Development of a Platform for Systemic Antiangiogenesis Therapy for Advanced Cervical Cancer

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Abstract: Women with metastatic, recurrent, or persistent cervical carcinoma historically have had extremely limited treatment options. Systemic chemotherapy in these settings is predominantly palliative and has been associated with platinum resistance, nondurable responses, rapid progression of disease with deterioration in quality of life, and early death. At the cooperative group level, efforts to breach this clinical impasse have focused on incorporation of antiangiogenesis therapy, medical optimization, and identification of less toxic regimens. Gynecologic Oncology Group protocols 204 and 240, along with the Japanese Clinical Oncology Group protocol 0505, make up the pivotal phase 3 clinical trials that have provided 3 distinct treatment options. These options incorporate the antiangiogenesis humanized monoclonal antibody bevacizumab in combination with either a platinum-based or nonplatinum-based chemotherapy doublet. This review will highlight the development of bevacizumab in advanced cervical cancer and address the relevance of the survival gain obtained using antiangiogenesis therapy in this high-risk population.

Introduction

An estimated 12,360 new cases of invasive cervical cancer will be diagnosed in 2014 in the United States.[1] This number is extremely low compared with the 500,000 patients who will be diagnosed with this disease globally, and reflects the results of successful screening programs in the United States and other developed countries using cytology and/or DNA testing for high-risk human papillomavirus (HPV) types.[2] Despite this success, nearly 4020 women are expected to die of cervical cancer in the United States this year.[1] Many of these women are relatively young—between the ages of 30 and 50 years—and are mothers to young children.

Early-stage cervical cancer that falls into the International Federation of Gynecology and Obstetrics (FIGO) stages IA2 to IB1 lends itself to either fertility-preserving radical trachelectomy with lymphadenectomy or radical hysterectomy with lymphadenectomy. Depending on the surgicopathologic findings, radical hysterectomy

may be followed by adjuvant therapy.[2] Although some patients with stage IB2 cervical cancer receive surgery, most patients with locally advanced disease (stages IB2 to IVA) are treated with cisplatin-based chemoradiation and high-dose-rate intracavitary brachytherapy. The cure rate for patients with locally advanced disease is 40% to 75%, with factors such as paraaortic nodal status, total treatment time, and nicotine dependence influencing recurrence rates.[3] Patients with metastatic disease (stage IVB) at the time of diagnosis, those with persistent disease following definitive chemoradiation, and those with disease recurrence in locations that preclude curative total pelvic exenteration make up a high-risk population for whom chemotherapy is often palliative with poor short-term results.[2]

One promising therapeutic avenue through which recent inroads have been made in advanced disease is tumor angiogenesis, which is dependent on oncogenic HPV infection.[4] On August 14, 2014, the United States Food and Drug Administration (FDA) approved the antiangiogenesis agent bevacizumab (Avastin, Genentech/Roche) for women with advanced cervical cancer.

Previous Trials

The Gynecologic Oncology Group (GOG) was one of the 9 cooperative groups of the National Cancer Institute (NCI). Following a highly productive period lasting more than 40 years, the GOG was recently rolled into the NCI's new National Clinical Trials Network. Today, the GOG, the Radiation Therapy Oncology Group, and the National Surgical Adjuvant Breast and Bowel Project together form NRG Oncology, which functions under the mandate of the NCI's Cancer Therapy Evaluation Program (CTEP). The treatment of women with metastatic and recurrent cervical cancer has represented a high unmet clinical need for many years, and the GOG has successfully completed 9 phase 3 randomized clinical trials in this population. The first 7 of these studies, and the development and early results of the eighth trial, have been examined by the current authors.[5] Here, we reflect only on the highlights of those first 7 clinical trials.

The first period of the GOG phase 3 experience in treating patients with metastatic and recurrent cervical carcinoma encompassed protocols 43, 64, and 77. These studies involved looking at cisplatin dose intensity, infusion times, and platinum analogues.[6-8] Because none of the investigational modalities in these trials led to significant differences in response rate (RR), progression-free survival (PFS), or overall survival (OS), the data did not furnish any convincing evidence for abandoning single-agent cisplatin (50 mg/m^{2} body surface area [BSA] every 21 days) as the agent of choice for advanced squamous cell carcinoma of the cervix. Unfortunately, despite an RR of approximately

20%, the impact of cisplatin alone on survival or quality of life in this incurable population remained unproven.

The second period of the GOG phase 3 experience (protocols 110, 149, 169, and 179) in metastatic and recurrent cervical cancer was when interesting things begin to happen.[9-12] In these studies, the GOG compared single-agent cisplatin with an array of antineo-plastic agents, including ifosfamide (with and without bleomycin); mitolactol; paclitaxel; topotecan; and the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen. Data from these trials underscored an improvement in PFS (GOG 110, 169, and 179) and for the first time yielded a statistically significant (albeit short) enhancement in overall survivorship (GOG 179, discussed below).[10-12]

The combined regimen of cisplatin plus paclitaxel was developed following a GOG phase 2 feasibility study in which the doublet performed well, with an impressive overall response rate (ORR) of 46.3%.[13] When studied head to head against cisplatin alone in GOG 169 on a 21-day schedule, Moore and colleagues reported that although the combined regimen (paclitaxel 135 mg/m^{2} BSA 24-hour infusion plus cisplatin 50 mg/m^{2} BSA on day 2) exhibited superior response rates (36% vs 19%) and a significant improvement in PFS, there was no OS benefit.[11]

The GOG next studied the combination of cisplatin plus topotecan in GOG 179.[12] This doublet was developed following the phase 2 experience by Fiorica and colleagues in which combining platinum with a 3-day infusion of topotecan yielded a 28% ORR in women with advanced cervical cancer.[14] Once again, in GOG 179 the control arm consisted of single-agent cisplatin at 50 mg/m^{2} BSA, and cycles were repeated every 21 days. Long and colleagues reported that the comparison of cisplatin vs cisplatin plus topotecan (cisplatin 50 mg/m^{2} BSA plus topotecan 0.75 mg/m^{2} BSA on days 1 to 3) yielded the first study that has shown a statistically significant impact on the ORR, median PFS, and median OS in this population, with all outcome measures favoring the 2-drug regimen.[12] Because GOG 179 was completed after the widespread adoption of cisplatin-based chemo-radiation for upfront management of locally advanced disease,[12] it is likely that the survival benefit observed reflects reduced activity of cisplatin at recurrence due to acquired drug resistance. Only 27% of patients in the previous study (GOG 169) had received platinum prior to recurrence,[11] as compared with 57% of patients in GOG 179 (Table 1).[12] The RRs for single-agent platinum were lower in GOG 179 than those observed in earlier studies.[12] In addition, the hazard ratios (HRs) in GOG 179 for OS were 0.63 (platinum-naive) and 0.78 (prior platinum),[12] suggesting a less beneficial effect in the pretreated group.

