

Novel Chemotherapy Approaches for Cervical Cancer

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Cancer of the cervix is the second most common malignancy among women worldwide. The last 20 years have lead to numerous advances in the medical management of locally advanced cervical cancer, including preventive vaccination, chemoradiation, and neoadjuvant chemotherapy. The treatment of metastatic disease is palliative at best. Platinum-based chemotherapy remains the standard of care for inoperable patients who have recurrent disease. However, because most patients initially receive concomitant platinum-based therapy with radiation, many recurrent tumors are refractory to platinum. The use of novel therapeutic approaches targeted to the carcinogenic processes that leads to the ontogenesis of cervical cancer should be promoted in clinical studies to improve patient outcomes. **Cancer 2009;115:3166–80. © 2009 American Cancer Society.**

KEY WORDS: adaptor proteins, epidermal growth factor receptor, uterine cervical cancer, drug therapy.

General Treatment Rules

Worldwide, carcinoma of the uterine cervix is the second most common malignancy among women and is a major cause of morbidity and mortality.¹ Cancer of the uterine cervix ranks third among female genital system malignancies in the United States, and approximately 11,070 new cases and 3870 deaths have been estimated for the year 2008.² In the United States, despite an increase in the incidence of carcinoma in situ, invasive cervical cancer rates have decreased steadily over the last decades because of early detection and treatment of preinvasive disease.

Women with cervical cancer usually present with early stage disease. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that only 8% of women with cervical cancer were diagnosed with metastatic disease at the time of presentation between 1988 and 2003.³ For stage 0 to IB1 cancers and for some stage IIA cancers, the treatment may include surgery, radiation therapy, or both, depending on patient and physician preference (Table 1). Bulky stage I (stage IB2) and locally advanced (stages II-IVA) cervical cancers are treated with concurrent chemoradiation in the United States. Palliation with platinum-based chemotherapy remains the standard of care for inoperable patients who have advanced disease.⁴ Selected patients with isolated central recurrence can be treated with curative intent by pelvic exenteration.

For this report, we reviewed published and developing chemotherapy approaches in the multidisciplinary and medical management of cervical cancer with a focus on biologic modalities of therapy (Fig. 1). Guidelines for workup and treatment suggestions for cervical cancer can be viewed online (available at: http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf accessed on May 1, 2009).

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Table 1. International Federation of Gynecology and Obstetrics Cervical Cancer Staging*

Stage	Description	Therapeutic Approach
0	Full-thickness involvement of the epithelium without invasion into the stroma (carcinoma in situ)	Surgical
IA1	Invasive carcinoma limited to the cervix; diagnosed only by microscopy; no visible lesions; stromal invasion <3 mm in depth and ≤7 mm in horizontal spread	Surgical (or radiotherapeutic)
IA2	Invasive carcinoma limited to the cervix; diagnosed only by microscopy; no visible lesions; stromal invasion between 3 mm and 5 mm with horizontal spread ≤7 mm	Surgical (or radiotherapeutic)
IB1	Visible lesion ≤4 cm in greatest dimension, or microscopic lesion with >5 mm of depth, or horizontal spread >7 mm	Surgical or radiotherapeutic
IB2	Visible lesion >4 cm	Multidisciplinary treatment
IIA	Invades beyond the cervix without parametrial invasion but involves the upper two-thirds of the vagina	Surgical or radiotherapeutic
IIB	Invades beyond the cervix with parametrial invasion	Multidisciplinary treatment
IIIA	Involves lower one-third of the vagina only	Multidisciplinary treatment
IIIB	Extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney	Multidisciplinary treatment
IVA	The tumor has invaded the mucosa of the bladder or rectum and has grown beyond the true pelvis	Multidisciplinary treatment
IVB	Distant spread of disease	Medical treatment

* Available at: <http://www.figo.org> accessed on May 1, 2009.

