Changing paradigms in the systemic treatment of advanced cervical cancer

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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

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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

when phase II data for gemcitabine-cisplatin and phase III data for topotecan-cisplatin became available. After a planned interim analysis, the study was closed for futility. This phase III trial showed that vinorelbine-cisplatin, gemcitabine-cisplatin, and topotecan-cisplatin were not superior to paclitaxel-cisplatin in RR, OS, or PFS and that there was no difference in quality of life between study arms.[17]

Despite improvements in cisplatin-based combination chemotherapy, RR remained low for advanced cervical cancer, which prompted a multivariate logistic regression analysis of data from GOG 110, 169, and 179 that identified 5 risk factors for poor response to therapy: black race, performance status >0, pelvic disease, previous radiosensitizer, and time interval from diagnosis to first recurrence <1 year. The authors developed a simple prognostic index that combined risk factors to create 3 groups: low risk (0-1 risk factor), mid risk (2-3 risk factors) and high risk (4-5 risk factors) and validated the index with the use of data from GOG 149.[18]

It has been suggested that therapeutic equivalency of cisplatin-paclitaxel (PT) and carboplatin-paclitaxel (CT) that is demonstrated in ovarian cancer may be extrapolated to cervical cancer. To evaluate this hypothesis, the Japanese Clinical Oncology Group developed a multicenter, open label, randomized phase III trial to evaluate efficacy, safety, and quality of life of CT compared with PT.[19] Median OS was 18.3 months for PT vs 17.5 months for CT (hazard ratio [HR], 0.994; 90% confidence interval [CI], 0.79−1.25), which demonstrated the noninferiority of CT with significantly longer proportion of non-hospitalization periods for patients who receive CT ($P < .001$). Median PFS was 6.9 months for PT vs 6.2 months for CT (HR, 1.041; 95% CI, 0.803−1.351). Among patients with no previous cisplatin treatment, OS was shorter with CT (13.0 vs 23.2 months; HR, 1.571; 95% CI, 1.06−2.32), which indicates that cisplatin remains superior for platinum-naïve patients.[20]

Over the past 30 years, cisplatin-based combination chemotherapy has been shown to produce the best PFS[15,16] and OS[16,20] for most patients with advanced and recurrent cervical cancer, with exceptions for those with high risk for nonresponse to cisplatin based on criteria of Moore et al.[18] Despite extensive research to improve chemotherapy for advanced and recurrent cervical cancer, OS continues to be measured in months. For this reason, investigations in recent years have delved into other pathways in the hope of eliciting improved response to treatment with prolongation of survival.

Angiogenesis blockade

Historically, options have been limited for patients with persistent or recurrent cervical cancer after platinum-based chemotherapy.[14-18,21,22] Angiogenesis, the process of new blood vessel formation, is essential not only for growth of new tissue, wound healing, and embryogenesis but also is fundamental for tumor proliferation. Vascular endothelial growth factor (VEGF) is the major mediator of tumor angiogenesis.[23] Neovascularization correlates directly with disease spread and inversely with survival. Ferrara et al[24] developed bevacizumab, a humanized anti-VEGF monoclonal antibody that bound with an affinity comparable with that of the original antibody. Bevacizumab was the first angiogenesis inhibitor to be approved by the Food and Drug Administration (FDA) for cancer treatment.[23]

Bevacizumab

In a retrospective case series of 6 patients with heavily pretreated recurrent cervical cancer, 5 of the 6 patients received 5-fluorouracil in combination with bevacizumab, and 1 of the 6 patients received capecitabine with bevacizumab (Table 2).[25] Among these 6 patients, complete response (17%; n = 1), partial response (17%; n = 1), or stable disease (33%; n = 2) was seen among 67% (n = 4), which demonstrates encouraging antitumor activity with minimal grade 4 adverse events (1 patient experienced neutropenic sepsis). Among the 4 patients whose condition demonstrated clinical benefit, median PFS was 4.3 months.

