

Chemotherapy in the Management of Cervical Carcinoma

Nefertiti C. duPont, MD, and Bradley J. Monk, MD

Dr. duPont is Clinical Instructor and Dr. Monk is Associate Professor of Obstetrics and Gynecology at the University of California, Irvine College of Medicine in Irvine, Calif

Address correspondence to:
Bradley J. Monk, MD, Associate Professor,
University of California, Irvine College
of Medicine, Department of Obstetrics
and Gynecology, Division of Gynecologic
Oncology, 101 The City Drive South,
Building 56, Room 260, Orange, CA
92868; Tel: 714-456-7974;
E-mail: bjmonk@uci.edu.

Abstract: Cervical carcinoma, although largely preventable, is one of the most prevalent cancers worldwide. Early-stage disease can be successfully treated with surgery alone, and women with locally advanced cervical carcinoma are treated with radiation and concurrent weekly cisplatin at a dose of 40 mg/m² for six doses. For women with advanced, persistent, or recurrent disease not amenable to local resection or radiation, however, few treatment options exist. In this subset of patients, palliative cytotoxic chemotherapy is playing an ever-increasing role. Only the combination of topotecan and cisplatin has been shown to prolong survival in this setting and although the benefit of combination therapy is modest, there has been no decrease in quality of life when this doublet is compared to single-agent cisplatin. Newer innovative agents are needed to treat metastatic and recurrent cervical cancer.

Although cervical cancer is a preventable cancer, it is the third leading cause of cancer-related mortality in women worldwide.¹ The American Cancer Society estimates that 10,370 women will be diagnosed with cervical cancer in the United States this year and approximately 3,710 women will die from this disease.² Human papillomavirus (HPV) is believed to be the etiologic agent responsible for approximately 99% of all cervical cancers.³ HPV-16, -18, -31, and -45 are the most common high-risk types associated with cervical cancer; HPV-16 accounts for 60% of all cervical cancers and HPV-18 accounts for 10–20% of these cancers.³ HPV vaccine trials using the L1 virus-like particle for HPV-16 and -18 are showing tremendous promise as a preventative tool, but in the meantime several clinical trials are seeking ways to identify more effective chemotherapeutic regimens.³

Surgery remains the mainstay of treatment for women with microinvasive (International Federation of Gynecology and Obstetrics [FIGO] stages IA₁–IA₂) and early-stage (FIGO stages IB₁–IIA) cervical cancer (Tables 1 and 2).^{4,5} Cisplatin-based concurrent chemoradiation is the current standard therapy for locally advanced disease.⁴⁻¹⁰ For patients with advanced, recurrent, or persistent disease, chemotherapy is often the only remaining treatment option.

Keywords

Chemotherapy, cisplatin, topotecan, tirapazamine, cervical cancer

Historical Perspective of Cisplatin-based Therapy in Cervical Cancer

In the 1960s cervical cancer was treated most often with radiotherapy although surgery was also used.¹¹ The National Cancer Institute's End Results Report showed that from 1965 to 1969 only 11% of 4,599 cervical cancer patients received chemotherapy as a part of their treatment.¹¹ When chemotherapy was used, it was given to patients with metastatic disease as palliative therapy. However, other squamous cell cancers began to be treated with cytotoxic chemotherapeutic agents, and as a result phase II trials were instituted in cervical cancer patients, with cyclophosphamide, 5-fluorouracil (5-FU), and methotrexate showing the most activity.¹¹ In 1969 cisplatin was shown to have antitumor activity in neoplasms and in 1972 cisplatin was first used in phase I trials.¹² In 1981, the Gynecologic Oncology Group (GOG) published results from a phase II trial in which cisplatin 50 mg/m² was administered every 3 weeks, showing a 50% response rate in women with advanced or recurrent cervical cancer who were chemo-naïve; however, the response rate was only 17% in patients who had received prior chemotherapy.¹² This study was followed by a dose intensity study that showed a 25% overall response rate with cisplatin 20 mg/m² given for 5 days, a 20.7% overall response rate with cisplatin 50 mg/m² given every 21 days, and a 31.4% overall response rate with cisplatin 100 mg/m² given every 21 days.¹³ Despite the fact that the 100 mg/m² dose of cisplatin given every 21 days produced a higher overall response rate, the median progression-free survival (PFS) rates were similar for the two 21-day regimens (7 months for the 50 mg/m² dose vs 7.1 months for the 100 mg/m² dose).¹³