Table 1. Comparison of GOG Protocols 169 and 179 With Impact of Prior Platinum Exposure on Response Rate

Modalities		GOG 169 (n=264)		GOG 179 (n=293)	
		CDDP	CDDP-Paclitaxel	CDDP	CDDP-Topotecan
RR		19%	36%	13%	27%
PFS		2.8 mo	4.8 mo	2.9 mo	4.6 mo
OS		8.8 mo	9.7 mo	6.5 mo	9.4 mo
		HR [95% CI]	*P*-value (2-sided)	HR [95% CI]	*P*-value (2-sided)
Multivariate Analysis	PFS	0.681 [0.530, 0.876]	.0027	0.634 [0.491, 0.819]	.00048
	OS	0.878 [0.679, 1.134]	.32	0.713 [0.542, 0.936]	.015
		CDDP	CDDP-Paclitaxel	CDDP	CDDP-Topotecan
No Prior Cisplatin	RR	26%	37%	20%	39%
Prior Cisplatin	RR	5%	32%[a]	8%	15%[b]

[a] 27% of patients in GOG 169 had prior exposure to cisplatin.

[b] 57% of patients in GOG 179 had prior exposure to cisplatin.

CDDP, cisplatin; HR, hazard ratio; mo, months; OS, overall survival; PFS, progression-free survival; RR, response rate.

Gynecologic Oncology Group Protocol 204

Clinical Trial Design and Results

The third era in the GOG's phase 3 experience in advanced cervical cancer was heralded by the activation of protocol 204 on May 27, 2003.[15] GOG 204 originally was designed to compare the cisplatin-paclitaxel doublet of GOG 169 with the cisplatin-vinorelbine doublet that had demonstrated an ORR of 30% in the GOG's prior phase 2 study.[16] A third and fourth arm were added when results from another phase 2 GOG study evaluating the cisplatin-gemcitabine doublet[17] and the phase 3 results from GOG 179[12] (discussed above) became available. Using the cisplatin-paclitaxel doublet as the control arm, GOG 204 studied 4 different platinum-based intravenous (IV) chemotherapy doublets on a 21-day schedule. For the first time, patients with glandular lesions were not excluded from trial participation. The primary endpoint was OS, with RR, PFS, and health-related quality of life (HRQOL) representing secondary endpoints. The targeted accrual for the entire study was 600 participants, and an interim analysis was planned after 232 deaths.

By April 24, 2007, the results of the scheduled interim analysis were made available. The NCI's Data and Safety Monitoring Board recommended early closure for futility, deeming that none of the experimental arms were likely to demonstrate improved survival over the control arm. Effective April 30, 2007, GOG 204 closed to patient entry. Monk and colleagues reported that the median OS was 12.87 months in the control arm of cisplatin-paclitaxel, 9.99 months with cisplatin-vinorelbine, 10.28 months with cisplatin-gemcitabine, and 10.25 months with cisplatin-topotecan.[15] Compared with the control arm, the hazards of death were 1.15 (95% CI, 0.79-1.67) for cisplatin-vincristine, 1.32

(95% CI, 0.91-1.92) for cisplatin-gemcitabine, and 1.26 (95% CI, 0.86-1.82) for cisplatin-topotecan.[15] The RRs for each doublet were 29.1% (cisplatin-paclitaxel), 25.9% (cisplatin-vinorelbine), 22.3% (cisplatin-gemcitabine), and 23.4% (cisplatin-topotecan).[15] The rate of grade 4 and 5 leukopenia for the cisplatin-gemcitabine arm was approximately one-half to one-third the rates in the other 3 arms. The rate of grade 4 and 5 neutropenia was approximately 50% in all of the arms except cisplatin-gemcitabine (15%). There were 11 grade 5 fatal adverse events, but no statistically significant association was detected between the type of regimen administered and treatment-related deaths (*P*=.84). The rate of grade 2 alopecia was significantly higher in the cisplatin-paclitaxel arm (54%) than in the cisplatin-vincristine (9%), cisplatin-gemcitabine (7%), or cisplatin-topotecan (26%) arms (*P*<.0001).[15]

Subsequent Impact on Clinical Trial Design

With a total of 513 patients, GOG 204 remains the largest phase 3 randomized study in advanced cervical cancer. It is principally cited for having established the cisplatin-paclitaxel backbone dose and schedule. This has made GOG 204 the first in a trilogy of pivotal, 21st century, phase 3, randomized trials in metastatic, recurrent, and persistent cervical carcinoma.[18-19]

GOG 204 also made us completely overhaul and reevaluate our therapeutic agenda in the advanced cervical cancer population.[20] Importantly, we had essentially exhausted our options concerning platinum-based chemotherapy doublets. Similar to what was observed when GOG 179 was compared with GOG 169, more patients treated in GOG 204 had received prior platinum with radiotherapy, and RRs were lower (eg, from 36% in GOG

169 to 28.1% in GOG 204 for the cisplatin-paclitaxel doublet). Although cross-trial comparisons are not valid, it must be recognized that with increasingly stringent eligibility criteria over time, the GOG 204 population made up a healthier cohort than that of GOG 169 (Table 2). The results of GOG 204 prompted a search for alternative therapies, including nonplatinum chemotherapy doublets.

