EXPERT OPINION

Integration of bevacizumab with chemotherapy doublets for advanced cervical cancer

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Introduction: Historically, treatment options were limited for women diagnosed with late-stage or recurrent cervical cancer until recently. The publication of the results of GOG240 marks the beginning of the anti-angiogenesis era in cervical cancer. This randomized controlled trial showed significant improvements in response rates, progression-free survival and overall survival when bevacizumab was added to conventional chemotherapy in patients with metastatic, recurrent, or persistent cervical cancer. Bevacizumab is the first new drug to be approved in this disease in over 8 years. It is also the first biologic agent to be approved for use in patients with a gynecologic malignancy.

Areas covered: This review will highlight the evolution of combination chemotherapy for advanced cervical carcinoma, with particular emphasis on the recent ground-breaking research on the anti-angiogenesis therapy.

Expert opinion: Experts believe that the discoveries surrounding angiogenesis inhibitors have changed the standard of practice for women with incurable invasive cervical cancer. We will explore the advantages and disadvantages of anti-angiogenesis therapies. Ultimately, we hope that the research summarized here will one day alter the face of this disease by offering this high-risk population a rare commodity: survivorship.

Keywords: angiogenesis, bevacizumab, chemotherapy, recurrent cervical cancer

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1. Introduction

Cervical cancer is the leading cause of death from gynecologic cancer worldwide with ~ 300,000 deaths per annum and until recently it was once one of the most common causes of cancer death for American women. This year in the United States (USA) ~ 12,360 women will be diagnosed with invasive cervical cancer and 4020 women will die [1]. The morbidity and mortality related to this disease have been reduced significantly by effective public health prevention and screening programs that utilize recent advances in cytology and human papillomavirus (HPV) DNA co-testing as well as vaccination against the high-risk HPV types that cause invasive cervical carcinoma. Fortunately metastatic disease is uncommon at the time of initial diagnosis, but between 15 and 61% of patients will be destined to develop persistent or recurrent disease within the first 2 years of completing primary treatment [2]. For patients with limited metastatic disease or central isolated pelvic recurrences, localized radiation or exenterative surgery may be appropriate. However, chemotherapy is the only treatment option for many patients with distant or inoperable metastatic and persistent disease. The options for effective second-line chemotherapies are very limited; therefore, discovering ways to improve first-line therapy remains paramount. This has led researchers to investigate potential avenues

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Article highlights.

- Reviews the rationale for anti-angiogenesis agents in cervical cancer.
- Evolution of chemotherapy regimen and key historical clinical trials.
- Describes the results and clinical relevance of GOG 240.
- Safety and efficacy of bevacizumab in cervical cancer.
- Suggestions for future studies, the replacement trial for GOG 240 and incorporating other anti-angiogenesis agents.

This box summarizes key points contained in the article.

for targeted biologic therapies in order to compound survival gains beyond conventional platinum-based cytotoxic chemotherapy [3].

There is a large body of evidence to suggest that the development of cervical cancer is largely driven by angiogenesis, which involves the formation of new blood vessels in the body [4]. Angiogenesis is critical to normal tissue growth, embryogenesis and wound healing but it is also fundamental to malignant transformation, invasion and metastasis of cervical tumors [5]. Vascular markings seen colposcopically represent harbors of angiogenesis and are hallmarks of high grade dysplasia and microinvasive disease. In addition, increased intratumoral microvessel density and enhanced expression of the endothelial antigen, CD31, confers a poor prognosis in several translational studies [6-8]. Furthermore, persistent infection with oncogenic strains of HPV activate several pro-angiogenic signaling cascades primarily through up-regulation of the VEGF pathway – a crucial mediator of angiogenesis in invasive cervical cancer [9]. Bevacizumab is a monoclonal antibody that binds extracellularly to VEGF and consequently acts as an angiogenesis inhibitor. VEGF-mediated angiogenesis is so critical to carcinogenesis in cervical cancer that researchers believe that the disruption of this pathway with molecularly targeted agents, such as bevacizumab, may be effective in retarding tumor growth and perhaps even eliminating small volume residual disease by crippling the tumors ability to nourish itself.