As our understanding of the pharmacokinetics of cisplatin has matured, other platinum analogs have been evaluated in phase II and phase III clinical trials to determine their effectiveness. One phase III trial, GOG 77, showed lower overall response rates for carboplatin and iproplatin (15% and 11%, respectively) than had been reported for cisplatin.¹⁴ Because these and other platinum analogs have not shown higher overall response rates when compared to cisplatin, most experts have accepted cisplatin as the dominant compound in this setting and have focused on adding a second cytotoxic agent to this marginally effective therapy. Moreover, because cisplatin doses above 50 mg/m² every 3 weeks have not resulted in improved survival, this dose and schedule has become the standard regimen in advanced and recurrent cervical cancer during the last two decades.

Table 1. International Federation of Gynecology and Obstetrics (FIGO) Staging Nomenclature for Cervical Carcinoma⁵

Clinical Stage	Characteristics
IA ₁	Measured stromal invasion ≤3 mm in depth and extension ≤7 mm
IA ₂	Measured stromal invasion >3 mm and ≤5 mm in depth with horizontal extension ≤7 mm
IB ₁	Clinically visible lesions ≤4 cm
IB ₂	Clinically visible lesions >4 cm
IIA	Cervical carcinoma invades beyond the uterus, with no parametrial involvement
IIB	Cervical carcinoma invades beyond the uterus with parametrial involvement
IIIA	Tumor involves lower third of the vagina with no extension to the pelvic sidewall
IIIB	Extension of the tumor to the pelvic sidewall, hydronephrosis, or a nonfunctioning kidney
IVA	Carcinoma extends beyond the true pelvis with direct extension to the mucosa of the rectum or bladder
IVB	Carcinoma extends beyond the true pelvis with spread to distant organs

Table 2. Primary Treatment Options for Cervical Carcinoma by Stage

Clinical Stage	Primary Treatment
IA ₁	<ul style="list-style-type: none"> Extrafascial hysterectomy or Observation if cone biopsy has negative margins and patient desires future fertility
IA ₂	<ul style="list-style-type: none"> Radical hysterectomy, pelvic lymph node dissection ± para-aortic lymph node sampling or brachytherapy and pelvic radiation (point A dose: 75–80 Gy)
IB ₁ and IIA (<4 cm)	<ul style="list-style-type: none"> Radical hysterectomy, pelvic lymph node dissection + para-aortic lymph node sampling + tailored postoperative adjuvant therapy or Concurrent cisplatin-based chemotherapy* + pelvic radiation + brachytherapy (point A dose: 80–85 Gy)
IB ₂ , IIA (>4 cm) and IIB–IVA	<ul style="list-style-type: none"> Concurrent cisplatin-based chemotherapy* + pelvic radiation + brachytherapy (point A dose: ≥85 Gy)

* 40 mg/m² intravenously (maximal dose of 70 mg) weekly times six.

Table 3. Concurrent Chemoradiation Trials That Led to the National Cancer Institute's 1999 Clinical Alert

Selected	Cooperative Group	Chemotherapy Treatment Regimen	Number of Patients	Stages	Relative Risk of Death in Chemoradiation Arm	Survival in Chemoradiation Group, %
Whitney et al ¹⁰	GOG 85	Cisplatin, 5-FU, RT vs hydroxyurea, RT	368	IIB–IVA	0.79	67 vs 57
Morris et al ⁸	RTOG 9001	Cisplatin, 5-FU, RT vs RT	388	IB–IIA (with positive pelvic lymph nodes) and IIB–IVA	0.48	73 vs 58
Peters et al ⁹	GOG 109/SWOG 8797	Cisplatin, 5-FU, RT vs RT	243	IA ₂ –IIA	NS	81 vs 71
Keys et al ⁷	GOG 123	Cisplatin, RT, adjuvant hysterectomy vs RT, adjuvant hysterectomy	369	IB (bulky)	0.54	83 vs 74
Rose et al ⁶	GOG 120	Cisplatin, RT vs cisplatin, 5-FU, hydroxyurea, RT vs hydroxyurea, RT	526	IIB–IVA	0.61 (cisplatin) 0.58 (cisplatin, 5-fluorouracil, hydroxyurea)	65 vs 65 vs 47

5-FU = 5-fluorouracil; GOG = Gynecologic Oncology Group; NS = not stated; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.