In designing the successor to GOG 204, two nonplatinum regimens underwent initial consideration for inclusion.[21-22] The phase 2 SCOTCERV trial (a phase 2 study of docetaxel and gemcitabine as second-line chemotherapy in cervical cancer) by Symonds and colleagues was evaluating docetaxel (75 mg/m^2 BSA on day 1) plus gemcitabine (1000 mg/m^2 BSA on days 1 and 8) in advanced disease, but results were not anticipated for several years.[23] The nonplatinum chemotherapy doublet, topotecan plus paclitaxel, was one for which there were more data, including a small phase 2 trial in recurrent disease and preclinical data that provided a biological rationale for the combination. Bahadori and colleagues demonstrated synergy between topotecan and microtubule-interfering agents such as paclitaxel and vinblastine.[24] Using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on a colon cancer cell line, these investigators noted that incubation with paclitaxel increased the efficacy of subsequent treatment with topotecan. Specifically, the concentration of topotecan necessary to induce a 50% decrease in cell survival was reduced by 10- to 40-fold. Immediately prior to the addition of topotecan, paclitaxel caused an increase in topoisomerase I protein levels (presumably through stabilization of topoisomerase I and RNA or through induced gene expression), fraction of S-phase cells (possibly through higher transformation of topotecan-topoisomerase I-DNA complexes), and extent of Bcl-xL phosphorylation (thus decreasing antiapoptotic activity).[24]

Tiersten and colleagues piloted topotecan plus paclitaxel in 15 patients with recurrent, persistent, or metastatic cervical carcinoma.[25] Fourteen had received prior pelvic irradiation. Patients were treated with paclitaxel 175 mg/m^2 on day 1 and topotecan 1 mg/m^2 on days 1 to 5 of a 21-day cycle with growth factor support.[25] Among 13 evaluable patients, there were 7 (54%) responses (1 complete, 6 partial), and 3 patients (23%) experienced stable disease. The PFS and OS were 3.77 and 8.62 months, respectively. Grade 3 and 4 toxicities included anemia (47%), leukopenia (27%), thrombocytopenia (13%), neurotoxicity (13%), and diarrhea (13%).[25]

Recognizing further that the inability of conventional cytotoxic agents to affect long-term survival is likely to be multifactorial in the advanced cervical cancer population, it became clear that the replacement trial for GOG 204 would represent an ideal platform upon which a novel biological stratagem could be studied. As discussed above, women suffering from metastatic cervical cancer typically have been treated previously with chemoradiation, and presumably harbor radioresistant and chemoresistant tumor cell populations. Furthermore, these patients often have nephropathy as a consequence of a blocked kidney, limiting their ability to clear cytotoxic compounds from the bloodstream. Finally, recurrent tumors within the irradiated, devascularized fields are difficult to bathe in chemotherapy. For these reasons, this patient population is not one that tolerates multiple lines of chemotherapy, unlike patients with breast or ovarian cancer where longer sustained responses to systemic therapy can be achieved.

Angiogenesis imparts a poor prognosis in cervical cancer. In fact, abnormal vascular markings seen via colposcopy among women with abnormal Papanicolaou test cytology are among the principal hallmarks of invasive disease and represent harbors of angiogenesis. Neutralizing anti–vascular endothelial growth factor (VEGF) monoclonal antibodies such as bevacizumab have demonstrated therapeutic activity in several solid tumors, including colorectal cancer, lung cancer, glioblastoma multiforme, renal cell carcinoma, breast cancer, and ovarian carcinoma. Despite this broad range of activity, it is not clear whether any benefit is conferred in the adjuvant setting. Perhaps viable, untreated/unresected disease is much more angiogenic than microscopic residual disease, and therefore a more vulnerable and attractive target for antiangiogenic therapy.

Given the efficacy of bevacizumab in non–small cell lung cancer and the potential shared tumor biology between non–small cell lung cancer and cervical cancer, a phase 2 evaluation of bevacizumab at 15 mg/kg every 21 days was undertaken by Monk and colleagues in response to a mass solicitation by CTEP on behalf of the GOG.[26] Among the 46 eligible and evaluable patients in GOG 227C, 38 (82.6%) had received prior pelvic irradiation as well as either 1 (n=34, 73.9%) or 2 (n=12, 26.1%) cytotoxic regimens for recurrent disease.[26] Notable grade 3/4 adverse events at least possibly related to bevacizumab included neutropenia (n=1), anemia (n=2), gastrointestinal effects (n=4), hypertension (n=7), thromboembolism (n=5), other cardiovascular effects (n=2), vaginal bleeding (n=1), and fistula (n=1). One grade 5 infection was observed. Five patients (10.9%; 2-sided 90% CI, 4%-22%) experienced partial responses, and 11 patients (23.9%; 2-sided 90% CI, 14%-37%) survived progression-free for at least 6 months. The median response duration was 6.21 months (range, 2.83-8.28 months). The median PFS and OS for all patients was 3.4 months (95% CI, 2.53-4.53) and 7.29 months (95% CI, 6.11-10.41), respectively.[26] These results indicated that bevacizumab is well-tolerated and active in the second- and third-line treatment of patients with recurrent cervical cancer, and performed favorably

Table 2. Eligibility Criteria in GOG Phase 3 Randomized Clinical Trials for Women With Recurrent, Persistent, or Metastatic Cervical Carcinoma

	GOG 149	GOG 169	GOG 179	GOG 204	GOG 240
Modalities	CDDP + IFX/ MESNA ± bleomycin	CDDP ± paclitaxel	CDDP ± topotecan	CDDP-paclitaxel vs CDDP-topotecan vs CDDP-gemcitabine vs CDDP-vinorelbine	CDDP-paclitaxel ± bevacizumab vs topotecan-paclitaxel ± bevacizumab
Stage	IVB, recurrent, or persistent SCC	IVB, recurrent, or persistent SCC	IVB, recurrent, or persistent SCC	IVB, recurrent, or persistent SCC, ACA, or ASC	IVB, recurrent, or persistent SCC, ACA, or ASC
PS	0-2	0-2	0-2	0-1	0-1
Hematologic	WBC ≥4 K; Plts ≥100 K	ANC ≥1500/μL; Plts ≥100 K	ANC ≥1500/μL; Plts ≥100 K	ANC ≥1500/μL; Plts ≥100 K	ANC ≥1500/μL; Plts ≥100 K
Renal	Cr ≤IN	Cr ≤2 mg/dL	Cr ≤1.5 mg/dL	Cr ≤1.2 mg/dL; if Cr >1.2 mg/dL but <1.5 mg/dL, must have 24-h CrCl ≥50 cc/min	Cr ≤ULN or CrCl ≥60 mL/min
Hepatic	Serum albumin ≥3; bilirubin ≤1.5 × IN; SGOT & alk phos ≤3 × IN	Bilirubin ≤1.5 × IN; SGOT & alk phos ≤3 × IN	Bilirubin ≤1.5 × IN; SGOT & alk phos ≤3 × IN	Bilirubin ≤1.5 × IN; SGOT & alk phos ≤3 × IN	Bilirubin ≤1.5 × IN; SGOT & alk phos ≤2.5 × IN