Recently, the Gynecologic Oncology Group (GOG), a member of the multi-institutional clinical trial cooperative group NRG Oncology, completed a large Phase III randomized controlled trial to determine if the addition of bevacizumab to one of two cytotoxic chemotherapy doublets could improve survival in women with cervical cancer in the metastatic, persistent, or recurrent and setting. The results of GOG 240 revealed that the combination of chemotherapy plus bevacizumab was associated with an improvement in progression-free survival (PFS) and overall survival (OS) [10]. Bevacizumab was the first targeted agent in a gynecologic cancer to reach the 'gold standard' primary endpoint of improving OS by 3.7 months. The median OS was 17.0 compared to 13.3 months with and without bevacizumab, respectively (hazard ratio [HR] of death = 0.71; 97.6% CI [0.54, 0.94]; p = 0.0035). The design and results of GOG 240 will be discussed in detail in Section 4.0.

The contribution that this study has had on the current and future management of women with cervical carcinoma is extraordinary and practice altering. Bevacizumab has now been officially approved for use in combination with chemotherapy in this setting, not only by the US FDA, but it was also rapidly adopted in England. The purpose of this review is to better understand the rationale and design behind GOG 240 and how the findings of this study have built on the foundations of earlier literature in order to advance the field of gynecologic oncology through the successful integration of anti-angiogenesis therapy for the management of recurrent, persistent and metastatic carcinoma of the cervix.

2. Evolution of first-line chemotherapy combinations

Over several decades cisplatin was widely adopted as the standard single-agent used for late-stage cervical cancer. Subsequently, combination chemotherapy regimens have demonstrated better activity than cisplatin-monotherapy with acceptable toxicity in several randomized controlled trials featuring a variety of chemotherapy doublets [11]. The goal of GOG 204, the predecessor to GOG 240, was to find the best platinum-based cytotoxic regimen for advanced cervical cancer [12]. This was a pivotal study that compared four doublet arms based on earlier studies Phase III trials of cisplatin/paclitaxel (GOG169 [13]) and cisplatin/topotecan (GOG 179 [14]) as well as two other doublets that had shown activity in other Phase II studies (gemcitabine and vinorelbine). Of the four platinum-based doublets cisplatin plus paclitaxel (PC), cisplatin plus gemcitabine (GC), cisplatin plus vinorelbine (VC) and cisplatin plus topotecan (TC) overall response rates (ORR) favored cisplatin plus paclitaxel although the differences were not statistically significant (ORR = 29.1 [PC] vs 25.9% [VC]; 22.3% [GC]; 23.4% [TC]). Similar trends toward superior outcome in the reference arm were detected in median PFS and OS with PC, 5.8 months and 12.9 months respectively. The OS HR comparing PC to each regimen did not significantly vary (VC: HR = 1.15, 95% CI [0.8 – 1.8]; GC: HR = 1.32, 95% CI [0.9 – 1.9]; TC HR = 1.26, 95% CI [0.9 – 1.8]). Consequently, because none of the investigational arms outperformed cisplatin/paclitaxel the favorable trend in response rates, PFS and OS demonstrated in GOG 204 established this doublet as the treatment of choice for future trials [12].

The closure of GOG 204 also led to the suggestion that treatment failures following conventional chemotherapy were likely multifactorial and the answer to longevity for these women is not likely to be found with cytotoxic therapy alone. The attenuated response rates observed in GOG 204 to cisplatin/paclitaxel when compared to earlier trials raised concerns about acquired platinum resistance, especially with the increased prevalence of prior chemoradiation in the GOG

204 population, which was high at 70% compared to only 31% in GOG 169 [15]. Designing the replacement trial for GOG 204 prompted the search for alternative therapies and provided the chance to incorporate novel biologic agents that target molecular pathways that are critical to the development and spread of cervical cancer (i.e., angiogenesis). Inhibition of angiogenesis has had so much success in other solid tumors that combining traditional chemotherapy with bevacizumab presented an ideal opportunity to finally achieve long-term durable responses in advanced cervical malignancies.