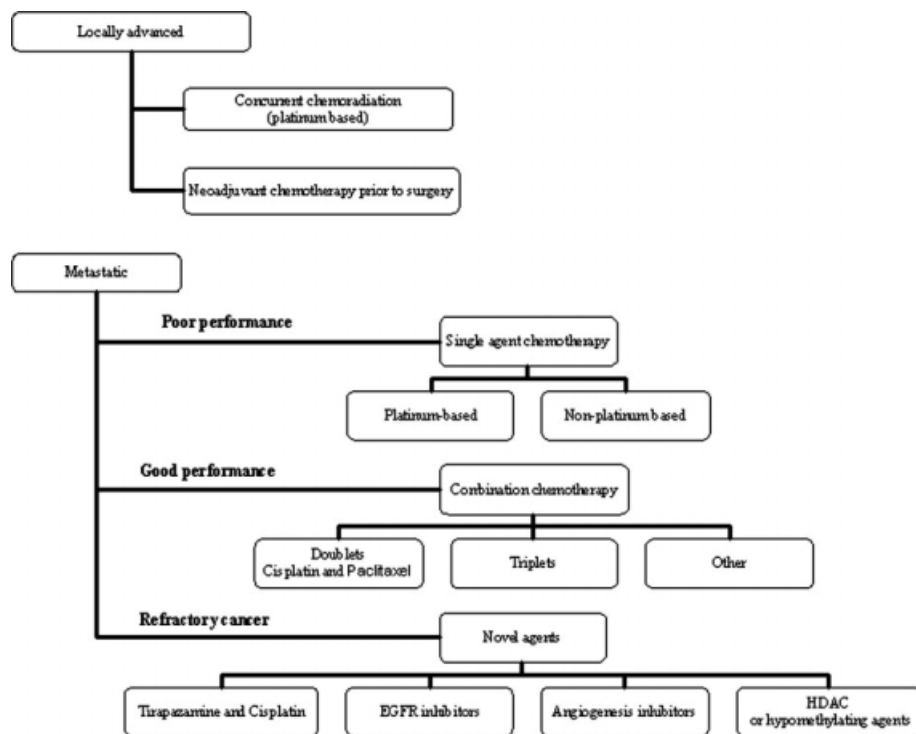


FIGURE 1. This is a treatment algorithm for the medical management of cervical cancer, including locally advanced, metastatic, and recurrent disease. EGFR indicates epidermal growth factor receptor; HDAC, histone deacetylation.

Multidisciplinary Treatment

Concurrent chemoradiation: The American approach

For bulky (stage IB2) or locally advanced (stage II-IVA) cervical cancer, the primary treatment consists of concurrent chemoradiation with platinum-based chemotherapy, because radiation alone fails to control the disease

in 35% to 90% of patients.⁵ Data from 5 phase 3 randomized trials, which, together, involved 1912 patients with cervical cancer, demonstrated that platinum-based chemotherapy given concurrently with radiation therapy prolongs survival in women who have locally advanced cervical cancer.⁶⁻¹⁰ On the basis of these data, in February 1999, the National Institutes of Health issued a treatment

consensus with the recommendation of giving strong consideration to the incorporation of concurrent chemotherapy with radiation therapy for women who require radiation therapy for cervical cancer (available at: <http://www.nih.gov/news/pr/feb99/nci-22.htm> accessed May 1, 2009). Recently, a Cochrane Library meta-analysis of 4921 patients in 24 randomized trials revealed improved overall survival (OS) (platinum group only) and progression-free survival (PFS) when concomitant chemoradiation was used for women with locally advanced disease.¹¹ In current practice, the most common regimen is cisplatin at a dose of 40 mg/m² weekly for 6 weeks during radiation treatment. To our knowledge, there is no consensus regarding adjuvant surgery or chemotherapy after the completion of chemoradiation.

Noncisplatin-based regimens

A few randomized trials are using agents other than cisplatin as part of a combined modality treatment in patients with locally advanced disease. All drugs studied in combination with radiation confer a significant survival advantage compared with radiation alone. These drugs include epirubicin,¹² mitomycin and 5-fluorouracil (5-FU),¹³ and capecitabine.¹⁴

Neoadjuvant chemotherapy before radiotherapy

The use of neoadjuvant chemotherapy (NACT) before radiation was studied extensively in the 1980s. The rationale for such treatment included reducing tumor mass and radiosensitizing tumors by decreasing the hypoxic cell fraction in large tumors. However, several randomized trials of NACT before radiation have not demonstrated a survival benefit compared with radiation therapy alone.¹⁵⁻²³ However, it is noteworthy that a meta-analysis of 2074 patients by the Neoadjuvant Chemotherapy for Locally Advanced Cervical Meta-analysis Collaboration group²⁴ reviewed 18 trials and observed that there was a survival advantage for NACT in studies that used higher doses of cisplatin (≥ 25 mg/m² per week) or chemotherapy cycles ≤ 14 days. In trials that used lower doses of cisplatin and longer chemotherapy cycles, there was an actual decrease in survival rates. That analysis suggested that the development of resistant tumor clones may be dependent on the schedule of chemotherapy and that there may be a benefit of short-duration,

high-intensity (also called dose-dense) chemotherapy treatments.

Neoadjuvant chemotherapy before surgery: The Italian, Asian, and South American approach

In many parts of the world, NACT before surgery is an accepted treatment for locally advanced stages of cervical cancer. An advantage of chemotherapy in this setting is the potential significant reduction in tumor burden, which facilitates surgical excision in previously inoperable tumors. If surgical margins are negative, then this approach also may obviate the need for radiation therapy and is the standard of care in regions where radiotherapy facilities are limited. Trials of NACT followed by surgery in locally advanced disease have demonstrated effectiveness without increase in surgical complication rates.²⁵⁻³⁷ Response to NACT is an important prognostic factor for survival.³⁷ In a separate analysis by the Neoadjuvant Chemotherapy for Locally Advanced Cervical Meta-analysis Collaboration group²⁴ of NACT followed by surgery compared with radical radiotherapy alone in patients with stage IB or higher disease, data from 5 trials and 872 patients were reviewed. There was a significant reduction in the risk of death with NACT with a 14% improvement in absolute survival at 5 years. In earlier operable stages, there was no advantage of NACT before definitive surgical treatment.³¹