ACA, adenocarcinoma; alk phos, alkaline phosphatase; ANC, absolute neutrophil count; ASC, adenosquamous carcinoma; CDDP, cisplatin; Cr, serum creatinine; CrCl, creatinine clearance; GOG, Gynecologic Oncology Group; h; hour/hours; IFX, ifosfamide; IN, institutional normal; MESNA, sodium 2-mercaptoethane sulfonate; plts, platelet count; PS, performance status; SCC, squamous cell carcinoma; SGOT, serum glutamic oxaloacetic transaminase; ULN, upper limit of normal; WBC, white blood cell count.

when compared with historical phase 2 GOG trials in this setting. The safety of combining bevacizumab with chemotherapy was suggested by a small case series by Wright and colleagues involving 6 heavily pretreated women with advanced cervical cancer.[27] Five had originally been treated with primary chemoradiation, and at recurrence all had multisite metastatic disease. Clinical benefit was noted in 67% of the subjects, including 1 patient with a complete response (17%), 1 patient with a partial response (17%), and 2 patients with stable disease (33%). The median time to progression for the 4 women who demonstrated clinical benefit was 4.3 months. Grade 4 toxicity occurred in just 1 patient, who developed neutropenic sepsis.[27]

We will return to this narrative after first discussing the second pivotal trial for advanced cervical cancer, which matured during the period when the replacement study for GOG 204 was accruing patients.

Japanese Clinical Oncology Group Protocol 0505

As discussed above, in 2009, GOG 204 established the cisplatin-paclitaxel chemotherapy doublet as the standard of care for women with incurable squamous cell carcinoma (SCC) and non-SCC of the cervix. Importantly,

with glandular lesions (eg, adenocarcinoma, adenosquamous carcinoma) comprising a larger percentage of the cervical cancer burden than in previous decades (eg, 20%-25% of cases in 2010 vs 5% in 1980), some suggested that the superiority of the cisplatin-paclitaxel regimen may be attributed to both the activity of cisplatin and the superiority of paclitaxel as a treatment for non-SCC.

Unfortunately, the combination of paclitaxel and cisplatin must be administered over 24 hours to reduce neurotoxicity. This mandates a hospital admission for each cycle of therapy, which results in both increased cost and diminished quality of life. The need is for more conveniently administered regimens with equivalent or better efficacy.

The use of carboplatin in this disease did not generate much interest initially. When administered as a single agent (340-400 mg/m² BSA) on a 28-day schedule, the drug has been less active than cisplatin, with RRs of 15%-28%.[28-30] Unlike cisplatin, the dose of carboplatin is calculated according to renal function.[31] Owing to less nephrotoxicity and neurotoxicity, when combined with paclitaxel, carboplatin enables a 3-hour outpatient administration of paclitaxel without hydration.[32] Equally important, paclitaxel has platelet-sparing activity when combined with carboplatin, which mitigates the dose-limiting toxicity of carboplatin.[33]

A single-institution, Japanese, phase 2 trial using carboplatin plus paclitaxel for recurrent or metastatic cervical cancer was conducted by Kitagawa and colleagues.[34] Women with incurable, measurable disease with adequate organ function and reasonable Eastern Cooperative Oncology Group (ECOG) performance status scores (ie, 0-2) were treated with carboplatin (area under the curve [AUC] 5 over 1 hour, IV) plus paclitaxel (175 mg/m² over 3 hours, IV) on a 21-day schedule until progression or completion of 6 cycles. Of the 28 patients enrolled, 23 were assessable for response and toxicity. The vast majority (91%) had received prior radiotherapy. The overall RR was 61% (95% CI, 41%-78%), with 2 CRs. The median PFS was 5.9 months (range, 1.0-14.1 months).[34] Among the 9 patients who had in-field recurrences, 67% responded to carboplatin-paclitaxel. As expected, RRs were reduced among women who had received prior chemotherapy (ie, 50% vs 73% in the chemotherapy-naive cohort). The only grade 4 toxicity observed was anemia, in 4 patients (17%). Nonhematologic toxicity included grade 3 febrile neutropenia in 3 patients (13%), which was managed without a need for hospitalization or growth factor administration, and grade 3 neuropathy in 2 patients (8%).[34]

The promising results from this single-institution phase 2 experience prompted the development and activation of a multi-institutional phase 2 study in Japan. Using similar eligibility and trial endpoints, as well as the same dosages and schedule of the earlier trial, Kitagawa and colleagues enrolled 41 women. Thirty-nine of these women were evaluable, of whom 33 (84.6%) had received prior radiotherapy.[35] The ORR was 59% (95% CI, 43%-75%), and 5 women (13%) achieved a CR. The median duration of response was 5.2 months.[35] The median PFS and OS were 5.3 months and 9.6 months, respectively. Neutropenia (79%), anemia (46%), thrombocytopenia (15%), and fatigue (8%) were the most frequent grade 3 or 4 adverse events, and no treatment-related deaths occurred.[35]

The confirmatory phase 3 randomized study to validate the efficacy and tolerability of the carboplatin-paclitaxel doublet was conducted on behalf of the Japan Clinical Oncology Group (JCOG) by Kitagawa and colleagues.[36,37] JCOG 0505 enrolled 253 patients from February 2006 to November 2009. Patients were randomly assigned to paclitaxel (135 mg/m² BSA over 24 hours on day 1) plus cisplatin (50 mg/m² over 2 hours on day 2) vs paclitaxel (175 mg/m² BSA over 3 hours on day 1) plus carboplatin (AUC 5 over 1 hour on day 1). Cycles were repeated every 21 days for a maximum of 6 cycles. OS was the primary endpoint, and in addition to PFS and frequency of adverse events as secondary endpoints, the proportion of nonhospitalization periods was evaluated as a surrogate for quality of life. The trial was powered

to confirm the noninferiority of carboplatin-paclitaxel to cisplatin-paclitaxel using a threshold hazard of death of 1.29 with a 1-sided alpha of 5%. At a median follow-up of 174 months, 71% of patients in each arm received 6 cycles of therapy. The median OS for the control arm was 18.3 months vs 17.5 months for carboplatin-paclitaxel (HR, 0.99; adjusted 90% CI, 0.79-1.25; noninferiority P=.032).[37] The median PFS was 6.9 months (cisplatin-paclitaxel) vs 6.21 months (HR, 1.04; 95% CI, 0.8-1.35). The carboplatin-paclitaxel doublet had a more favorable toxicity profile for grade 3/4 neutropenia, grade 3/4 febrile neutropenia, and grade 2 to 4 nephrotoxicity; grade 3/4 thrombocytopenia occurred more commonly (23.5% vs 3.3%) among patients receiving carboplatin-paclitaxel.[37]