3. Phase II evidence for angiogenesis blockade

Bevacizumab was first shown in a small case series to exhibit activity in patients with recurrent cervical carcinoma when combined with cytotoxic chemotherapy and more importantly the safety was established. Six heavily pretreated women with recurrent cervical cancer with multi-site metastatic disease were identified retrospectively and had received bevacizumab in combination with either intravenous 5-fluorouracil (83%) or capecitabine (17%) [2]. Clinical benefit was seen in five of six patients with one complete response, one partial response and two patients with stable disease. There was a median time progression of 4.3 months in the latter four women. The only observed grade 4 toxicity was neutropenic sepsis in a single patient.

The GOG then conducted the first prospective Phase II trial of bevacizumab in cervical cancer. GOG 227C was a multicenter Phase II study of bevacizumab as a single agent that demonstrated the safety and efficacy recurrent cervical cancer [16]. Palliative monotherapy with bevacizumab in 46 patients was associated with objective tumor regression in 11% of patients and 24% had stable disease without progression for at least 6 months. Bevacizumab performed even better than expected in this heavily pretreated patient population–particularly in comparison to other historical control groups [17]. Zighelboim *et al.* demonstrated a modest effect of combining bevacizumab with cisplatin-topotecan in another Phase II trial, but unfortunately the use of this regimen resulted in unacceptable toxicity and this chemotherapy doublet did not warrant further investigation [18].

The success of bevacizumab has inspired several subsequent investigations of other agents with anti-angiogenic activity in advanced and recurrent cervical cancer. Pazopanib is an oral tyrosine kinase inhibitor that targets VEGF receptors (VEGR) as well as platelet-derived growth factor and c-kit. Lapatinib is a dual anti-epidermal growth factor receptor (EGFR) and anti-HER2/neu. These two drugs were studied in a Phase II trial that compared pazopanib (800 mg/day) or lapatinib (1500 mg/day) monotherapy versus combination therapy with both agents [19]. However, the combination treatment arm was later closed for futility and unacceptable toxicity after the first interim-analysis [19]. This head-to-head comparison demonstrated the superiority of anti-VEGF over another targeted therapy. Pazopanib improved PFS compared to lapatinib (4.5 vs 4.3 months; HR 0.66: 90% CI [0.48, 0.91]; $p < 0.013$), but did not reach a statistically significant OS advantage over lapatinib (12.4 vs 11 months; HR 0.67: 90% CI [0.46, 0.99]; p 0.045). This study provided additional support for pursuing anti-VEGF treatments in cervical cancer further, but unfortunately EGFR-based therapies, such as lapatinib, cetuximab and erlotinib and other oral tyrosine kinase inhibitors such as sunitinib, have resulted in several negative clinical trials.

Most recently, the annual meeting of the European Society for Medical Oncology (ESMO) featured a report on the newest Phase II study of another angiogenesis inhibitor in late-stage cervical cancer. Cediranib is an oral tyrosine kinase inhibitor that was used in combination with a conventional chemotherapy in patients with metastatic or recurrent cervical cancer. Sixty-nine patients were randomized to carboplatin (AUC 5) and paclitaxel (175 mg/m^2) every 21 days plus either cediranib 20 mg or placebo orally once per day [20]. The authors demonstrated that combining chemotherapy plus cediranib was associated with a statistically significant improvement in median PFS compared to placebo (35 vs 30 weeks; HR 0.61; 80% CI [0.41, 0.89]: $p = 0.046$). The measurement of median change in VEGF inhibition levels in the blood of subjects receiving cediranib was also significantly higher. The adverse events rates reported appeared to be on par with other similar biologic agents. Overall, cediranib appears to be safe and active in advanced cervical cancer [20]. The study was not intended or powered to assess OS but further investigation with a larger Phase III trial is warranted. **Table 1** provides a summary of three promising prospective Phase II clinical trials featuring VEGF-based therapies in advanced or recurrent cervical cancer. Bevacizumab was the only targeted agent that was deemed worthy of further investigation when the study design for GOG 240 was conceived in 2009.