An early case series by Wright et al[25] suggested that bevacizumab in combination with chemotherapy was active in recurrent cervical cancer. A phase II study to evaluate bevacizumab monotherapy in this population was activated through the Gynecologic Oncology Group (ie, GOG 227C).[26] Among the 46 women who were enrolled, 82.6% (n = 38) had received previous radiation, and 1 (n = 34; 73.9%) or 2 (n = 12; 26.1%) previous cytotoxic regimens for recurrent disease. Eleven of the 46 patients (23.9%; 2-sided 90% CI, 14−37%) achieved PFS for at least 6 months, and another 5 patients (10.9%; 2-sided 90% CI, 4−22%) achieved partial response. Median PFS of 3.40 months (95% CI, 2.53−4.53 months) and OS of 7.29 months (95% CI, 6.11−10.41 months) with bevacizumab compared favorably with other phase II trials for persistent or recurrent disease, which prompted the development of a phase III trial.[26]

Because bevacizumab had demonstrated clinical activity in pretreated populations, the Radiation Therapy Oncology Group designed a phase II single-arm study (protocol 0407) of bevacizumab in addition to standard chemoradiation for bulky stage IB-IIIB cervical cancer to investigate efficacy and safety.[27] Among the 60 patients enrolled, 49 cases were evaluable and had a median follow-up time of 12.4 months (range, 4.6−31.4 months) with no serious adverse events.[27] This study was not powered for PFS or OS analysis; however, in a report of secondary endpoints, over a median follow-up time of 3.8 years (range, 0.8−6.0 years), the 3-year OS was 81.3% (95% CI, 67.2−89.8%), and the PFS was 68.7% (95% CI, 53.5−79.8%).[28] This phase II trial indicated that further study of bevacizumab for treatment of locally advanced disease is warranted.

In a multicenter phase II trial that evaluated a regimen of topotecan, cisplatin, and bevacizumab for persistent or recurrent cervical cancer, 27 patients with no previous chemotherapy for recurrence received a median of 3 treatment cycles (range, 1−19 cycles) and a median of 10 months (range, 1.7−33.4 months) of follow up.[29] Among the

TABLE 2
Bevacizumab in cervical cancer treatment

Case series	Lead author	Pathologic condition	Arms	Response rate, %	Overall survival, mo	Mean progression-free survival, mo	Conclusion
	Wright[25]	SCC, AS	5-fluorouracil 250-500 mg IV every week + bevacizumab 5-15 mg/kg IV every 2-3 wks	33	5.1	None reported	Bevacizumab is well-tolerated and displays antitumor activity in recurrent cervical cancer
			Capecitabine 2000 mg orally twice daily + bevacizumab 5-15 mg/kg IV every 2-3 wks				
Gynecologic Oncology Group 227C	Monk[26]	SCC, AS	Bevacizumab 15 mg/kg IV every 3 wks	35	7.3	3.4	Bevacizumab is well-tolerated and active as second- and third-line therapy for recurrent cervical cancer and warrants a phase III trial
Radiation Therapy Oncology Group 0417	Schefter[27,28]	SCC	Cisplatin 40 mg/m^2 + RT + brachytherapy + bevacizumab 10 mg/kg every 2 wks for 3 cycles	None reported	3-year; 81.3%	3-year; 68.7%	Bevacizumab in addition to standard chemoradiation for locally advanced cervical cancer is feasible and safe
	Zighelboim[29]	SCC, AC	Cisplatin 50 mg/m^2 day 1 + topotecan 0.75 mg/m^2 days 1-3 + bevacizumab 15 mg/kg day 1 every 3 wks	35	13.2	7.1	Addition of bevacizumab to cisplatin and topotecan produces an active by highly toxic regimen
Gynecologic Oncology Group 240	Tewari[30]	SCC, AS, or AC	Cisplatin 50 mg/m^2 + paclitaxel 135 or 175 mg/m^2		14.3	5.9	Bevacizumab resulted in 3.7-month increased overall survival (17 mo compared with 13.3 mo)
			Cisplatin 50 mg/m^2 + paclitaxel 135 or 175 mg/m^2 + bevacizumab 15 mg/kg		17.5	8.2	
			Topotecan 0.75 mg/m^2 days 1-3 + paclitaxel 175 mg/m^2		12.7		
			Topotecan 0.75 mg/m^2 days 1-3 + paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg		16.2		

AC, adenocarcinoma; *AS*, adenosquamous carcinoma; *IV*, intravenously; *RT*, pelvic radiotherapy; *SCC*, squamous cell carcinoma.