Locally Advanced Disease

On February 22, 1999, the National Cancer Institute issued a clinical alert urging physicians to adopt cisplatin-based concurrent chemoradiation as the standard of care for women with locally advanced cervical cancer, FIGO stages IIB–IVA. This clinical alert summarized data from five clinical trials showing a 30–50% decreased risk of death in women with FIGO stages IB₂–IVA cervical cancer (Table 3). Cisplatin is a radiation sensitizer and is thought to work by reducing the hypoxic fraction of cells, synchronizing the cell cycle, and inhibiting the cells' radiation repair mechanisms.¹⁵ Not only does cisplatin act as a sensitizing agent to ionizing radiation, but many of these trials also demonstrated a reduction in distant failure as well.

Whitney and colleagues¹⁰ demonstrated a survival benefit ($P=.018$) and a longer PFS rate in patients with FIGO stages IIB–IVA cervical cancer who received chemoradiation with 5-FU and cisplatin over patients who received chemoradiation with single-agent hydroxyurea (relative risk, 0.79). The Radiation

Therapy Oncology Group trial by Morris and coworkers⁸ examined a cohort of patients with high-risk cervical cancer (FIGO stages IB–IIA with positive pelvic lymph nodes or stages IIB–IVA). Patients were randomized to receive concurrent cisplatin/5-FU with pelvic radiotherapy or extended-field radiation to include pelvic and para-aortic fields. The group that received chemoradiation had a 67% disease-free 5-year survival rate versus 40% for the group that received radiation alone ($P=.004$). Similarly, GOG 123 compared patients with FIGO stage IB cervical cancer who had 6 weeks of concurrent cisplatin-based chemoradiation followed by adjuvant hysterectomy to similarly staged patients who had pelvic radiation followed by adjuvant hysterectomy.⁷ In this study the 3-year survival rate was lower in the radiation-only group (74% vs 83%, $P=.008$). Peters and associates,^{9,16} in GOG 109/Southwest Oncology Group 8797, compared patients with FIGO stages IA₂–IIA who had positive surgical margins or positive pelvic nodes after a radical hysterectomy to four cycles of adjuvant chemoradiation with cisplatin/5-FU or adjuvant pelvic radiotherapy. The

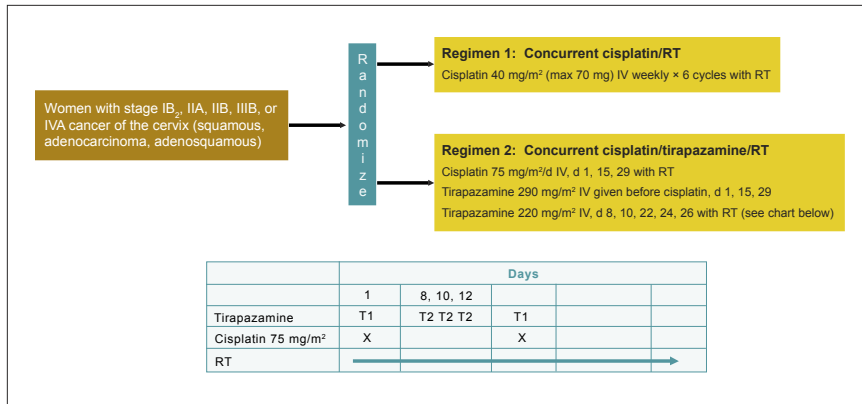


Figure 1. Schema for Gynecologic Oncology Group protocol 219.

IV = intravenous; RT = radiotherapy; T1 = tirapazamine dose on same day as cisplatin; T2 = tirapazamine dose not given on same days as cisplatin.

chemoradiation group had a prolonged overall survival and increased PFS ($P=.007$ and $P=.003$, respectively).⁹ The fifth study in this series, GOG 120, randomized 526 women with FIGO stages IIB–IVA to three different chemotherapy regimens.⁶ One third of the women in this study received single-agent cisplatin; one third received cisplatin/5-FU/hydroxyurea; and the last group received single-agent hydroxyurea. The PFS was highest in the single-agent cisplatin group (67%) and lowest in the single-agent hydroxyurea group (47%). The triple-drug regimen had a PFS of 64% and the most hematologic toxicities. Because single-agent cisplatin at a dose of 40 mg/m² (maximum absolute dose of 70 mg) every week for six doses was equally efficacious and less toxic than the multidrug combination in this trial, this dose and schedule have become the world standard when cisplatin is added to radiation in the management of cervical cancer. Importantly, neither 5-FU alone nor in combination with cisplatin has been shown to be more effective than cisplatin alone when added to radiation in the care of patients with locally advanced cervical cancer.¹⁷ The results from these five clinical trials provide substantial evidence for the role of chemoradiation in locally advanced cervical cancer and provide the framework by which subsequent clinical trials should be based.

