fujiwara K, Oda T, et al. Combination chemotherapy of docetaxel and carboplatin in advanced or recurrent cervix cancer. A pilot study. *Gynecol Oncol* 2005;96:805–809.
15. Moore DH, Tian C, Monk BJ, et al. Factors predictive of response to cisplatin-based chemotherapy in stage IVB persistent or recurrent cervical carcinoma: a multivariate analysis of three Gynecologic Oncology Group trials [abstract]. *J Clin Oncol* 2007;25(Suppl 1):282s. Abstract 5534.
16. Bonner JA, Giralt J, Harari PM, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: a phase III study of high dose radiation therapy with or without cetuximab [abstract]. *J Clin Oncol* 2004;22(Suppl 1):Abstract 5507.
17. Mathur SP, Mathur RS, Rust PF, et al. Human papilloma virus (HPV)-E6/E7 and epidermal growth factor receptor (EGF-R) protein levels in cervical cancer and cervical intraepithelial neoplasia (CIN). *Am J Reprod Immunol* 2001;46:280–287.