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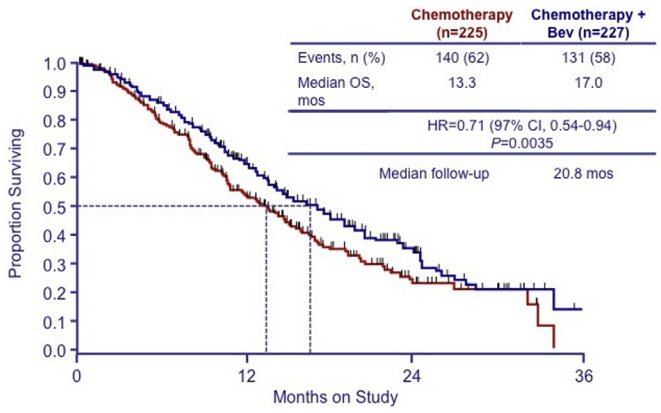
26 evaluable cases, 59% (80% CI, 46–70%) experienced 6-month PFS; 1 patient (4%; 80% CI, 0.4–14%) experienced complete response, and 8 patients (31%; 80% CI, 19–45%) experienced partial response that lasted a median of 4.4 months. Median PFS was 7.1 months (80% CI, 4.7–10.1 months), and median OS was 13.2 months (80% CI, 8.0–15.4 months). Unfortunately, grade 3-4 hematologic toxicity was common with high incidence (78%) of unanticipated hospitalizations.

The first phase III randomized trial (GOG 240) of bevacizumab for advanced cervical cancer randomly assigned women to 1 of 4 arms: (1) cisplatin plus paclitaxel, (2) cisplatin, paclitaxel, and bevacizumab, (3) topotecan plus paclitaxel, and (4) topotecan, paclitaxel, and bevacizumab.[30] Inclusion criteria included adequate hepatic, bone marrow, and renal function and good nutritional status. Most of the study group (75%) previously had received platinum and were distributed evenly between the 2 backbones. Addition of bevacizumab to chemotherapy resulted in a 3.7-month increase in median OS (17.0 vs 13.3 months; Figure 1) and higher RR (48% vs 36%; $P = .008$). Subanalysis showed beneficial effects of

FIGURE 1
Overall survival in Gynecologic Oncology Group 240 according to chemotherapy regimen



Overall survival among patients who were assigned to cisplatin-paclitaxel chemotherapy with or without bevacizumab and those who were assigned to topotecan-paclitaxel chemotherapy with or without bevacizumab.

Bev, bevacizumab; *CI*, confidence interval; *HR*, hazard ratio; *mos*, months; *OS*, overall survival.

From Massachusetts Medical Society. Reprinted with permission from Tewari KS et al.[30]

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bevacizumab in patients who had been exposed previously to platinum and among those with recurrent or persistent disease. Additionally, benefits of bevacizumab were demonstrated in patients with recurrent disease in a previously irradiated field. Grade 2 or higher hypertension, grade 3 or higher gastrointestinal, or genitourinary fistulas and grade 3 or higher thromboembolic events were all significantly higher among patients who received bevacizumab, but quality-of-life scores indicated that the addition of bevacizumab did not affect health-related quality of life adversely. In the final protocol-specified OS analysis, bevacizumab improved OS to 16.8 months vs 13.3 months for chemotherapy alone (HR, 0.765; 95% CI, 0.62−0.95; P = .0068).[31]

One exploratory objective of GOG 240 was to validate pooled clinical prognostic factors prospectively (criteria of Moore et al[18]). High-risk patients (4-5 factors) had significantly worse OS (P < .0001). Hazard ratios of death for treatment with topotecan in low-risk (0-1 factors), mid-risk (2-3 factors), and high-risk (4-5 factors) subsets were 1.18 (95% CI, 0.63−2.24), 1.11 (95% CI, 0.82−1.5), and 0.84 (95% CI, 0.50−1.42), respectively; HRs of death for treatment with bevacizumab in low-risk, mid-risk, and high-risk subsets were 0.96 (95% CI, 0.51−1.83; P = .9087), 0.673 (95% CI, 0.5−0.91; P = .0094), and 0.536 (95% CI, 0.32−0.905; P = .0196), respectively. Toxicity concerns and lack of statistically significant survival benefit in the low-risk group of patients may justify the reservation of bevacizumab for mid-risk and high-risk populations, unless larger studies demonstrate benefit for the low-risk population.[32]