JCOG 0505 was presented at the 2012 Annual Meeting of the American Society of Clinical Oncology. This phase 3 study is noteworthy for having demonstrated significant noninferiority of carboplatin-paclitaxel in OS when compared with cisplatin-paclitaxel. With less toxicity and easier feasibility, this chemotherapy doublet has recently emerged as a new standard backbone therapy for women with advanced cervical cancer. For patients with recurrent disease who had received prior extended-field radiotherapy, the cisplatin-paclitaxel backbone from GOG 204 is preferred in order to circumvent severe myelosuppression.

The identification of even more tolerable and efficacious alternatives is ongoing. Like carboplatin, nedaplatin (cis-diammine [glycolato] platinum) is also a less nephrotoxic cisplatin analogue. Neurotoxicity is rarely observed. A phase 2 study of paclitaxel (175 mg/m² BSA over 3 hours on day 1) plus nedaplatin (80 mg/m² over 1 hour on day 1) was reported in 2012 by Takekuma and colleagues.[38] Among 45 eligible patients, the ORR was 42.2% and included 11 CRs and 8 partial responses.[38] Grades 3 or 4 adverse events included neutropenia (32.7%), febrile neutropenia (2%), and anemia (18.4%). No significant thrombocytopenia was observed, and nonhematologic toxicity was mild and without a dominant pattern. The median PFS was 7.5 months and the median OS was 15.7 months.[38] With a favorable RR and a toxicity profile that does not include thrombocytopenia, a phase 3 study comparing the nedaplatin-paclitaxel backbone with the carboplatin-paclitaxel backbone is being considered.

Gynecologic Oncology Group Protocol 240

In an effort to circumvent platinum resistance and independently harness the therapeutic potential of targeting the VEGF pathway to inhibit tumor-associated angiogenesis, GOG protocol 240 was activated in 2009 throughout the United States, Canada, and Spain. Assuming that the factors under consideration (ie, nonplatinum doublet and bevacizumab) did not interact, a 2 × 2 facto-
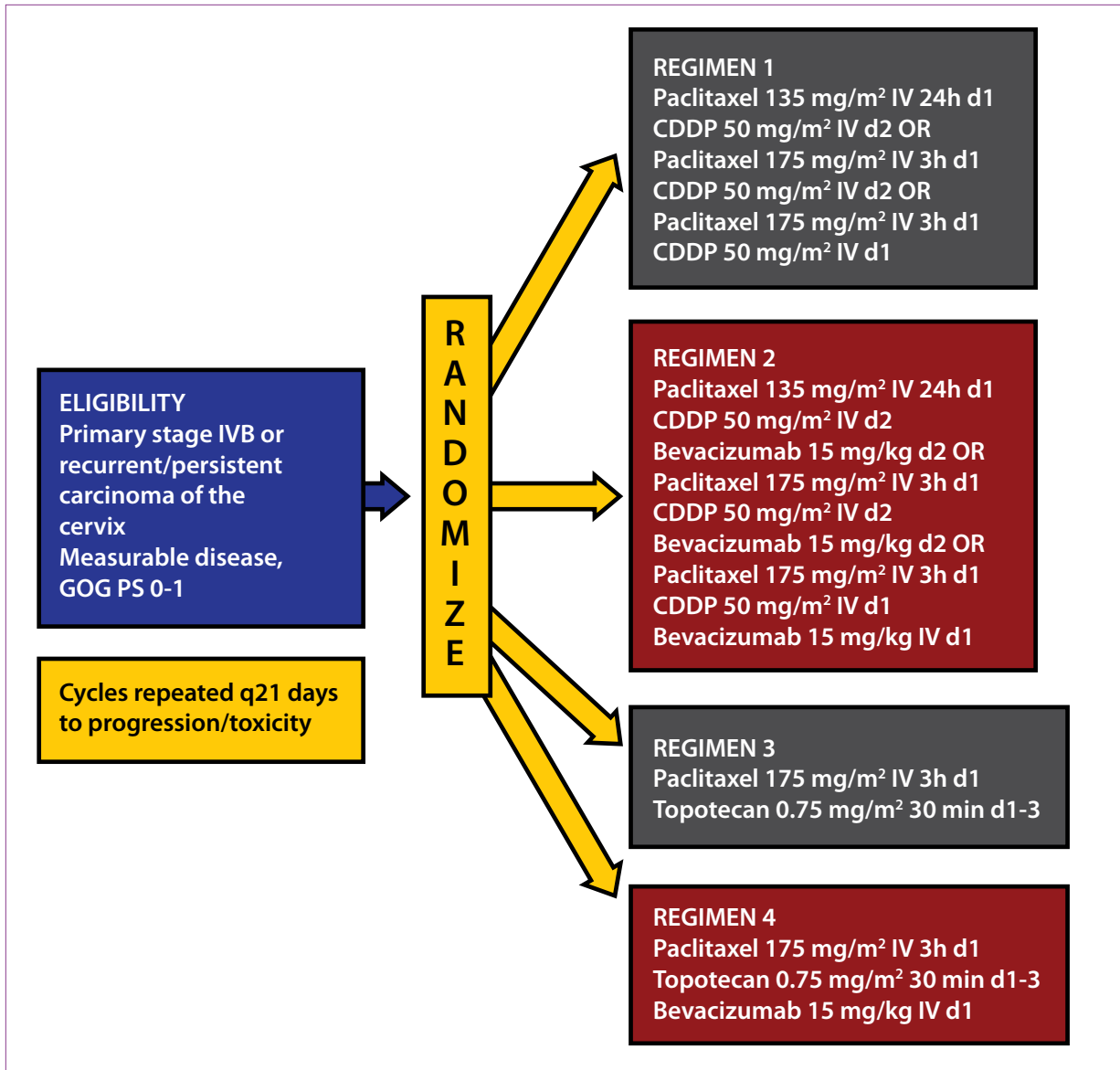
Figure 1. GOG 240 clinical trial design.