The optimal NACT regimen is yet to be defined. A randomized phase 3 trial of paclitaxel, ifosfamide, and cisplatin versus cisplatin and ifosfamide as neoadjuvant to surgery indicated that the pathologic response rate was significantly higher in the 3-drug group (48% vs 23%), but OS did not differ.²⁸

Chemotherapy for Advanced Disease

Women with distant metastatic and recurrent disease traditionally have been treated with cisplatin-based chemotherapy. Unfortunately, recent randomized trials of recurrent disease indicate that there is a negative impact from the use of cisplatin during primary treatment. In patients with recurrent disease who receive previous cisplatin-based chemoradiation, response rates to cisplatin reinduction are lower than the rates in

Table 2. Nonplatinum-based, Single-agent Trials for Metastatic or Recurrent Disease

Agent	Study	No. of Patients	Regimen	ORR, %*	OS, Months
Standard reference for single-agent studies					
Cisplatin	Thigpen 1981 ³⁹	146	Cisplatin 50 mg/m ² every 3 wk	13	OS: 6.5 months
Single-agent studies					
Vinorelbine	Lhomme, 2000 ⁹²	41	Vinorelbine 30 mg/m ² weekly	17	Not stated
	Muggia 2005 ⁹³	44 (Squamous)	Vinorelbine 30 mg/m ² (D1, D8) every 3 wk)	13.7	Not stated
Paclitaxel	Mcguire 1996 ⁹⁴	52	Paclitaxel 170 mg/m ² every 3 wk	17	Not stated
	Kudelka 1997 ⁹⁵	32	Paclitaxel 250 mg/m ² every 3 wk	25	7.3
Pemetrexed	Goedhals 2006 ⁹⁶	34	Pemetrexed 500 or 600 mg/m ² every 3 wk	18 (Untreated, including locally advanced)	15.2
	Ferrandina 2008 ⁹⁷	18	Pemetrexed 500 mg/m ² every 3 wk	17	7.5
Ifosfamide	Meanwell 1996 ⁹⁸	30	Ifosfamide 5 g/m ² CI over 24 h every 3 wk	33	11
	Verschraegen 1997 ⁹⁹	42	Irinotecan 125 mg/m ² weekly for 4 wk every 6 wk	21	6.4
Irinotecan	Lhomme 1999 ¹⁰⁰	51	Irinotecan 350 mg/m ² every 3 wk	16	6.4
	Look 1998 ¹⁰¹	45	Irinotecan 125 mg/m ² weekly for 4 wk every 6 wk	13	8.2
	Takeuchi 1991 ¹⁰²	55	Irinotecan 100 mg/m ² weekly or 150 mg/m ² every 2 wk	24	Not stated
Topotecan	Muderspach 2001 ¹⁰³	49	Topotecan 1.5 mg/m ² daily ×5 every 3 wk	18 (Untreated)	6.4
Capecitabine	Garcia 2007 ¹⁰⁴	26 (Squamous)	Capecitabine 1800-2500 mg/m ² (D1-D14) every 3 wk	15	5.9
S-1	Hirai 2008 ¹⁰⁵	36	S-1 twice daily for 28 d followed by 14 d of rest	33	Not stated

ORR indicates objective response OS, overall survival; CI, continuous infusion.

chemotherapy-naïve patients.³⁸ Therefore, newer, non-platinum-based regimens are being explored in patients with recurrent disease who have previous platinum exposure.

Single-agent chemotherapy

Single-agent cisplatin at a dose of 50 mg/m² every 3 weeks became the standard of care in the 1980s and had a response rate of 38%.³⁹ Bonomi et al⁴⁰ evaluated higher doses of cisplatin and observed that, although objective response rates were higher, they did not translate into survival differences. In addition, the higher dose group had increased rates of myelosuppression and nephrotoxicity. Studies have evaluated other platinum agents, such as carboplatin and oxaliplatin.⁴¹⁻⁴³ A phase 2 study of carboplatin at a dose of 400 mg/m² every 4 weeks in patients who had received prior radiation revealed a response rate of 28%. Side effects related to cisplatin, such as neurotoxicity and nephrotoxicity, were minimal or nonexistent.

Other active agents include paclitaxel, irinotecan, topotecan, vinorelbine, gemcitabine, and ifosfamide (Table 2). Single-agent therapy may palliate patients who have a poor performance status or other significant comorbidities.

Combination chemotherapy

Many single-arm trials have evaluated combinations of a platinum analog with ifosfamide, paclitaxel, irinotecan, pegylated doxorubicin, or vinorelbine and have produced improvements in response rates compared with single-agent treatment but no improvements in OS (Tables 3, 4). A randomized comparison of cisplatin versus cisplatin plus paclitaxel by Moore et al⁴⁴ demonstrated a doubling of the response rate and PFS but no difference in OS. A quality-of-life assessment of these same data using the Functional Assessment of Cancer Therapy for the cervix, (FACT-Cx) (general scale, cervical cancer-specific form, pain inventory, and neurotoxicity subscale)

Table 3. Combination Doublets for Metastatic or Recurrent Disease—Phase 2 Studies