Other antiangiogenesis agents

Other antiangiogenic agents under study include sunitinib, pazopanib, lapatinib, and cediranib (Table 3). Sunitinib malate is an orally bioavailable small molecule that inhibits members of the split-kinase domain family of receptor tyrosine kinases, including VEGF and platelet-derived growth factor.[33] Sunitinib is FDA approved for patients with metastatic renal cell carcinoma and gastrointestinal stromal tumors. A multicenter phase II trial was performed to evaluate sunitinib in women with locally advanced or metastatic cervical carcinoma who had received up to 1 previous line of chemotherapy with a primary endpoint of objective RR.[34] Among 19 patients who were enrolled in the study, 16 patients had stable disease but no objective response after a median duration of 4.4 months. Five patients (26.3%) experienced fistula, although 4 of these patients had received previous radiation, which made it difficult to determine the contribution of sunitinib to fistula development. Regardless, this study showed that sunitinib does not have sufficient activity as a single agent in cervical cancer.

A phase II open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy confirmed activity of antiangiogenesis agents in advanced and recurrent cervical cancer. Pazopanib is an oral angiogenesis inhibitor that targets VEGF receptor, platelet-derived growth factor receptor, and c-Kit and is FDA approved for use in metastatic soft tissue sarcomas and metastatic renal cell carcinoma. Lapatinib is an oral small-molecule dual tyrosine kinase inhibitor that targets epidermal growth factor receptor and human epidermal growth factor receptor 2 (HER2/neu) and is FDA approved for use in combination with capecitabine for patients with advanced or metastatic breast cancer. The combined arm in this study was closed for futility after interim analysis, but the trial demonstrated improved PFS for pazopanib monotherapy compared with lapatinib monotherapy.[35] Interim analysis data indicated improved OS in the pazopanib arm; however, the study was not powered for OS, and final analysis failed to show any significant difference.[36]

A randomized double-blind phase II trial of CT plus cediranib vs CT plus placebo in metastatic and recurrent cervical cancer was performed in the United Kingdom.[37] Cediranib is a tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3 and has been formulated as an oral medication. The randomized double-blind phase II trial randomly assigned patients to receive cediranib 20 mg or

TABLE 3
Other antiangiogenesis agents in cervical cancer treatment

Trial	Lead author	Pathology	Arms	Response rate, %	Overall survival, wk	Progression-free survival, wk	Conclusion
NCIC CTG IND.184	Mackay[34]	SCC, AS, or AC	Sunitinib 50 mg orally, daily for 4 wks	0	None reported	24.6	Higher rate of fistula formation (26.3%) than expected; insufficient activity as single agent
	Monk[35,36]	SCC, AS, or AC	Pazopanib 800 mg orally, daily	9	50.7	18.1	Pazopanib improved progression-free survival and overall survival
			Lapatinib 1500 mg orally, daily	5	39.1	17.1	
CRUK/10/001	Symonds[37]	SCC, AS, or AC	Cediranib 20 mg orally, daily + carboplatin AUC5 + paclitaxel 175 mg/m^2 every 21 days	66	59	35	Addition of cediranib to carboplatin and paclitaxel results in prolonged progression-free survival with no change in overall survival
			Placebo daily + carboplatin AUC5 + paclitaxel 175 mg/m^2 every 21 days	42	63	30	

AC, adenocarcinoma; *AS*, adenosquamous carcinoma; *AUC5*, area under the concentration vs time curve 5; *SCC*, squamous cell carcinoma.