4. Combination chemotherapy plus bevacizumab

As previously mentioned, GOG 240 was the first Phase III randomized controlled trial of anti-angiogenesis therapy in cervical cancer [10]. The design of GOG 240 aimed to address two critical issues in this setting of recurrent, metastatic or persistent cervical cancer—the effectiveness of anti-angiogenesis therapy by adding bevacizumab to conventional chemotherapy with cisplatin/paclitaxel was first, stemming from the results of GOG 169 and 204 as mentioned above. The second aim was to determine if the non-platinum-based chemotherapy doublet topotecan/paclitaxel would be effective in circumventing platinum resistance based on the hypothesis generating results of GOG 179. Therefore a 2×2 factorial design was utilized to answer these two questions. In this study, 452 participants were randomized to one of four regimens: cisplatin (50 mg/m^2) plus paclitaxel (135 or

Table 1. Phase II studies of VEGF-based therapies in metastatic or recurrent cervical malignancies.

Study	Design	Response rates	Median PFS	Median OS	Toxicity
GOG 227C [16]	Bevacizumab monotherapy 15 mg/kg q 21 d (n = 46)	PR = 10.9% PFS > 6 mo = 23.9%	3.4 mo (2.5 – 4.5)	7.3 mo (6.1 – 10.4)	Common G3/4 AEs: HTN (7), VTE (5), and GI (4); Grade 5 infection (1)
VEG105281 [19]	Pazopanib monotherapy 800 mg once daily (arm P; n = 74)	Arm P = 9%	18.1 weeks (4.5 mo)	50.7 weeks (12.7 mo)	Common AEs (%): Diarrhea (54 vs 58; G3 = 11 vs 13);
	Lapatinib monotherapy 1500 mg once daily (arm L; n = 78)	Arm L = 5%	17.1 weeks (4.3 mo)	39.1 weeks (9.8 mo)	Nausea (36 vs 33), HTN (30 vs 3), Anorexia (28 vs 32), any G4 (12 vs 9)
	Combination therapy (discontinued for futility and unacceptable toxicity)		HR = 0.66 (0.48 – 0.91)	HR = 0.67 (0.46 – 0.99)	Arm P versus arm L, respectively
CIRCCa [20]	Carboplatin/paclitaxel + cediranib 20 mg daily (arm C; n = 34)	Arm C = 66%	35 weeks (8.8 mo)	59 weeks (14.8 mo)	G2-4 AEs (%): Diarrhea (50 vs 18)
	Carboplatin/paclitaxel + placebo (arm Z; n = 35)	Arm Z = 42%	30 weeks (7.5 mo) HR = 0.61 (0.41 – 0.89)	63 weeks (15.8 mo) HR = 0.93 (0.64 – 1.36)	HTN (34 vs 12) Any grade (19 vs 9) Arm C versus arm Z, respectively

AE: Adverse event; CIRRCa: Cediranib for advanced cervical cancer; d: Days; G: Grade; GI: Gastrointestinal; GOG: Gynecologic Oncology Group; HR: Hazard ratio; HTN: Hypertension; mo: Months; n: Number of subjects; PFS: Progression free survival; PR: Partial response; VTE: Venous thromboembolism.