Agents	Study	No. of Patients	Regimen	ORR, %*	OS, Months
Cisplatin-based combinations					
Cisplatin and topotecan	Long 2005 ⁴⁶	147	Cisplatin 50 mg/m ² (D1), topotecan 0.75 mg/m ² (D1-D3) every 3 wk	27	9.4
Cisplatin and gemcitabine	Lorvidhaya 2004 ¹⁰⁶	40	Cisplatin 70 mg/m ² (D1), gemcitabine 1250 mg/m ² (D1, D8) every 3 wk	75	9.6
Cisplatin and irinotecan	Brewer 2006 ¹⁰⁷	32	Cisplatin 30 mg/m ² (D1, D8), gemcitabine 800 mg/m ² (D1, D8) every 4 wk	22	Not stated; TTP, 3.5 mo
	Matulis 2006 ¹⁰⁸	27	Cisplatin 50 mg/m ² (D1), gemcitabine 600-1000 mg/m ² (D1, D8, D15) every 4 wk	15	11.9
Cisplatin and irinotecan	Chitapanarux 2003 ¹⁰⁹	30	Cisplatin 60 mg/m ² (D1), irinotecan 60 mg/m ² (D1, D8, D15) every 4 wk	67	16.9
	Muggia 2004 ¹¹⁰	27	Cisplatin 25 mg/m ² (D1, D8, D15), irinotecan 65 mg/m ² (D1, D8, D15) every 4 wks	19	Not stated
Cisplatin and vinorelbine	Gebbia 2002 ¹¹¹	42	Cisplatin 80 mg/m ² (D1), vinorelbine 25 mg/m ² (D1, D8) every 3 wk	48	9.1
	Morris 2004 ¹¹²	67	Cisplatin 75 mg/m ² every 4 wk, vinorelbine 30 mg/m ² every wk	30	Not stated
Cisplatin and paclitaxel	Goedhals 2005 ¹¹³	37	Cisplatin 100 mg/m ² (D1), vinorelbine 30 mg/m ² (D1, D8) every 4 wk	65 (Untreated)	20.6
	Papadimitriou 1999 ¹¹⁴	34	Cisplatin 75 mg/m ² , paclitaxel 175 mg/m ² every 3 wk	47	9
Cisplatin and mitomycin-C	Wagenaar 2001 ¹¹⁵	33	Cisplatin, 50 mg/m ² , mitomycin-C 6 mg/m ² every 4 wk	42	11.2
Cisplatin and ifosfamide	Coleman 1990 ¹¹⁶	42	Cisplatin 50 mg/m ² (D1), ifosfamide 1.5 g/m ² (D1-D5)	38	8
Cisplatin and decitabine	Pohlmann 2002 ⁸⁵	21	Cisplatin 40 mg/m ² (D1-D3), decitabine 50 mg/m ² (D1-D3) every 3 wk	38	4.4
Cisplatin and tirapazamine	Smith 2006 ¹¹⁷	53	Cisplatin 75 mg/m ² (D1), tirapazamine 260 mg/m ² (D1) every 3 wk	32	5.3 (Patients who had not received previous radiosensitizing chemotherapy) vs 1.8
Cisplatin and capecitabine					
Cisplatin and capecitabine	Maluf et al 2006 ¹¹⁸	36	Cisplatin 75 mg/m ² (D1), tirapazamine 330 mg/m ² (D1) every 3 wk	28	Not stated; TTP, 7.6 mo
	Benjipal 2007 ¹¹⁹	16	Cisplatin 50 mg/m ² (D1), capecitabine 2000 mg/m ² (D1-D14) every 3 wk	50	23
Cisplatin and 5-fluorouracil	Errihanni 2008 ¹²⁰	22	Cisplatin 50 mg/m ² (D1), capecitabine 2500 mg/m ² (D1-14) every 3 wk	32	20
	Weiss 1990 ¹²¹	52	Cisplatin 100 mg/m ² , 5-fluorouracil 1000 mg/m ² /d (CI for 4 d)	28	Not stated
Cisplatin and cyclophosphamide	Eralp 2003 ¹²²	30	Cisplatin 75 mg/m ² , cyclophosphamide 750 mg/m ² D1 every 3 wk	20	11
Carboplatin-based combinations					
Carboplatin and docetaxel	Nagao 2005 ¹²³	17	Carboplatin AUC 6, docetaxel 60 mg/m ² every 3 wk	76 (Untreated)	Not stated
Carboplatin and docil	Secord 2007 ¹²⁴	15	Carboplatin AUC 2 (D1,8,15), docetaxel 80 mg/m ² (D1, D8, D15) every 4 wk	20	7.6
	Verschraegen 2001 ¹²⁵	35	Carboplatin AUC 5 (D1), docil 40 mg/m ² (D1) every 4 wk	38	8.6
Carboplatin and etoposide	Tebbitt 1998 ¹²⁶	16	Carboplatin 100 mg/m ² (D1-D3), etoposide 120 mg/m ² (D1-D3) every 4 wk	13	Not stated
Nonplatinum, camptothecin-based combinations					
Topotecan and paclitaxel	Tiersten 2004 ¹²⁷	13	Topotecan 1 mg/m ² (D1-D5), paclitaxel 175 mg/m ² (D1) every 3 wk	54	8.6
Irinotecan and mitomycin-C	Umesaki 2004 ¹²⁸	51	Irinotecan 100 mg/m ² (D1, D8, D15), mitomycin-C 10 mg/m ² (D1) every 4 wk	51	Not stated

ORR indicates objective response OS, overall survival; TTP, time to disease progression; CI, continuous infusion; AUC, area under the curve.