CDDP, cisplatin; GOG, Gynecologic Oncology Group; PS, performance status.

rial design was used. Patients with metastatic, recurrent, or persistent SCC, adenocarcinoma, or adenosquamous carcinoma were randomly assigned to one of 4 treatment arms: paclitaxel 135 mg/m² BSA on day 1 plus cisplatin 50 mg/m² BSA on day 2—with or without bevacizumab 15 mg/kg on day 2—or paclitaxel 175 mg/m² BSA on day 1 plus topotecan 0.75 mg/m² BSA on days 1 to 3, with or without bevacizumab 15 mg/kg on day 1 (Figure 1). The primary endpoints were OS and toxicity. The secondary endpoints included PFS and RR, and tertiary objectives involved patient-reported outcomes and prospective validation of previously identified pooled prognostic factors known as the Moore criteria.[39] Translational endpoints

included the prevalence of nicotine use and its impact on survival, correlation of clearance of circulating tumor cells with survival, and prognostic value of surrogate markers of angiogenesis.

Unlike the previous trials—for which only 6 cycles of therapy were specified and permission from the study chair had to be sought to deliver more chemotherapy—patients in GOG 240 were treated every 21 days until disease progression or unacceptable toxicity. In addition, with each successive trial (from GOG 149 through 169, 179, 204, and 240), the eligibility criteria had become progressively more stringent, resulting in a medically and nutritionally optimized patient population in GOG 240

(Table 2). In other words, among the advanced cervical cancer population, the eligibility criteria provided the "healthiest" cohort to go on trial to maximize the potential benefits of novel investigational therapy. GOG 240 met its accrual goal in 2012 with 452 patients, and following a prespecified interim analysis in which 173 events had occurred, the NCI announced in early 2012 that the nonplatinum chemotherapy doublet of topotecan plus paclitaxel was not superior to the cisplatin plus paclitaxel backbone treatment (Figure 2A).[40]

Following a second analysis in late 2012 when 271 deaths had occurred, the NCI's Data Safety Monitoring Board (DSMB) recommended ending the trial at 20.8 months' median follow-up, noting that the arms administering the anti-VEGF humanized monoclonal antibody bevacizumab (using either chemotherapy backbone) were associated with a statistically significant improvement in OS (17.0 vs 13.3 months; HR of death, 0.71 (98% CI, 0.54-0.95; 1-sided P=.004), PFS (8.2 vs 5.9 months; HR of progression 0.67 [95% CI, 0.54-0.82]; 2-sided P=.002), and RR (48% vs 36%; relative probability of response, 1.35 [95% CI, 1.08-1.68]; 2-sided P=.008), without any significant deterioration in HRQOL based on patient-reported outcomes (Figure 2B).[41-43] The clinical benefit observed with bevacizumab was sustained even among patients with disease in the previously irradiated pelvis.[42] The major treatment-related toxicities included fistula (6%), thromboembolism (8%), and manageable hypertension (25%).[42] Following validation of the Moore criteria in the GOG 240 population,[44] it was determined that those patients with the highest risk scores received the most benefit from bevacizumab.[45]

Within 1 month of public presentation of the data, in June 2013, the cisplatin-paclitaxel-bevacizumab triplet from GOG 240 was listed as category 2A in the National Comprehensive Cancer Network Clinical Practice Guidelines for Cervical Cancer (Table 3).[46] This resulted in significant use of bevacizumab for recurrent and metastatic cervical cancer, well ahead of publication of the primary manuscript[42] in February 2014. In March 2014, the United Kingdom's Cancer Drug Fund approved bevacizumab for women with advanced cervical cancer.[47] During the second quarter of 2014, both Genentech and Roche filed with the FDA and the European Medicines Agency, respectively.

Bevacizumab is the first targeted agent to demonstrate an OS advantage in a gynecologic malignancy. The 3.7-month gain in OS created by the regimens that administered bevacizumab did not come at the cost of QOL, and may represent a therapeutic window through which a patient could receive other novel therapies, including other types of antiangiogenesis treatment and/or immunotherapy (Figure 2C). Bevacizumab has been approved by the FDA for the treatment of colorectal
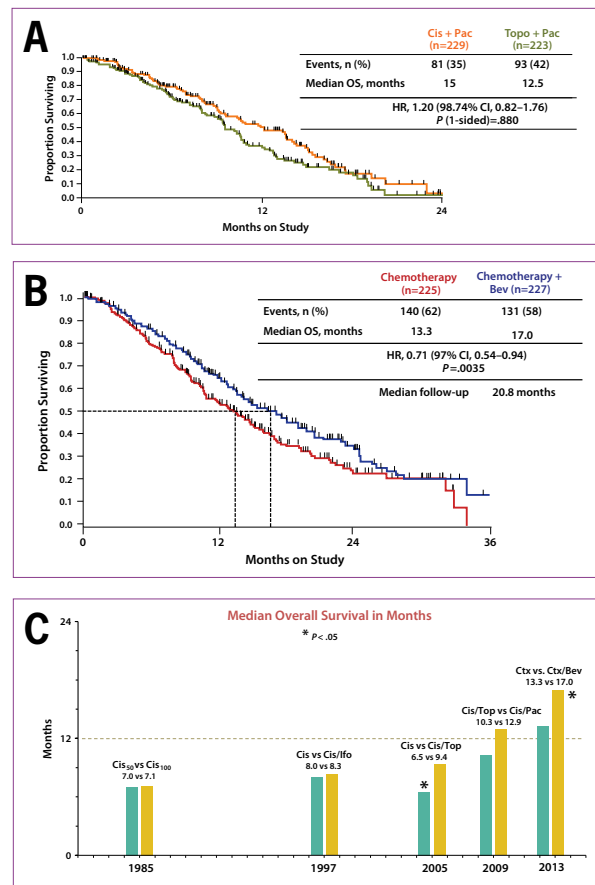

Figure 2. Proof of concept of efficacy of antiangiogenesis therapy in advanced cervical cancer.

A, Nonsuperiority of the topotecan-paclitaxel nonplatinum chemotherapy doublet (GOG 240 interim analysis).
B, Superiority of chemotherapy plus bevacizumab over chemotherapy alone (GOG 240 second analysis).
C, Gynecologic Oncology Group phase 3 clinical trial experience in advanced cervical cancer demonstrating improvements in overall survival over time.