Currently the GOG is conducting protocol 219 (Figure 1). This study compares concurrent cisplatin-based chemoradiation, the current gold standard, to concurrent cisplatin-based chemoradiation plus tirapazamine in patients with FIGO stages IB₂–IVA cervical cancer. Tirapazamine is a bioreductively activated, hypoxia-selective antitumor agent of the benzotriazine series that increases cisplatin cytotoxicity both in vitro and in vivo.¹⁸ Two dosing schedules of tirapazamine are being employed: 290 mg/m² given on the days of cisplatin therapy, and 220 mg/m² given on days 8, 10, and 12 of each 14-day cycle.

Advanced, Recurrent, or Persistent Disease

Patients with advanced, recurrent, or persistent cervical cancer are the most difficult to treat, and for this patient population chemotherapy offers the best hope.¹⁹ When disease recurs at the site of a previously irradiated field, additional radiotherapy is not an option and treatment for these patients is largely palliative. If recurrent disease presents in the central pelvis, then pelvic exenteration with experienced surgeons may yield 5-year success rates of 32–62% in the appropriate patient.⁵ When surgery is not feasible, patients with advanced, recurrent, or persistent disease should be offered enrollment in clinical trials.

Many studies have attempted to identify active agents in this patient population, and most of the studies have established cisplatin as the most active agent.^{13,14} Several phase II protocols have evaluated novel single agents or combinations of cisplatin with other agents such as mitolactol, ifosfamide, gemcitabine, topotecan, paclitaxel, or vinorelbine. All have shown promising results.^{20–33} Active agents identified in these phase II trials have led to careful phase III studies that are attempting to find optimal agents to improve the activity of single-agent cisplatin.

The GOG has published results from four randomized phase III trials (Protocols 110, 149, 169, and 179) trying to find the optimal platinum doublet to treat women with metastatic cervical cancer (Table 4). In 1997 Omura and associates³⁴ published the results from GOG 110. This phase III trial compared single-agent cisplatin to cisplatin/mitolactol and cisplatin/ifosfamide. The overall response was 17.8% in the cisplatin-only arm, 21.1% in the cisplatin/mitolactol arm, and 31.1% in the cisplatin/ifosfamide arm ($P=.004$ vs cisplatin alone). Despite statistical significance in the overall response rate, no significant difference was seen in the overall survival rate among these three groups ($P=.835$) and, as expected, toxicity was greater with the cisplatin/ifosfamide regimen.

Table 4. Summary of the Gynecologic Oncology Group's (GOG) Phase III Trial Experience in Metastatic Cervical Carcinoma³⁷