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placebo daily in addition to carboplatin AUC5 and paclitaxel 175 mg/m^2 every 21 days for a maximum of 6 cycles. Median PFS was 30 weeks with placebo vs 35 weeks with cediranib (HR, 0.61; 80% CI, 0.41−0.89; $P = .046$). Median OS was 63 weeks with placebo vs 59 weeks with cediranib (HR, 0.93; 80% CI, 0.64−1.36; $P = .401$). RR was higher in those who received cediranib (66% vs 42%; $P = .030$) as was toxicity; 19% of patients experienced grade 2-4 toxicity compared with 9% in the placebo group.

Antiangiogenesis agents other than bevacizumab have failed to demonstrate statistically significant benefit in OS for advanced and recurrent cervical cancer. A phase II study of sunitinib monotherapy failed to show an objective response.[34] Other phase II trials of antiangiogenesis agents have demonstrated improved PFS with no benefit to OS. Pazopanib monotherapy showed improved PFS compared with lapatinib monotherapy but was not powered to assess OS[35,36]; cediranib added to a CT chemotherapy backbone showed improved PFS compared with placebo (35 vs 30 weeks) but no statistically significant difference in OS.[37] Additional phase II trials are needed to determine which antiangiogenesis agents may produce an OS benefit for patients with advanced or recurrent cervical cancer.