175 mg/m^2) with or without bevacizumab (15 mg/kg) or topotecan (0.75 mg/m^2 on days 1 – 3) plus paclitaxel (135 or 175 mg/m^2) with or without bevacizumab (15 mg/kg) with cycles repeated every 21 days until disease progression or unacceptable toxicity. The results confirmed that the topotecan/paclitaxel chemotherapy doublet was not inferior to cisplatin/paclitaxel (median OS 12.5 vs 15 months; HR 1.20; 99% CI [0.82, 1.76]; p = 0.88) [10]. The final analysis did reveal superior outcomes when bevacizumab was added to either chemotherapy regimen leading to an HR of death of 0.71 (97.6%, CI [0.54, 0.94]; p = 0.0035). The median OS for patients who received cisplatin plus paclitaxel was 14.3 months, significantly less than the 17.5 months for those who received cisplatin, paclitaxel, and bevacizumab (p = 0.0348). In parallel, the median OS for those who received topotecan plus paclitaxel was lower compared to when bevacizumab was added to that regimen, 12.7 months compared to 16.2 months respectively (p = 0.0896). GOG 240 is a landmark trial because it is the first time that a targeted agent has reached its primary endpoint of improving OS in a gynecologic malignancy (**Figure 1**).

The publication of the final results of GOG 240 revealed bevacizumab to be a 'triple-threat,' meaning that in addition to achieving the gold standard for clinical trials—prolonged OS —bevacizumab also associated with improved PFS (HR 0.67; 95% CI [0.54, 0.82]; p = 0.0002) and higher overall response rates (48 vs 36% (p = 0.008). Even patients with target lesions contained within a previously irradiated field experienced sustained clinical benefit from bevacizumab, which was a unique finding and a departure from previous studies that had suggested that these lesions are chemoresistant.

4.1 Cisplatin-paclitaxel-bevacizumab

Bevacizumab has well-documented and generally manageable side effects. The adverse events observed in GOG 240 revealed a relative low incidence of serious adverse events (< 10%) related to bevacizumab containing regimens and no new toxicities were reported but these VEGF-related side effects can occur with any regimen containing bevacizumab. The National Comprehensive Cancer Network (NCCN) suggests that the optimal choice of regimen should be individualized based on previous treatments, toxicity and cost. For example, the clinical indication for the use of paclitaxel 24 h prior to cisplatin infusion is to reduce neurotoxicity and is ideal in the patient who has received prior extended field radiation or the elderly frail previously irradiated patient and any others whose bone marrow reserves are similarly compromised. Health-related quality of life measures were equivalent between all groups in GOG 240 [10].

4.2 Carboplatin-paclitaxel-bevacizumab

The combination of carboplatin and paclitaxel has also been approved for the use of first-line therapy in advanced cervical cancer. However, the addition of bevacizumab to this regimen has not been previously tested in this setting and is not approved by the FDA. Many practitioners have extrapolated from the data presented by GOG 240 that there may be a