GOG ID	Author	Year	Arms	N	Objective Response			Response Measurement,* mo	Median Survival,† mo
					PR, %	CR, %	Overall, %		
43	Bonomi et al ^{13,16}	1985	Cisplatin 50 mg/m ² IV q 21 days	150	10.7	10.0	20.7	4.9	7.1
			Cisplatin 100 mg/m ² IV q 21 days	166	18.7	12.7	31.4	4.1	7.0
			Cisplatin 20 mg/m ² IV × 5 days q 21 days	128	16.4	8.6	25.0	4.8	6.1
64	Thigpen et al ⁴⁷	1989	Cisplatin 50 mg/m ² 24-hr continuous infusion	156	12	6	18	5.5	6.4
			Cisplatin 1 mg/min rapid infusion	164	11	6	17	4.5	6.2
77	McGuire et al ¹⁴	1989	Carboplatin 340–400 mg/m ² IV q 28 days	175	9.7	5.7	15.4	2.7	6.2
			Iproplatin 230–270 mg/m ² IV q 28 days	177	6.8	4.0	10.8	3.0	5.5
110	Omura et al ³⁴	1997	Cisplatin 50 mg/m ² IV q 21 days	140	11.4	6.4	17.8	3.2	8.0
			Cisplatin 50 mg/m ² IV + mitolactol 180 mg/m ² PO days 2, 6 q 21 days	147	11.6	9.5	21.1	3.3	7.3
			Cisplatin 50 mg/m ² IV + ifosfamide 5 g/m ² 24-hr infusion + mesna 6 g/m ² q 21 days	151	18.5	12.6	31.1 <i>P</i> =.004	4.6 <i>P</i> =.003	8.3
149	Bloss et al ³⁵	2002	Cisplatin 50 mg/m ² IV + Ifosfamide 5 g/m ² 24-hr infusion + mesna 6 g/m ² q 21 days	146	NS	NS	32.2	4.6	8.5
			Bleomycin 30 units 24-hr infusion, followed by cisplatin 50 mg/m ² IV + ifosfamide 5 g/m ² 24-hr infusion + mesna 6 g/m ² q 21 days	141	NS	NS	32.1	5.1	8.4
169	Moore et al ³⁶	2004	Cisplatin 50 mg/m ² IV q 21 days	134	13	6	19	2.8	8.8
			Paclitaxel 135 mg/m ² 24-hr infusion + cisplatin 50 mg/m ² IV q 21 days	130	21	15	36 <i>P</i> =.002	4.8 <i>P</i> <.001	9.7
179	Long et al ³²	2005	Cisplatin 50 mg/m ² IV q 21 days	145	10	13	13	2.9	6.5
			Topotecan 0.75 mg/m ² IV days 1–3 + cisplatin 50 mg/m ² IV q 21 days	148	16	10	26 <i>P</i> =.004	4.6 <i>P</i> =.00048	9.4 <i>P</i> =.015
			MVAC q 4 wks (analysis forthcoming) ⁶⁶	63	9	13	22	4.4	9.4

* GOG 43 and 64 = median duration of response; GOG 77 = median progression-free interval; GOG 110, 149, 169, and 179 = median progression-free survival.

† GOG 43 survival = progression-free survival.

CR = complete response; IV = intravenous; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin (this arm was closed due to unacceptable mortality); NS = not specified; PFS = progression-free survival; PO = orally; PR = partial response.

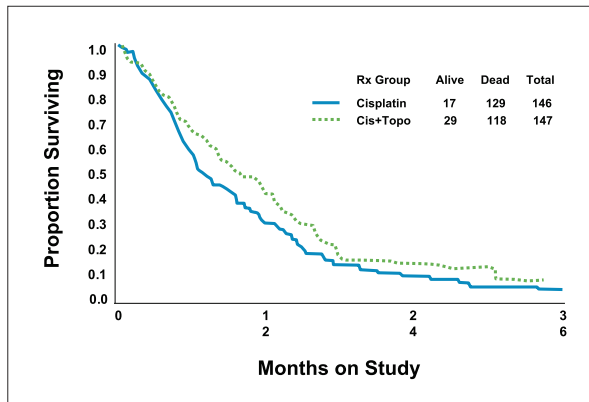


Figure 2. Gynecologic Oncology Group protocol 179 survival rates by treatment arm. The control group received single-agent cisplatin 50 mg/m² intravenously (IV) every 21 days for a maximum of six cycles or until disease progression. The study group received combination therapy with cisplatin 50 mg/m² IV on day 1 and topotecan 0.75 mg/m² IV given on days 1, 2, and 3 every 21 days for a maximum of six cycles or until disease progression.

Long H, et. al. *J Clin Oncol.* 2005;23:4626-4633.³²

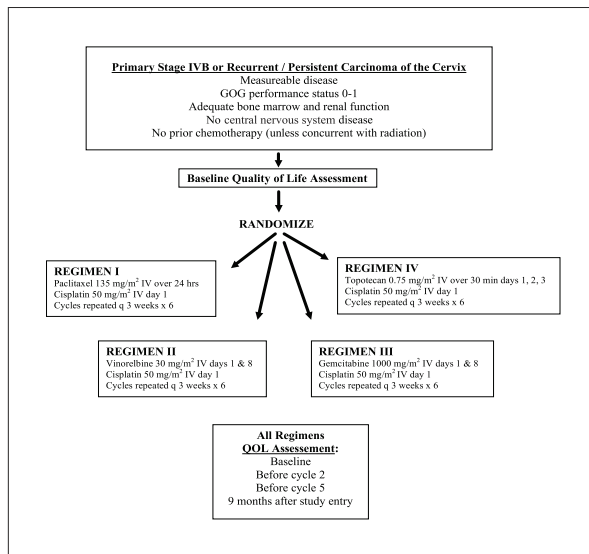


Figure 3. Treatment and assessment scheme for Gynecologic Oncology Group (GOG) protocol 204.