Table 4. Combination Triplets/Quadruplets for Metastatic or Recurrent Disease: Phase 2 Studies

Agents	Study	No. of Patients	Regimen	ORR, %*	OS, Months
Older cisplatin combinations Methotrexate, vinblastine, doxorubicin, and cisplatin	Papadimitriou 1997 ¹²⁹	27	Methotrexate, 30 mg/m ² (D1, D15, D22), vinblastine 3 mg/m ² (D2, D15, D22), doxorubicin 30 mg/m ² (D2), and cisplatin 70 mg/m ² (D2) every 4 wk	52	11
	Van Lwijk 2007 ¹³⁰	131	Bleomycin 15 mg/d as a CI (D2-D4), vindesine 3 mg/m ² (D1, D8), mitomycin-C 8 mg/m ² (D5 of alternate cycles), and cisplatin 50 mg/m ² (D1) every 3 wk	45 (No previous chemotherapy)	9.3
	Long 2006 ¹³¹	63	Methotrexate 30 mg/m ² (D1, D15, D22), vinblastine 3 mg/m ² (D1, D15, D22), doxorubicin 30 mg/m ² (D2), and cisplatin 70 mg/m ² (D2) every 4 wk	22	9.4
Carboplatin combination Bleomycin, ifosfamide, and carboplatin	Murad 1994 ¹³²	35	Bleomycin 30 mg D1, ifosfamide 2 g/m ² (D1-D3), and carboplatin 200 mg/m ² (D1) every 4 wk	60	11
Paclitaxel combinations Ifosfamide, paclitaxel, and cisplatin	Dimopoulos 2002 ¹³³	56	Ifosfamide 1500 mg/m ² (D1-D3), paclitaxel 175 mg/m ² (D1), and cisplatin 75 mg/m ² (D2) every 4 wk	46	18.6
	Choi 2006 ¹³⁴	45	Ifosfamide 1500 mg/m ² (D1-D3), paclitaxel 135 mg/m ² (D1), and cisplatin 50 mg/m ² (D1) every 3 wk	47	19

ORR indicates objective response OS, overall survival; CI, continuous infusion.

revealed no significant differences in overall scores between treatment arms or between successive chemotherapy cycles. Consequently, the consensus regimen became using the cisplatin-paclitaxel combination because of improved response rate and PFS.⁴⁵ In another randomized phase 3 trial by Long et al⁴⁶ of cisplatin plus topotecan (3-day regimen) versus cisplatin alone, the OS was longer (9.4 months vs 6.5 months), the median PFS was longer (4.6 months vs 2.9 months), and the response rate was better (27% vs 13%) for the combination group. For the first time, combination therapy offered a survival benefit, and myelosuppression was the major adverse effect. Additional side effects included nausea and vomiting, mucositis, rash, and hepatotoxicity. This led to the approval of topotecan by the US Food and Drug Administration on June 14, 2006 for use in combination with cisplatin to treat women with stage IVB, recurrent, or persistent carcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy.⁴⁷ Comparing the studies of Long et al and Moore et al, it is possible that the increased number of patients who received previous cisplatin (57% in the topotecan study and 27% in the paclitaxel study) changed the outcome of the single-agent cisplatin arm, yielding inferior response rates. Indeed, Table 3 indicates that most cisplatin-doublet studies produced an OS of approximately 9 months. Subsequently, a large Gynecologic Oncology Group (GOG) phase 3 study was designed to compare various doublets of cisplatin (GOG-204) in the advanced cervical cancer population. That study was stopped at a planned interim analysis after a preliminary analysis of the 3 experimental arms—cisplatin with topotecan (relative risk [RR], 23.4%), gemcitabine (RR, 22.3%), and vinorelbine (RR, 25.9%)—did not reveal a significant benefit compared with the control arm (cisplatin and paclitaxel: RR, 29.1%).⁴ The FACT-Cx, the FACT/GOG 4-item neurotoxicity scale, and the Brief Pain Inventory 0 to 10 pain intensity item were used to compare quality of life in the 4 arms. At the interim analysis, there were no statistically different outcomes in quality-of-life scores.⁴⁸ It is noteworthy that eligibility criteria for these GOG randomized studies were restricted to better populations over time. Hence, the survival rates are not comparable between these studies. To address the use of carboplatin, Moore et al⁴⁹ published a small retrospective comparison of cisplatin and carboplatin, both with paclitaxel. In that com-

parison, there was no difference in outcome, but the carboplatin combination was less toxic and easier to administer.