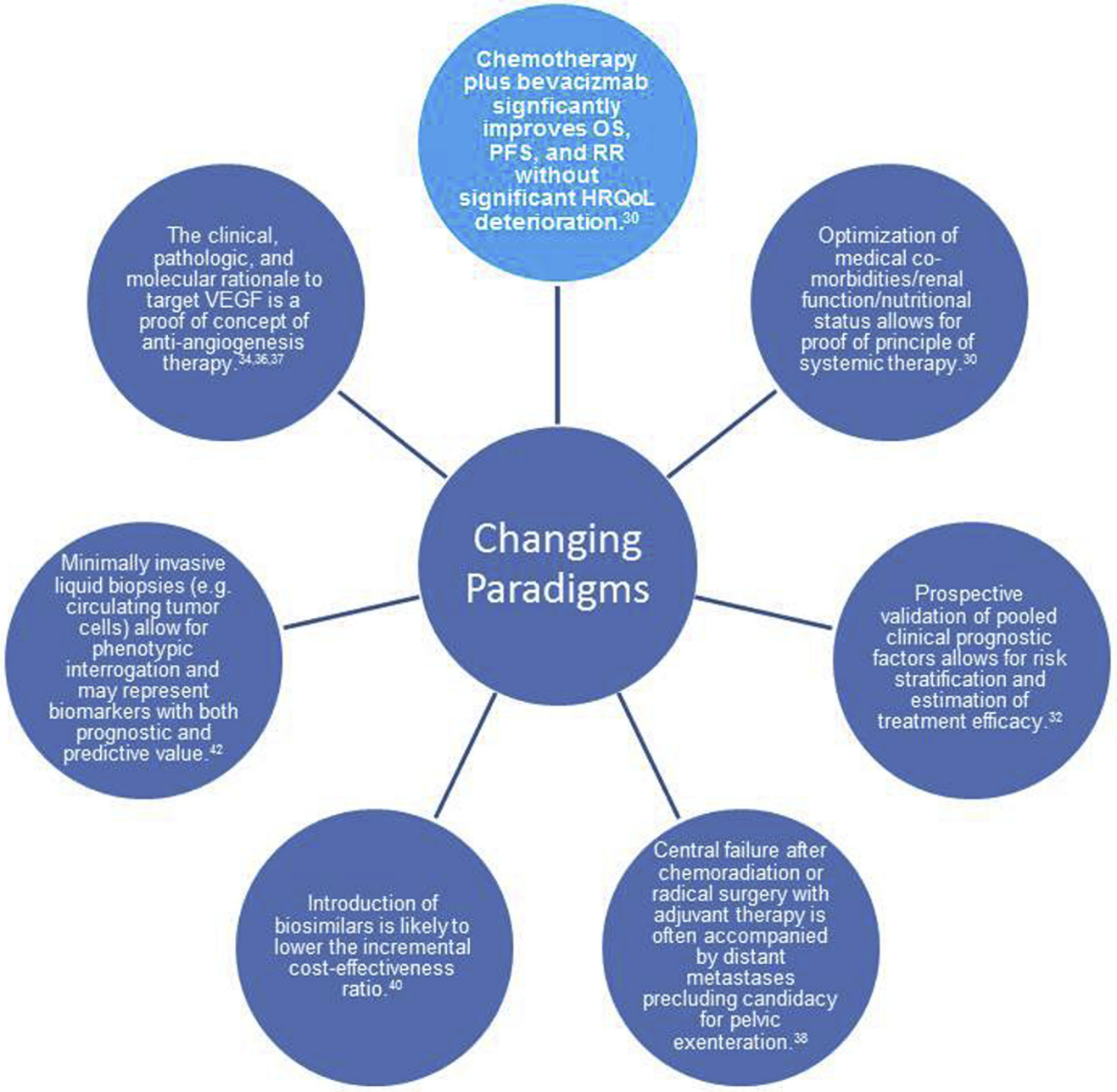
Changing paradigms

Although women with advanced cervical cancer are at high risk for persistence and recurrence, major paradigm shifts have occurred in recent years that have changed that outlook for these women (Figure 2). The clinical, pathologic, and molecular rationale to target VEGF is a proof of concept of antiangiogenesis therapy. Although a phase II trial of sunitinib failed to show significant single-agent activity for advanced or metastatic cervical cancer,[34] a phase II open-label study of pazopanib and lapatinib confirmed activity of antiangiogenesis agents in advanced and recurrent cervical cancer.[36] Addition of cediranib to carboplatin and paclitaxel resulted in a 5-week prolongation of PFS, although it had no significant impact on OS.[37] These studies demonstrated potential benefit of antiangiogenesis therapy in the treatment of advanced and recurrent disease.

Chemotherapy plus bevacizumab significantly improves OS, PFS, and RR without significant deterioration in health-related quality of life. Single-agent cisplatin was established as the backbone of chemotherapy treatment for cervical cancer many years ago, but more recent trials have shown a benefit for chemotherapy doublets and more recently with angiogenesis inhibitors. Although many trials have shown improved RR or PFS for 1 chemotherapy regimen compared with another, rarely has improved OS be demonstrated. Recently, GOG 240 transformed treatment for advanced, recurrent, and metastatic cervical cancer by demonstrating that targeted agents can improve survival significantly. The findings of GOG 240 that revealed a 3.7-month increase in OS with no significant deterioration in quality of life serves as proof of principle in the value of systemic therapy and proof of concept of the efficacy of angiogenesis blockade therapy.[30]

The significant increase in OS with the addition of bevacizumab to chemotherapy creates a potential window of opportunity through which patients deriving benefit may be

FIGURE 2
Changing paradigms in advanced, metastatic and recurrent cervical cancer



The paradigm changes described in the text are given.

HRQoL, health-related quality of life; *OS*, overall survival; *PFS*, progression-free survival; *RR*, response rate; *VEGF*, vascular endothelial growth factor.

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treated with other novel agents, including other classes of antiangiogenesis drugs, immunotherapy, poly-ADP-ribose polymerase 1 inhibitors, and mammalian target of rapamycin inhibitors, thereby potentially extending survival further.

Optimization of medical comorbidities, renal function, and nutritional status allows for proof of principle of systemic therapy. Patients who previously were thought to be too sick to benefit from systemic therapy experienced rapid deterioration in their quality of life and short survival after diagnosis. In GOG 204, the PT and topotecan-paclitaxel arms had an OS of 12.9 and 10.3 months, respectively.[17] In GOG 240, after optimization of medical comorbidities, the PT and topotecan-paclitaxel arms without bevacizumab had an OS

of 14.3 and 12.7 months, respectively.[30] Reducing medical comorbidities such as improving renal function with the use of stents and nephrostomy tubes, improvement of performance status through optimization of pain control, and correction of malnutrition can make patients eligible for systemic therapy and contribute to prolonged OS.