Bev, bevacizumab; Cis, cisplatin; Ctx; cetuximab; HR, hazard ratio; Ifo, ifosfomide; OS, overall survival; Pac, paclitaxel; Topo, topotecan.

Panels A and B are from Tewari KS et al. *N Engl J Med.* 2014;370:734-743.[42] Copyright © 2014, Massachusetts Medical Society. Reprinted with permission. Panel C is used with permission from Gottfried E. Konecny, MD.

cancer, lung cancer, renal cell cancers, and glioblastoma; accelerated approval for breast cancer was granted in 2009 and revoked in 2012. In Europe, bevacizumab is also approved for frontline therapy in ovarian cancer. On July 14, 2014, the FDA accepted the Genentech/Roche application for priority review, and this news was carried in a July 15, 2014, press release by Genentech,[48] as well as by the *Wall Street Journal*, Reuters, and other medical news media (Table 3). Priority review is granted only to those interventions that are anticipated to have a significant clinical impact. Although a final decision was projected to

Table 3. GOG 240 Timeline of Noteworthy Events

April 6, 2009	Protocol activation nationwide
January 2012	Target accrual met (n=452)
February 6, 2012	173 events trigger preplanned interim analysis
March 13, 2012	National Cancer Institute's Data Safety Monitoring Board reports nonsuperiority of topotecan-paclitaxel backbone
	"Dear Doctor" and "Dear Patient" letters prepared
December 12, 2012	Second data freeze at 271 deaths
January 25, 2013	National Cancer Institute's Data Safety Monitoring Board announces superiority of bevacizumab-containing regimens
February 7, 2013	National Cancer Institute–Gynecologic Oncology Group joint press release
	"Dear Doctor" and "Dear Patient" letters prepared
March 2013	American Society of Clinical Oncology makes rare exception to embargo and places abstract in public domain
March 9, 2013	Plenary presentation of topotecan-paclitaxel data at the 44th Annual Meeting of the Society of Gynecologic Oncology, Los Angeles, CA (abstract 1)
June 2, 2013	American Society of Clinical Oncology 2013 Press Briefing
	Plenary presentation of the bevacizumab data at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL (abstract 3)
July 2013	National Comprehensive Cancer Network lists the CDDP-paclitaxel-bevacizumab triplet as category 2A
July 2013–February 2014	40% uptake of bevacizumab in the United States for advanced cervical cancer
October 1, 2013	Plenary presentation of the heath-related quality of life data at the 2013 Annual Meeting of the European Society of Medical Oncology, Amsterdam, Netherlands (LBA 42)
February 20, 2014	Publication of primary manuscript (*N Engl J Med.* 2014;370:734-743)[42]
March 5, 2014	United Kingdom's Cancer Drugs Fund approves bevacizumab for women in England with advanced cervical cancer
March 12, 2014	Plenary presentation of prognostic factors validation data at the 45th Annual Meeting of the Society of Gynecologic Oncology
July 14, 2014	US Food & Drug Administration grants Priority Review for Genentech/Roche application to expand the label of bevacizumab to include advanced cervical cancer
July 15, 2014	Genentech press release concerning Priority Review
August 14, 2014	US Food and Drug Administration approves bevacizumab for advanced cervical cancer
August 19+, 2014	National Comprehensive Cancer Network upgrades CDDP-paclitaxel-bevacizumab triplet to category 1 and lists topotecan-paclitaxel-bevacizumab triplet as category 2B
September 2014	National Comprehensive Cancer Network upgrades topotecan-paclitaxel-bevacizumab triplet to category 1
September 28, 2014	Final protocol-specified overall survival data presentation at the 2014 Congress of the European Society of Medical Oncology, Madrid, Spain (LBA 26)
Anticipated	European Medicines Agency to approve or disapprove expansion of bevacizumab label to include metastatic, recurrent, and persistent cervical cancer

be announced on October 24, 2014, the FDA approved bevacizumab on August 14, 2014, for advanced cervical cancer.[49] This regulatory milestone underscores the agency's commitment to bringing promising therapies to patients expeditiously. Both bevacizumab-containing triplet regimens (cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab) are now listed as category 1 in the National Comprehensive Cancer Network Clinical Practice Guidelines for Cervical Cancer.