IV= intravenous; QOL = quality of life.

Another phase III study, GOG 149, demonstrated that the addition of bleomycin did not enhance the activity of the cisplatin/ifosfamide doublet, and GOG 169 showed that the addition of paclitaxel to cisplatin, similar to adding ifosfamide or increasing the dose of single-agent cisplatin, only improved the response rate (36% vs 19%; $P=.002$) and prolonged PFS (4.8 vs 2.8 months; $P<.001$) without an improvement in survival.³⁵⁻³⁷

Most recently, the GOG completed protocol 179, which represents the first positive trial in this group of women. This phase III trial randomized 294 patients to cisplatin 50 mg/m² given every 21 days or to topotecan 0.75 mg/m² given on days 1–3 followed by cisplatin 50 mg/m² given on day 1. This trial had a third group of patients given methotrexate, vinblastine, doxorubicin, and cisplatin every 4 weeks, but this arm was closed after four treatment-related deaths occurred among the first 63 enrolled patients. In the remaining two arms of this trial, a 2.9-month improvement in median survival was seen in the cisplatin/topotecan arm ($P=.017$; Figure 2).³² This trial also demonstrated that the cisplatin/topotecan doublet did not impair quality of life, making this combination the new standard regimen in the setting of stage IVB or recurrent cervical cancer.³⁸ Since there is no convincing evidence that squamous lesions and adenocarcinomas respond to palliative chemotherapy differently, this regimen would be appropriate for either cell type.

An ongoing phase III trial, GOG 204, is comparing cisplatin/paclitaxel to cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine in patients with advanced, recurrent, or persistent disease in an attempt to find the optimal platinum doublet (Figure 3). Paclitaxel is included despite showing a lack of survival benefit in GOG 169 because there is a trend for cisplatin to be less effective in recurrent cancer among women who receive this drug as part of their primary radiation therapy and thus the cisplatin/paclitaxel combination might show different results in the new era of radiosensitizing chemotherapy.³⁹

Neoadjuvant Chemotherapy

The role of neoadjuvant chemotherapy in cervical cancer has largely been studied in patients with bulky locally advanced disease who are candidates for surgical management if the local tumor burden can be diminished. Large tumors are technically more difficult to remove surgically so neoadjuvant chemotherapy has been used to improve surgical operability.⁴⁰ Proponents for neoadjuvant chemotherapy have shown that large tumors have decreased response rates to radiotherapy due to increased tissue hypoxia. In a recent study, 219 patients with FIGO stages IB₂–IVA squamous cell cervical cancer were randomized to an ifosfamide/cisplatin neoadjuvant regimen given

every 3 weeks for three cycles or to an ifosfamide/cisplatin/paclitaxel neoadjuvant regimen for the same duration.⁴¹ Patients who were deemed operable were treated with a radical hysterectomy. Patients who were not operable were treated with radiotherapy at the completion of their three cycles of chemotherapy. The results of this trial revealed that hematologic toxicity was greater in the triplet-regimen arm, but the study was not powered to detect an improvement in overall survival.

Sardi and coworkers⁴⁰ published results of a trial of neoadjuvant chemotherapy before radical hysterectomy in patients with FIGO stage IB tumors. The patients in the neoadjuvant group were compared to a control group of patients who received the customary treatment with radical hysterectomy and pelvic radiotherapy. No survival advantage was seen in the neoadjuvant chemotherapy group, but there was an improved resectability rate in patients who received neoadjuvant chemotherapy (85% in control group vs 100% in neoadjuvant group). Many neoadjuvant trials have been published to date, but few of them demonstrate an improved overall survival rate.⁴²⁻⁴⁶ A meta-analysis of 21 randomized trials showed that short chemotherapy cycles and cisplatin dose intensities greater than 25 mg/m² per week had a survival advantage over long chemotherapy cycles and low cisplatin dose intensities.⁴⁶ This meta-analysis also showed a reduction in the risk of death when neoadjuvant chemotherapy was used in the properly selected patient. However, though the idea of creating a smaller tumor burden and controlling micrometastatic disease before surgery may be beneficial in a select group of patients, more randomized clinical trials are needed before neoadjuvant chemotherapy can be instituted outside of research protocols.

