Changing paradigms in the systemic treatment of advanced cervical cancer

Krista S. Pfaendler, MD; Krishnansu S. Tewari, MD

Despite availability of primary and secondary prevention measures, cervical cancer persists as one of the most common cancers among women around the world. Although early-stage disease can be cured with radical and even fertility-sparing surgery, patients with metastatic and recurrent cervical cancer have poor prognosis with historically limited treatment options and incurable disease. Significant advances in cervical cancer treatment have emerged as the result of clinical trials that have sought to determine the best therapy to prolong overall and progression-free survival. Most recently, trials that have involved angiogenesis blockade in addition to standard chemotherapy have demonstrated improved overall and progression-free survival. This review serves to highlight pivotal trials in chemotherapy development for advanced, metastatic, and recurrent cervical cancer that includes the paradigm-shifting work that demonstrates increased overall survival with angiogenesis blockade.

Key words: antiangiogenesis, bevacizumab, cervical cancer

Cervical cancer is diagnosed in 528,000 women annually and results in 266,000 deaths worldwide each year.[1] The American Cancer Society estimates that there will be 12,900 new diagnoses and 4100 cervical cancer-related deaths in the United States in 2015.[2] Cervical cancer is 1 of many cancers caused by human papillomavirus (HPV) infection, but it is the only cancer for which HPV has been demonstrated to be the necessary precursor.[3-5] Risk factors for cervical cancer are those associated with HPV exposure, such as an increased number of sexual partners, although cigarette smoking and immunosuppression increase risk of HPV persistence.[6] Despite high efficacy and availability of HPV vaccines[3,7,8] and the recommendation for routine vaccination,[9] completion of the vaccine series among adolescent girls 13-17 years old in the United States remains <40%.[10] Given difficulties of the achievement of widespread compliance with HPV vaccination and the inability to include all oncogenic subtypes in the vaccines, the importance of continued secondary prevention remains. Most women who are diagnosed with cervical cancer report an inability to recall when they last had a Papanicolaou smear or that it was at least 10 years earlier; however, even among women compliant with screening guidelines, cervical cancer may develop.[11]

Although the goals for HPV vaccination, Papanicolaou smears, and HPV testing are prevention and early diagnosis, approximately 5% of women who are diagnosed with cervical cancer in North America have stage IV disease[12] with 5-year survival rates of 9.3-21.6%.[13] Even among women with earlier stages at diagnosis, 15-61% will experience metastatic disease, usually within the first 2 years of completing treatment. For women who are diagnosed with recurrent disease, 5-year survival is <5%.[12] This review focuses on changes in systemic treatment for women with metastatic or recurrent cervical cancer.

Development of standard chemotherapy

Single-agent cisplatin was established as the backbone of chemotherapy treatment for advanced cervical cancer >30 years ago when a phase II trial of cisplatin 50 mg/m^2 demonstrated a 44% objective response rate (RR) in 25 treatment-naïve patients.[14] In a Gynecologic Oncology Group (GOG) phase III study of cisplatin with or without paclitaxel for stage IVB, recurrent or persistent squamous cell carcinoma of the cervix (GOG 169) is an objective response that occurred in 19% of patients who received cisplatin vs 36% of patients who received cisplatin with paclitaxel (Table 1).[15] There was a significant increase in median progression-free survival (PFS); however, there was no difference in overall survival (OS), and patients in the doublet arm experienced increased grade 3-4 anemia and neutropenia.

Phase II reports of high RR with the use of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) prompted the development of GOG 179, a randomized phase III trial that compared MVAC with cisplatin plus topotecan or cisplatin alone.[16] The MVAC arm was closed by the Data Safety Monitoring Board because of 4 treatment-related deaths among

From the Division of Gynecologic Oncology (both authors), University of California, Irvine, Irvine Medical Center (Dr Tewari), University of California, Orange, CA.

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Corresponding author: Krishnansu S. Tewari, MD. ktewari@uci.edu

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TABLE 1
Pivotal trials that contributed to chemotherapy standards for advanced, metastatic, and recurrent cervical cancer

Trial	Lead author	Eligibility	Arms	Relative risk (%)	Mean overall survival, mo	Mean progression-free survival, mo	Conclusion
Gynecologic Oncology Group							
169	Moore[15]	Stage IVB, recurrent or persistent SCC	Cisplatin 50 mg/m^2	19	8.8	2.8	Combined regimen superior for response rate and progression-free survival without detriment to quality of life
			Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	36	9.7	4.8	No change in overall survival
179	Long[16]	Stage IVB, recurrent or persistent	Cisplatin 50 mg/m^2	13	6.5	2.9	Improved overall survival with doublet
			Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 day 1-3	26	9.4	4.6	Results most favorable for patients with no previous radiosensitizing cisplatin
			Methotrexate 30 mg/m^2 days 1, 15, 22 + vinblastine 3 mg/m^2 days 2, 15, 22 + doxorubicin 30 mg/m^2 day 2 + cisplatin 70 mg/m^2 day 2	N/A	N/A	N/A	
204	Monk[17]	Stage IVB, recurrent or persistent	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	29	12.9	5.8	Closed for futility
			Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 days 1-3	23.4	10.3	4.7	
			Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2	22.3	10.3	4.6	
			Cisplatin 50 mg/m^2 + vinorelbine 30 mg/m^2	25.9	10	4.0	
Japan Clinical Oncology Group Study 0505	Kitagawa[20]	Stage IVB, recurrent or persistent	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	58.8	18.3	6.9	Noninferiority of carboplatin/paclitaxel doublet except in platinum-naïve patients
			Carboplatin AUC 5 mg/mL/min + paclitaxel 175 mg/m^2	62.6	17.5	6.2	

AUC 5, area under the concentration vs time curve 5; *N/A*, not applicable (study arm closed early after 4 treatment-related deaths); *SCC*, squamous cell carcinoma.

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63 patients. Among the remaining patients who were assigned randomly to cisplatin or cisplatin plus topotecan, patients who received the doublet had improved RR (27% vs 13%), median PFS (4.6 vs 2.9 months), and median OS (9.4 vs 6.5 months) and more grade 3 and 4 hematologic toxicity, although without detriment to quality of life. This seminal study was the first randomized phase III trial to demonstrate statistically significant increased survival with combined chemotherapy over cisplatin alone for treatment of advanced or recurrent cervical cancer.

After phase II trials showed promise for a doublet of vinorelbine plus cisplatin, a phase III trial (GOG 204) was planned with 2 arms that compared paclitaxel-cisplatin with vinorelbine-cisplatin; however, 2 additional arms that compared gemcitabine-cisplatin and topotecan-cisplatin were added