Chemotherapy Targeting Hypoxia

Tirapazamine

Tirapazamine (SR4233, WIN59075) is a benzotriazine di-N-oxide. In preclinical testing, cytotoxicity is directed selectively toward hypoxic cells, which tend to be resistant to radiotherapy and chemotherapy. It is known that cervical cancers are hypoxic tumors because of early necrotic development. In the face of hypoxia, tirapazamine is metabolized to free radicals, which induce DNA breaks. Tirapazamine enhances radiation-induced cell kill in hypoxic cells through a dose-dependent and schedule-dependent manner. Preclinical testing also has revealed that the simultaneous administration of cisplatin and tirapazamine induces an additive cytotoxicity. The clinical development of tirapazamine in cervical cancer led to an ongoing phase 3 trial (GOG-219), which will determine whether the addition of tirapazamine to cisplatin during radiation therapy has acceptable toxicity and improves PFS and OS for primary treatment of locally advanced cervical cancer.

Sanazol

Sanazol (AK-2123) is a nitrotriazole that also has the potential to sensitize hypoxic tissue to radiation. A multicenter randomized study of 333 patients that examined radiation alone versus radiation with sanazol in women with advanced cervical cancer (stages III and IV) demonstrated an improvement in both the objective response rate and the crude survival rate. Grade 1 or 2 neuropathy was the main drug-related side effect but usually was reversible.⁵⁰

Biologic Agents

Epidermal Growth Factor Receptor Inhibitors

EGFR, a membrane tyrosine kinase receptor that regulates multiple functions such as cell growth, differentiation, gene expression, and development, is a 170-kDa cell surface glycoprotein that is present in many tissues and cell types (Fig. 2). EGFR is overexpressed in a wide variety of solid tumors, including cervical cancer.⁵¹⁻⁶⁰ In