Conclusions

Improved cervical cancer screening has led to a decline in the incidence of cervical cancer in developed countries, but cervical cancer remains a leading cause of cancer-related mortality worldwide. Advances in the treatment of cervical cancer have led to the use of cisplatin-based concurrent chemoradiation in locally advanced disease, but few treatment options remain for women with advanced, recurrent, or persistent disease. Cisplatin-based combination chemotherapeutic regimens have produced higher PFS rates over cisplatin alone and one combination has even prolonged survival, but newer agents are needed to move from palliation to cure.

References

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2002;55:74-108.
2. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55:10-30.
3. Mahdavi A, Monk BJ. Vaccines against human papillomavirus and cervical cancer: promises and challenges. *Oncologist.* 2005;10:528-538.
4. National Comprehensive Cancer Network. *NCCN Practice Guidelines in Oncology: Cervical Cancer, Version 1.2004.* Jenkintown, Pa: National Comprehensive Cancer Network.
5. DiSaia P, Creasman W. *Clinical Gynecologic Oncology.* 6th ed. St. Louis: Mosby, Inc.; 2002.
6. Rose P, Bundy B, Watkins E, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340:1144-1153.
7. Keys H, Bundy B, Stehman F, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage 1B cervical carcinoma. *N Engl J Med.* 1999;340:1154-1161.
8. Morris M, Eifel P, Lu J, et al. Pelvic Radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high risk cervical cancer. *N Engl J Med.* 1999;340:1137-1143.
9. Peters W, Liu PY, Barrett R, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high risk early-stage cancer of the cervix. *J Clin Oncol.* 2000;18:1606-1613.
10. Whitney C, Sause W, Bundy B, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a gynecologic oncology group and southwest oncology group study. *J Clin Oncol.* 1999;17:1339-1348.
11. DeVita VT Jr, Wasserman T, Young R, Carter S. Perspectives on research in gynecologic oncology. *Cancer.* 1976;38:509-525.
12. Thigpen J, Shingleton H, Homesley H, et al. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a Phase II study of the Gynecologic Oncology Group. *Cancer.* 1981;48:899-903.
13. Bonomi P, Blessing J, Stehman F, DiSaia P, Walton L, Major F. 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.
14. McGuire W III, Arseneau J, Blessing J, 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.
15. Kirwan J, Symonds P, Green J, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol.* 2003;68:217-226.
16. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group Trial. *Gynecol Oncol.* 2005;96:721-728.
17. Lanciano R, Calkins A, Bundy BN, et al. A Randomized Comparison of Weekly Cisplatin or Protracted Venous Infusion of Fluorouracil in Combination with Pelvic Radiation in Advanced Cervix Cancer: A Gynecologic Oncology Group Study. *J Clin Oncol.* 2005. October 15 [E print].
18. Craighead PS, Pearcey R, Stuart G. A phase I/II evaluation of tirapazamine administered intravenously concurrent with cisplatin and radiotherapy in women with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys.* 2000;48:791-795.
19. Saad A, Lo S, Han I, et al. Radiation Therapy with or without Chemotherapy for Cervical Cancer with Periaortic Lymph Node Metastasis. *Am J Clin Oncol.* 2004;27:256-263.
20. Duenas-Gonzalez A, Hinojosa-Garcia LM, Lopez-Graniel C, et al. Weekly cisplatin/low dose gemcitabine combination for advanced and recurrent cervical carcinoma. *Am J Clin Oncol.* 2001;24:201-203.