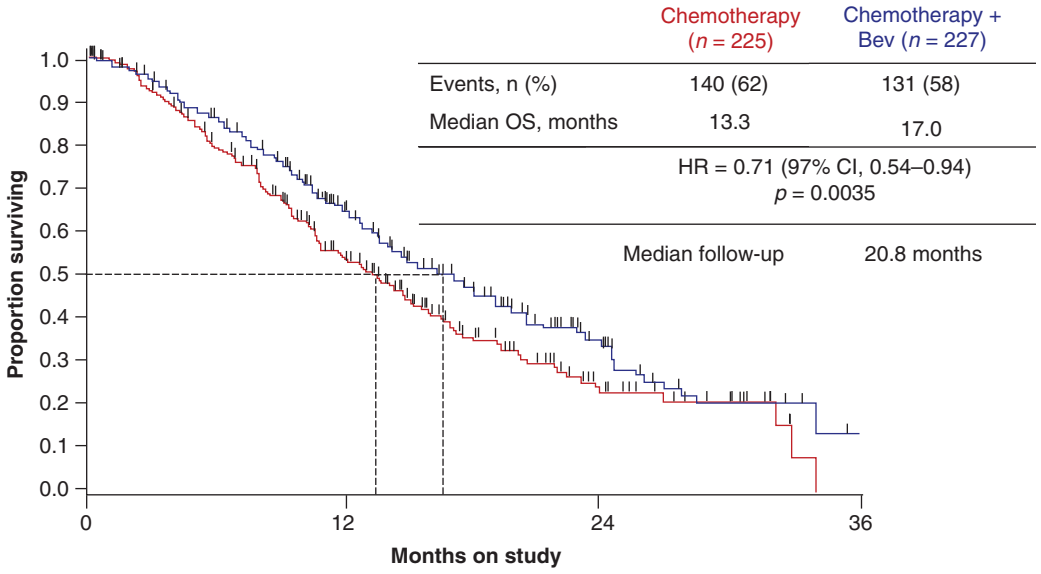

Figure 1. Phase III study of bevacziumab for advanced cervival cancer: GOG 240 overall survival curves.
Adapted with permission from [10]. © 2014 Massachusetts Medical Society.
Bev: Bevacizumab; HR: Hazard ratio; n: Number; OS: Overall survival.

similar benefit of including bevacizumab with this commonly used combination, even though they have not been studied together specifically [11]. Previous clinical research has demonstrated that oncologic outcomes appear to be equivalent between carboplatin/paclitaxel and cisplatin/paclitaxel doublets in this population (Category 2A according to NCCN) [21,22].

Recently, the Japanese Clinical Oncology Group (JCOG) conducted the only confirmatory trial to validate the safety and efficacy of substituting carboplatin for cisplatin in combination with paclitaxel for a similar patient population to GOG 240. In this study researchers administer paclitaxel 175 mg/m^2 body surface area (BSA) infused over 3 h followed by carboplatin at an AUC of 5 mg/ml/min over 1 h on Day 1 repeated every 21 days [23]. Kitagawa *et al.* reported that the median PFS and OS were 5.3 and 9.6 months respectively, which are on par with previous doublets. Higher response rates were seen than had previously been reported at 59%. Interestingly, the authors also reported ORR stratified by previous platinum therapy. No complete responses were observed in patients with a platinum-free interval of < 6 months. The toxicity profile of carboplatin/paclitaxel was predictable and not unexpected, most adverse events grades 3 or 4 were hematologic, and overall 79% experienced neutropenia, anemia in 46% but only 15% thrombocytopenia. The authors concluded that carboplatin/paclitaxel appeared to have similar effectiveness to previous publication on cisplatin – doublets and warranted further investigation. Therefore, a Phase III study was performed to compare the above-mentioned carboplatin/paclitaxel arm to reference arm with paclitaxel (135 mg/m^2 BSA over 24 h Day 1) and cisplatin (50 mg/m^2 BSA over 2 h on Day 2) and cycles were repeated every 21 days for a maximum of six cycles. JCOG 0505 confirmed that the carboplatin plus paclitaxel chemotherapy doublet was not inferior to cisplatin plus paclitaxel (median OS 17.5 vs 18.3 months, respectively; HR = 0.99, 90% CI [0.79, 1.25]; noninferiority p = 0.032). Carboplatin/paclitaxel showed a more favorable toxicity profile in terms of grade 3 – 4 neutropenia and nephrotoxicity but thrombocytopenia was more common in this group (23.3% than the control arm (3.3%) [24].

Overall, carboplatin/paclitaxel appears to be an attractive and valid alternative to cisplatin/paclitaxel but its use with bevacizumab was not specifically tested in GOG 240. Carboplatin offers the additional benefit of convenient administration compared to cisplatin when combined with paclitaxel and there is precedent for the substitution of cisplatin for the less toxic and better tolerated carboplatin in ovarian cancer. It is a much more attractive regimen in the real-world practice because it is well tolerated and can be infused over a single day as an outpatient. Future confirmatory Phase II trials are justified to establish the safety of carboplatin/paclitaxel plus bevacizumab in advanced cervical cancer and are planned to be conducted in Europe shortly.