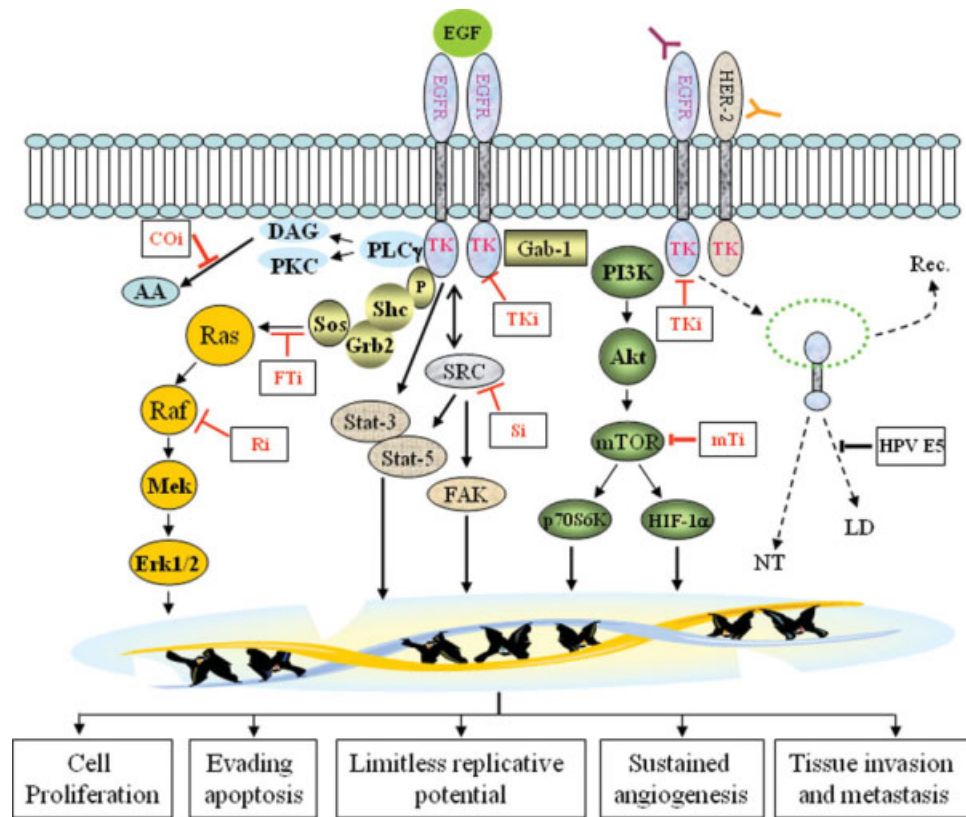


FIGURE 2. Epidermal growth factor (EGF) receptor (EGFR) signaling pathways and their inhibitors are shown. The activation of EGFR by EGF leads to homodimerization (EGFR-EGFR) and/or heterodimerization (EGFR-HER-2 shown here), phosphorylation of specific tyrosine residues, and recruitment of several docking proteins (gray-yellow) at the intracellular portion of the receptors. These adaptor proteins pass downstream of the signal using either the Ras/Raf/mitogen-activated kinase (MAPK) pathway (orange) or phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway (dark-green), whereas the phospholipase $C\gamma$ (PLC γ) (blue) and signal transducer and activator of transcription (Stat) transcription factors (gray-pink) bind directly to the receptor. PI3K also can bind directly any of the *erbB* partners (HER-2, HER-3, and HER-4) of EGFR heterodimers. The activated receptors undergo endocytosis (green dotted circle) and follow 3 possible routes: recycling (Rec.) back to the membrane, lysosomal degradation (LD), or nuclear translocation (NT). Once in the nucleus, EGFR can behave either as a true transcription factor or as coregulator of other gene transactivators. Both pathways result in nuclear activation of genes associated with cell proliferation, evasion of apoptosis, invasion, and metastasis. In cervical cancers, the human papilloma virus type 33 (HPV E5) proteins inhibit the lysosomal degradation of EGFR, leading to increased EGFR recycling and, hence, augmented EGFR levels. A few of the available inhibitors are illustrated. Monoclonal antibodies (Y-shaped orange and purple molecules) act extracellularly, avoiding EGFR ligand binding, whereas tyrosine kinase inhibitors (TKi) compete with the ATP binding to the tyrosine kinase (TK) domain (pink) of the EGFR receptor. COi indicates cyclooxygenase inhibitor; DAG, 1,2-diacylglycerol; PKC, protein kinase C; Gab-1, growth factor receptor-bound protein 2-associated binding protein 1; AA, arachidonic acid; Sos, son of sevenless; Shc, Src homology 2 domain containing transforming protein 1 isoform 3; Grb2, growth factor receptor-bound protein 2; P, phosphate; FTi, farnesyltransferase inhibitor; SRC, v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian); Akt, v-akt murine thymoma viral oncogene homolog 1; Ri, Raf inhibitor; Si, SRC inhibitor; mTOR, mammalian target of rapamycin; mTi, mTOR inhibitor; Mek, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; FAK, focal adhesion kinase; p70S6K, ribosomal protein S6 kinase 1; HIF-1 α , hypoxia-inducible factor 1 α ; Erk1/2, extracellular signal-regulated kinase 1 and 2.⁸⁷⁻⁹¹

the majority of studies, high tumor EGFR levels have been associated with reduced PFS or OS rates.⁶⁰⁻⁶² Commonly, high expression of EGFR is thought of as the main mechanism by which EGFR signaling is increased in cancer cells. However, several alternative mechanisms are likely to be of importance, including activating EGFR

mutations (point mutations in the tyrosine kinase domain or the presence of the truncated form, EGFR-VIII), increased coexpression of receptor ligands (epidermal growth factor, transforming growth factor α , amphiregulin), gene amplification, decreased levels of phosphatase, heterodimerization and cross-talk between other

members of the *erbB* receptor family, and interaction with other cell signaling systems and viral proteins (Fig. 2).⁶³ In particular, human papillomavirus (HPV) proteins seem to play an important role in EGFR expression. HPV is considered the primary etiologic factor in the development of nearly all cervical cancers.⁶⁴ The HPV E5 oncoprotein inhibits degradation of internalized EGFR,^{65,66} resulting in an increase in EGFR recycling and over expression of EGFR. Furthermore, expression of high-risk HPV E6 has been linked to an increase in EGFR levels,^{67,68} and changes in functional levels of the HPV E6/E7 proteins may alter the growth rate of cervical cancer cell lines by reducing the stability of EGFR at the post-transcriptional level.⁶⁹

EGFR inhibitors have been approved for the treatment of various cancers. Currently, there are 2 different ways of pharmacologically targeting EGFR: anti-EGFR monoclonal antibodies and inhibitors of the EGFR tyrosine kinase. The EGFR tyrosine kinase inhibitor, gefitinib, was ineffective in patients with refractory cervical cancer, although 87% of tumors expressed high levels of EGFR.⁷⁰ A phase 2 study of combined erlotinib, cisplatin, and radiation therapy⁷¹ in 23 patients with untreated stage IIB to IIIB squamous cell carcinoma induced a complete remission rate of 91.3%, which was higher than the rates produced in trials of cisplatin and radiation alone. Additional studies of EGFR kinase domain inhibition with lapatinib, an EGFR and HER2 dual inhibitor, with or without pazopanib, a tyrosine kinase small molecule inhibitor against the VEGF receptor (VEGFR), has accrued, but the results are pending.

No *EGFR* point mutations of exons 18 through 21 were detected in 89 cervical cancer samples and cell lines.⁷² This lack of mutation may prevent the activity of small-molecule tyrosine inhibitors, such as gefitinib and erlotinib, in contrast to monoclonal antibodies, such as cetuximab and panitumumab, which block extracellular ligand binding to EGFR. In fact, preclinical studies of cetuximab (Erbix), a chimeric monoclonal antibody against EGFR, produced significant inhibition (range, 37%-58%) in all EGFR-positive cervical cancer cell lines tested.⁷³ A study that combined cetuximab with the combination of cisplatin and topotecan was terminated prematurely because of excessive hematologic, renal, and infectious toxicity.⁷⁴ Previous treatment and poor performance status of the patients may have contributed to

those toxicities, but a pharmacokinetic or pharmacodynamic interaction cannot be excluded. A current phase 2 study that is being conducted by the GOG will determine the efficacy of single-agent cetuximab in patients with persistent or recurrent cervical cancer. Recent analyses in patients with lung and colon cancers have suggested that mutations of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) are associated with lower response rates and, in certain situations, a detrimental effect to treatment with EGFR tyrosine kinase inhibitors and antibodies.⁷⁵ *RAS* genes are members of the guanidine triphosphatase (GTPase) gene superfamily. *RAS* mutations result in the inhibition of GTPase activity and cause tumor cells to divide independent of EGFR signaling. Kang et al⁷⁶ evaluated 258 tissue samples of primary cervical cancer and demonstrated that 13.9% of adenocarcinomas had *KRAS* mutations; whereas, in squamous cell carcinoma samples, the mutation was observed in only 1.4%. The role of *KRAS* mutations in the treatment of cervical cancer is an area that needs further investigation.