Prospective validation of pooled clinical prognostic factors allows for risk stratification and estimation of treatment efficacy.[32] One of the objectives of GOG 240 was to validate prospectively the 5 risk factors for poor response to cisplatin-based therapy that were identified by Moore et al.[18] Median OS was not significantly different for low-risk patients who received bevacizumab in addition to chemotherapy; however, among high-risk patients, the median OS was 6.3 months for chemotherapy alone vs 12.1 months for chemotherapy with bevacizumab. Although there was a clinical benefit for the receipt of bevacizumab in all groups, those with highest risk for poor response to cisplatin-based therapy derived the greatest benefit from the inclusion of bevacizumab in their treatment regimens.

Central failure after chemoradiation or radical surgery with adjuvant therapy is often accompanied by distant metastases, which precludes candidacy for pelvic exenteration.[38] Isolated central pelvic recurrences that lend themselves to pelvic exenteration are becoming increasingly rare in the era of concurrent chemoradiation plus brachytherapy. Although feasible and potentially curative, pelvic exenteration has high morbidity rates, even in the hands of an experienced gynecologic oncologist.[39] However, since the original introduction of the procedure by Brunschwig in 1948, technical advances such as the intestinal conduit for urinary diversion and end-to-end anastomosis with the intestinal stapling device for preservation of fecal stream have produced significant improvements in morbidity.[38]

The introduction of biosimilars is likely to lower the incremental cost-effectiveness ratio. Bevacizumab therapy adds $73,791 per 3.5 months of life gained or $5775 per month of added life and $24,597 per quality-adjusted life month. A Markov model that was created based on GOG 240 indicates that cost reductions through availability of biosimilars result in declines in the incremental cost-effectiveness ratio, because increased costs are largely direct costs because of the drug rather than indirect costs for the management of bevacizumab-induced complications.[40] As biosimilars are introduced to the market, the use of bevacizumab in advanced and recurrent cervical cancer will gain cost efficacy; however, it may be many years before bevacizumab is affordable for women in low- and middle-income countries where the overwhelming majority of advanced cervical cancer cases occur.

Minimally invasive liquid biopsies allow for phenotypic interrogation and may represent biomarkers with both prognostic and predictive value.[41,42] The primary translational research objective of GOG 240 was to determine whether circulating tumor cells (CTCs) could be isolated from patients and whether CTC counts would be associated with hazard of death. Median CTC count was 7 CTCs/8.5 mL whole blood (range, 0−18) precycle 1 and 4 CTCs/8.5 mL whole blood (range, 0−17) 36 days postcycle 1. The hazard of death for pretreatment CTC counts was 0.9 (95% CI, 0.81−0.99) within the cisplatin-paclitaxel-bevacizumab group, and patients with greater declines had a lower hazard of death (HR, 0.87; 95% CI, 0.79−0.95).

Feldman et al[41] evaluated 592 cervical cancer specimens in their repository using next-generation sequencing, in situ hybridization, and immunohistochemistry. Mutational hotspots were identified that corresponded to *PI3KCA* (26%), *BRCA2* (21%), *BRCA1* (10%), *KRAS* (10%), *TP53* (10%), and *FBXW7* (10%) with the use of next-generation sequencing on 224 specimens. They also observed gene amplification (in situ hybridization) of *EGFR* (20/174 specimens; 11%), and *HER2* (32/395 specimens; 8%). Immunohistochemistry studies showed overexpression of estrogen receptor (118/590 specimens; 20%), progesterone receptor (48/589 specimens; 8%), and androgen receptor (22/578 specimens; 4%) in addition to other protein signatures. These data suggest that theranostic biomarkers may help to guide therapy for patients whose condition does not respond to antiangiogenesis therapy. The next-generation sequencing, in situ hybridization, and IHC results suggest that *PI3K/AKT/mechanistic target of rapamycin pathway inhibitors*, *EGFR*- and *HER2*-directed therapy, immunotherapy, and hormonal therapy may be promising areas for future research.

Additional work is needed to develop and test molecularly targeted drugs and immune system modulation to achieve improved outcomes for women with persistent, metastatic, and recurrent cervical cancer. Further study of theranostic biomarkers may help to guide therapy for patients whose disease progresses on antiangiogenesis therapy or is otherwise incurable.[41] With continued exploration of these avenues, new therapeutic paradigms are likely to emerge that further improve survival and quality of life in this vulnerable population. ■

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