4.3 Topotecan-paclitaxel-bevacizumab

In GOG 240, topotecan and paclitaxel with or without bevacizumab was associated with a higher risk of progression compared to cisplatin/paclitaxel (median PFS 5.7 vs 7.6 months: HR 1.39; 95% CI [1.09, 1.77]) but no impact was observed

in OS (12.5 vs 15 months; HR = 1.2, 95% CI [0.82, 1.76]). However, this regimen may be beneficial in patients with a history of platinum hypersensitivity or renal insufficiency. Conversely, cisplatin/topotecan or cisplatin/gemcitabine (GOG 204 regimens) may be reasonable NCCN-listed alternatives for patients who are not candidates for taxanes but these have also not been studied in combination with bevacizumab.

4.4 Side effects of cytotoxic chemotherapy and angiogenesis inhibitors

One of the most common treatment-related toxicities observed in GOG 240 with the incorporation of bevacizumab compared to chemotherapy alone included hypertension (25 vs 2%) [10]. The management of this particular toxicity can be better informed by the experience in other solid tumors that are commonly treated with bevacizumab. From the colorectal literature, there are evidence-based recommendations for the management of VEGF-induced hypertension and also take into account aggressive blood pressures control without compromising the anti-tumor effects [25]. Bevacizumab inhibits the dose-dependent vasodilatory and hypotensive effects that VEGF normally has on endothelial cells.

In most cases, blood pressure can be managed with oral antihypertensives in accordance with published guidelines. The preferred first-line agents are ace-inhibitors, thiazide diuretics, angiotensis receptor blockers, β-blockers, or calcium channel blockers. There are several published algorithms that recommend individualize step-wise approaches for patients currently on medication or with various medical co-morbidities. Loop diuretics and other nitrate-based therapies that affect nitrous oxide production should be avoided as they may interfere with the efficacy of VEGF inhibition. Fortunately, hypertension is often successfully managed with medication and does not require cessation of bevacizumab but it should be withheld in the presence of uncontrolled hypertension or hypertensive crisis. Periodic monitor for proteinuria is recommended and referral to nephrology should be made for patients with signs of nephroxicity. Fortunately, renal dysfunction is not usually associated with proteinuria seen in patients taking bevacziumab and even nephrotic range proteinuria resolves after the drug is stopped. The mechanism is not well understood but it is thought that glomerular endothelial repair may require VEGF [26]. There appears to be a correlation between hypertension, proteinuria, and efficacy of antiangiogenesis therapy in lung, breast, renal and colon cancer.

Gastrointestinal (GI) perforations were reported in 2.3% of patients in GOG 240 receiving bevacizumab, all of whom had prior radiotherapy. Grade 2 or higher fistula occurred in 8.6% of patients treated with bevacizumab compared to only 1% of those treated with chemotherapy alone. Patients need to be appropriately counseled on these risks and managed accordingly by balancing the risks and benefits of any treatment regimen. Grade 3+ venous thromboembolic events were reported in 8.2 and 1.8% with chemotherapy with or without bevacizumab respectively. Venous thromboembolism is also not uncommon in the gynecologic oncology population. Patients who were diagnosed during clinical trials were taken off bevacizumab but in clinical practice once a patient is stable on anticoagulation it may be appropriate to resume bevacizumab based on the published literature in colon cancer.

Patients on bevacizumab should also be monitored for bleeding but serious life-threatening bleeding is rare. Clinical relevant (grade > 3) bleeding was uncommon, occurring in only 12 patients and was limited to the GI and genitourinary tract. There was no significant CNS or pulmonary bleeding encountered. Fatal adverse events occurred in eight patients in all groups 1.8% received chemotherapy alone and 1.8% receiving chemotherapy plus bevacizumab. Almost all of the fatal adverse events that occurred during treatment on GOG 240 were related to sepsis and febrile neutropenia. Grade 4 neutropenia was observed in 35% of patients receiving chemotherapy plus bevacizumab versus 26% in chemotherapy alone arm. Although the degree of neutropenia seen with bevacizumab may be influenced by the chemotherapy backbone certainly the issue of monitoring hematologic toxicity becomes relevant during integration with cytotoxic regimens.