Angiogenesis inhibitors

Angiogenesis plays an important role in tumor growth and progression in a variety of cancers and is visible clearly in cervical intraepithelial neoplasia before the invasive state. Several studies have demonstrated decreased survival in patients with cervical cancer who have increased tumor vascularization and lymphovascular invasion. VEGF is 1 of the most important factors involved in regulating angiogenesis.^{51,77,78} Gaffney et al⁵¹ examined tumor specimens from 55 patients with stage IB through IVA cervical cancer and observed that increased VEGF levels were associated with decreased disease-free survival and OS. Studies by Lancaster et al⁷⁹ and Cheng et al⁸⁰ also have linked VEGF over expression with a poor prognosis.

Bevacizumab, a monoclonal antivascular EGF antibody, currently is being used in the treatment of colon, lung, breast, and renal cell cancers. In a retrospective study by Wright et al,⁸¹ 6 women with metastatic disease who received previous 5-fluorouracil and then bevacizumab had a 67% clinical benefit rate with a median time to disease progression of 4.3 months. Currently, the GOG is conducting a phase 2 trial of bevacizumab in patients with persistent or recurrent squamous cell carcinoma of the cervix. A phase 3 study comparing the platinum standard

with a nonplatinum regimen will test bevacizumab further with a 2×2 factorial design (GOG-240).

Therapeutic vaccination and immunotherapy

HPV has been implicated in the development of essentially all cases of invasive cervical cancer.⁸² The recently approved Gardasil vaccine (Merck & Company, Inc., Rahway, NJ) has a near 100% protective effect against HPV type 6 (HPV-6), HPV-11, HPV-16, and HPV-18-related diseases when given to sexually naive girls and young women, but it does not have any therapeutic effects against already established infections.⁸³

In a study by the Eastern Cooperative Oncology Group of 29 women with metastatic or recurrent cervical cancer, interleukin-12 (IL-12) was given for 5 days every 21 days. IL-12, an immunopotentiator of T-cell function, may facilitate a lymphoproliferative response to peptides from HPV. Blood was obtained at periodic intervals to assess immune response to the HPV type 16 E4, E6, and E7 peptides. Although there was an improvement in immune response with therapy, there was no difference in objective response or survival.⁸⁴ Single-agent activity of interferon is low (<10% response rate); however, a biochemotherapy trial of interferon in combination with paclitaxel and retinoic acid is producing promising results.

Epigenetics

Epigenetics refer to changes in genes because of modifications in DNA. Two of the most studied epigenetic mechanisms are DNA methylation and histone deacetylation. The objective of therapeutic agents that target such mechanisms is to reactivate the expression of silenced tumor suppressor genes. HPV is the primary causative agent for the development of cervical cancer; therefore, it is necessary to consider epigenetic processes in the host and in the virus that could lead to carcinogenesis. In a small phase 2 trial of cisplatin and decitabine (a DNA-hypomethylating agent), 8 of 21 women who had advanced cervical cancer achieved a partial response, and 5 women had stable disease.⁸⁵ A recent phase 1 study of magnesium valproate in 12 women with newly diagnosed cervical cancer indicated that doses of valproic acid between 20 mg/kg and 40 mg/kg were effective at inhibiting histone deacetylase activity.⁸⁶ It is noteworthy that hypomethylating agents and histone deacetylase inhibi-

tors are known as radiosensitizers; therefore, studies of chemoradiation with the addition of these agents currently are underway.

In conclusion, as a neoadjuvant approach, chemotherapy has had an impact on the survival of patients with advanced but localized cervical cancer and may allow surgical therapy in patients who initially would not be considered resectable. However, the NACT algorithm has not been adopted readily in the United States because of successful chemoradiation strategies in locally advanced disease. Studies of new radiation sensitizers are being conducted with agents that target selectively hypoxic cells and epigenetic phenomena. When cervical cancer persists or recurs after definitive treatment, currently available, single-agent and combination chemotherapy regimens are palliative at best. Pelvic exenterative surgery may allow for a secondary cure in very selected patients who have central recurrences only. No improvement in survival has been achieved over the last 25 years in the metastatic or recurrent patient population, underlying the need to test new therapeutic approaches. Because of the link between HPV and cervical cancer, it is essential to gain a better understanding of the biology of carcinogenesis of the uterine cervix and the interaction with the host immune response. When biologic targets are overexpressed, they can be inhibited by designed monoclonal antibodies or small-molecule inhibitors. Many biologic targets currently are under study, such as EGFR and VEGFR.

Conflict of Interest Disclosures

The authors made no disclosures.

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