The identification of predictive biomarkers may be used to select patients with advanced cervical cancer who are likely to derive benefit from antiangiogenesis therapy. Using an ovarian cancer microarray test, investigators from the United Kingdom recently reported on a proangiogenic subgroup of patients for whom there was a trend toward improved PFS when treated with bevacizumab.[50] A proposal is on the table to study this proangiogenic signature in specimens from patients treated in GOG 240.
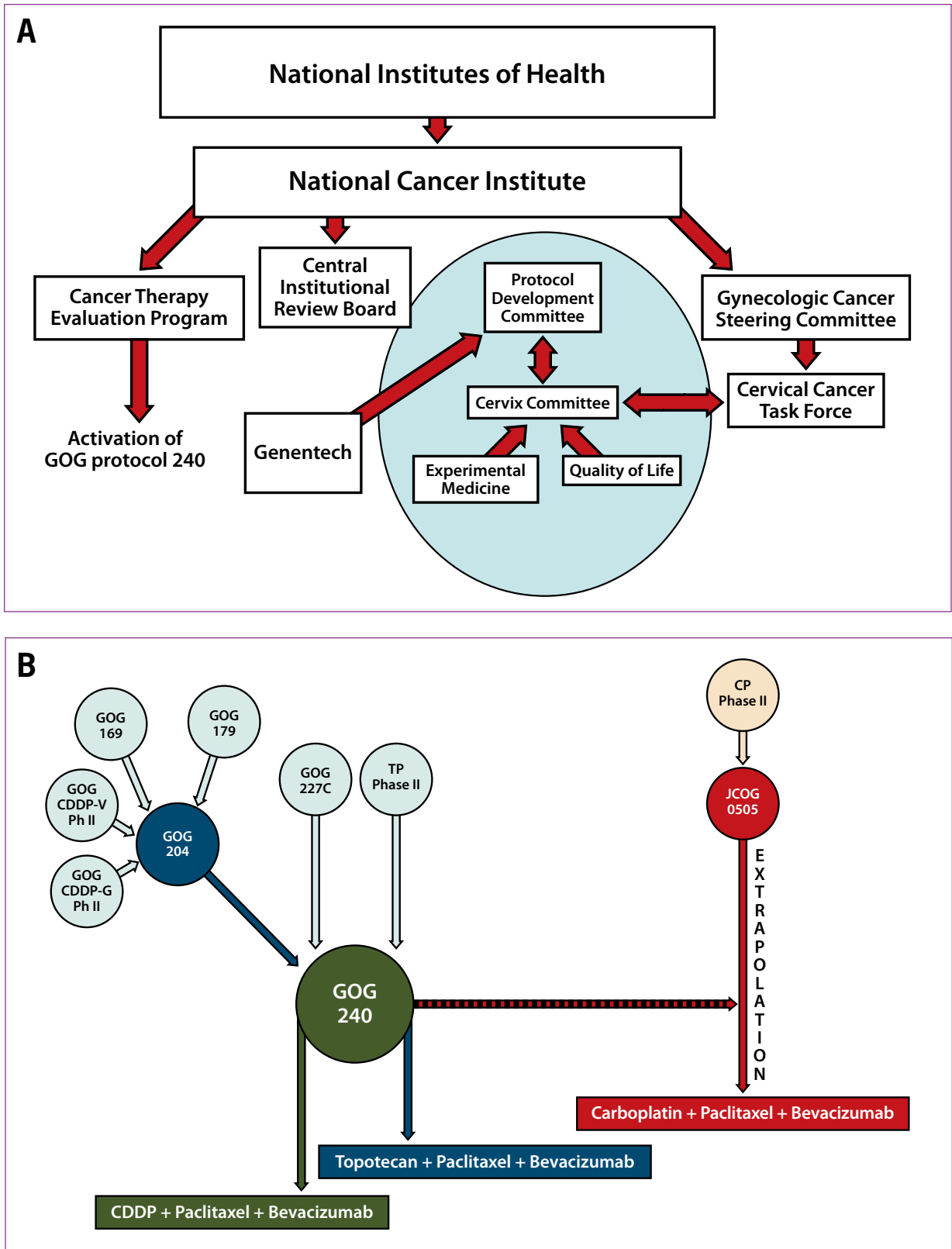
Figure 3. Development of bevacizumab in advanced cervical cancer.
A, GOG 240 protocol development. **B,** Evolution of bevacizumab-containing triplets.

CDDP, cisplatin; CDDP-G, cisplatin-gemcitabine; CDDP-V, cisplatin-vinorelbine; CP, carboplatin-paclitaxel; GOG, Gynecologic Oncology Group; JCOG, Japan Clinical Oncology Group; TP, topotecan-paclitaxel.

Table 4. Chemotherapy Options Incorporating Antiangiogenesis Therapy

Bevacizumab-Containing Regimens	Indication
Paclitaxel 135 mg/m² BSA IV 24 h, day 1 plus **cisplatin** 50 mg/m² BSA IV, day 2 plus **bevacizumab** 15 mg/kg body weight IV, day 2 every 21 days	Stage IVB SCC, ACA, ASC Recurrent/persistent SCC, ACA, ASC s/p chemoradiation plus high-dose-rate intracavitary brachytherapy **and extended-field radiotherapy**
Topotecan 0.75 mg/m² BSA IV, days 1-3 plus **paclitaxel** 175 mg/m² BSA IV, day 1 plus **bevacizumab** 15 mg/kg body weight IV, day 1 every 21 days	Stage IVB SCC, ACA, ASC Recurrent/persistent SCC, ACA, ASC s/p chemoradiation plus high-dose-rate intracavitary brachytherapy; **unable to tolerate platinum** (eg, hypersensitivity, increased emetogenicity, neuropathy)
Paclitaxel 175 mg/m² BSA IV 3 h, day 1 plus **carboplatin** AUC 6 IV, day 1 plus **bevacizumab** 15 mg/kg body weight IV, day 1 every 21 days	Stage IVB SCC, ACA, ASC; Recurrent/persistent SCC, ACA, ASC s/p chemoradiation plus high-dose-rate intracavitary brachytherapy

AUC, area under the concentration vs time curve; ACA, adenocarcinoma; ASC, adenosquamous carcinoma; BSA, body surface area; h, hour/hours; SCC, squamous cell carcinoma; s/p, status post.

Notes: Cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab were formally studied in GOG 240.[42] Carboplatin-paclitaxel-bevacizumab is not listed in the National Comprehensive Cancer Network Clinical Practice Guidelines for Cervical Cancer and has not yet been formally studied in a randomized trial, but noninferiority of carboplatin-paclitaxel to cisplatin-paclitaxel was established in JCOG 0505.[37]

Conclusion

The proof of concept concerning the efficacy and tolerability of systemic antiangiogenesis therapy for advanced cervical cancer was only realized through the concerted efforts of several entities. More than 3 decades of research was conducted by the GOG to evaluate the activity of platinum-based chemotherapy in both previously irradiated patients as well as those with prior platinum exposure following adoption of chemoradiation protocols for locally advanced disease.[51] The provision by Genentech of the novel antiangiogenesis drug bevacizumab[52] through the NCI's cooperative group mechanism and original CTEP mass solicitation allowed for state-of-the-science cervical cancer therapeutics[53] to be developed in a protocol that would ultimately pass through all regulatory channels and be open to participation by women struggling with advanced disease (Figure 3A). Together with international collaboration by GEICO (Spanish Group for Investigation on Ovarian Cancer) and the JCOG, 3 complementary pivotal phase 3 clinical trials have emerged in the 21st century (Figure 3B). Three distinct chemotherapy regimens administering bevacizumab for women with metastatic, recurrent, and persistent cervical cancer have now been developed (Table 4). The cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab triplets were formally studied in GOG 240,[42,54] and a carboplatin-paclitaxel-bevacizumab triplet[55] can be inferred through extrapolation of GOG 240 and JCOG 0505 and by pooling of knowledge from other disease sites.[56] Although much work still needs to be done, through the integration of bevacizumab with chemotherapy a potential therapeutic window of nearly 4 months has been opened through which patients demonstrating benefit to antian-giogenesis therapy may be treated with other novel agents and/or immunotherapy before they ultimately progress. We believe that this work heralds the beginning of the end of advanced cervical cancer.[57]

Disclosures

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