21. Burnett A, Roman L, Garcia A, et al. A phase II study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix. *Gynecol Oncol.* 2000;76:63-66.
22. Matulonis U, Campos S, Seiden M, et al. Phase I study of cisplatin and gemcitabine for recurrent cervix cancer following primary radiotherapy or newly diagnosed metastatic cervix cancer [abstract]. *Proc Am Soci Clin Oncol.* 2003;22:466.
23. Matulonis U, Campos S, Seiden M, et al. Phase I study of cisplatin and gemcitabine for recurrent cervix cancer following primary radiotherapy [abstract]. *Proc Am Soci Clin Oncol.* 2000;92:397a.
24. Bouzid K, Mahfouf H. A phase II study of gemcitabine and cisplatin combination in the treatment of recurrent cervical squamous cell carcinoma [abstract]. *Proc Am Soci Clin Oncol.* 2003;22:473.
25. Lorvidhaya V, Chitapanarux P, Kamnerdpaphon P, et al. Gemcitabine and cisplatin in patients with metastatic cervical cancer [abstract]. *Proc Am Soci Clin Oncol.* 2000;19:393a.
26. Long H, Bundy B, Grendys E, et al. Randomized phase III trial of cisplatin versus cisplatin plus topotecan versus MVAC in stage IVB, recurrent, or persistent carcinoma of the uterine cervix: a gynecologic oncology group study [abstract]. *Gynecol Oncol.* 2004;92:397.
27. Rose P, Blessing J, Gershenson D, et al. Paclitaxel and cisplatin as first line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. *J Clin Oncol.* 1999;17:2676-2680.
28. Papadimitriou C, Sarris K, Mouloupoulos L, et al. Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. *J Clin Oncol.* 1999;17:761-766.
29. Morris M, Blessing J, Monk BJ, et al. Phase II study of cisplatin and vinorelbine in squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol.* 2004;22:3340-3344.
30. Muggia F, Blessing J, Waggoner S, et al. Evaluation of vinorelbine in persistent or recurrent nonsquamous carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol.* 2005;96:108-111.
31. Pignata S, Silvestro G, Ferrari E, et al. Phase II trial of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix. *J Clin Oncol.* 1999;17:756-760.
32. Long HJ 3rd, Bundy B, Grendys EC Jr, 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.
33. Zanetta G, Fei F, Mangioni C. Chemotherapy with paclitaxel, ifosfamide, and cisplatin for the treatment of squamous cell cervical cancer: the experience of monza. *Semin Oncol.* 2000;27(Suppl 1):23-27.
34. Omura G, Blessing J, Vaccarello L, et al. 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.
35. Bloss J, Blessing J, Behrens B, 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.
36. Moore D, Blessing J, McQuellon R, 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.
37. Tewari KS, Monk BJ. Gynecologic oncology group trials of chemotherapy for metastatic and recurrent cervical cancer. *Curr Oncol Rep.* 2005;7:419-434.
38. Monk BJ, Huang H, Cella D, et al. 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.
39. Monk BJ. Chemotherapy for advanced and recurrent cervical carcinoma in the new era of upfront chemotherapy and radiation: have we arrived? *The Women's Oncol Rev.* 2005;5:77-79.
40. Sardi J, Giaroli A, Sananes C, et al. Long term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage IB squamous carcinoma of the cervix: the final results. *Gynecol Oncol.* 1997;67:61-69.
41. Buda A, Fossati R, Colombo N, et al. Randomized Trial of Neoadjuvant Chemotherapy Comparing Paclitaxel, Ifosfamide, and Cisplatin with Ifosfamide and Cisplatin Followed by Radical Surgery in Patients with Locally Advanced Squamous Cell Cervical Carcinoma: The SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study. *J Clin Oncol.* 2005;23:4137-4145.
42. Symonds RP, Habeshaw T, Reed NS, et al. The scottish and manchester randomised trial of neo-adjuvant chemotherapy for advanced cervical cancer. *Euro J Cancer.* 2000;36:994-1001.
43. Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the italian multicenter randomized study. *J Clin Oncol.* 2002;20:179-188.
44. Vallejo C, Machiavelli M, Perez J, et al. Docetaxel as Neoadjuvant Chemotherapy in Patients with Advanced Cervical Carcinoma. *Am J Clin Oncol.* 2003;26:477-482.
45. Seoud M, Geara F, Shamseddine A, et al. Short duration neoadjuvant chemotherapy followed by radiotherapy for advanced carcinoma of the cervix: results and prognostic variables. *Euro J Gynecol Oncol.* 2003;24:163-168.
46. Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systemic review and meta-analysis of individual patient data from 21 randomised trials. *Euro J Cancer.* 2003;39:2419-2421.
47. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of a 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.