5. Conclusion

In summary, the data presented describe the evolution of three distinct regimens for patients with metastatic, persistent or recurrent cervical cancer: cisplatin, carboplatin or topotecan combined with paclitaxel plus bevacizumab. In a large randomized controlled trial (GOG 240) bevacizumab effectively improved OS, PFS and response rates when combined with standard cytotoxic chemotherapy regimens and was associated with a reasonable toxicity profile consistent with previous reports with this drug in other malignancies. The excitement surrounding the final results of GOG 240 will promote the continued study of other classes of anti-angiogenesis inhibitors in advanced carcinomas of the cervix. In the pursuit of a cure for women affected by invasive cervical cancer, the observed benefits associated with anti-angiogenesis agents will allow previously incurable patients to live longer, increasing the demand for second- and third-line therapies, and allowing these patients to participate in future investigations with novel agents and cutting-edge treatment paradigms moving forward. However, we have also demonstrated that efficacy is not always paramount. Particularly when therapies are not curative, outside of a clinical trial real world practice must take into account the net benefit of each treatment for individual patients. Clinicians must always endeavor to balance the therapeutic index between toxicity, cost, patient quality of life and effectiveness for all women suffering from gynecologic malignancies.

6. Expert opinion

In the face of the success we have seen with the addition of bevacizumab to standard cytotoxic chemotherapy for late-stage cervical cancer as practitioners we are inevitably drawn to the bottom line—how and why should these results be incorporated into my standard practice?

The proof of concept for the use of systemic angiogenesis therapy for advanced cervical cancer was not realized overnight. It required dedicated researchers several decades to move the science forward from the bench to the bedside. However, the successful integration of bevacizumab with chemotherapy has opened an important therapeutic window from which we will witness the beginning of the end of advanced cervical cancer.

The results of GOG 240 have made medical headline news because it was the first clinical trial to show an OS advantage with a targeted agent in a gynecologic malignancy. We will briefly highlight noteworthy events in the timeline thus far. In June 2013, the National Cancer Institute issued a practice changing press release after the initial results from GOG 240 were presented at the American Society of Clinical Oncology (ASCO) annual meeting in June 2013 in support of bevacizumab for late-stage cervical cancer [27]. The next month the NCCN updated their recommendations for the treatment of cervical cancer to include the winning GOG 240 practice guidelines for recurrent and metastatic disease (category 1; updated from category 2008/2014) [28]. Following publication of the manuscript in the New England Journal of Medicine, pursuing regulatory milestones was a crucial step in enhancing the care of women with invasive cervical cancer because it is often required for insurance coverage for women [29]. The United Kingdom's Cancer Drugs Fund was the first to approve bevacizumab in England. Additionally, under the FDA's priority review program bevacizumab became the first biologic agent approved for use in patient with late-stage cervical within 6 months of publication emphasizing the commitment the agency has made to prioritizing the evaluation of cutting edge treatments for life-threatening conditions, which benefits the highest risk patients [30]. The trend of expeditious acceptance continued in some countries in Latin America, including Brazil and Ecuador where the incidence of the disease is relatively high. The acceptance of anti-angiogenesis therapy based on scientific rationale, clinical evidence-based medicine, and regulatory bodies reflects the importance of successfully addressing a historically unfulfilled clinical need in advanced cervical cancer. The data justify revising the standard practice for women diagnosed with recurrent/persistent and metastatic cervical cancer.

Regulatory approval is important but cost can also be a major barrier to universal access to new treatments. Following the FDA-approval of the chemotherapy plus bevacizumab combinations featured in GOG 240 became widely available in the USA because this regulatory designation is necessary for coverage by Medicare and Medicaid. Regulatory approval is a crucial step in enhancing the care of women with this disease who need our support the most but we also need to find a way to make it accessible to resource poor countries that carry a disproportionately higher burden of advanced cervical cancer. However, in places with limited resources primary prevention and effective screening programs probably will and should remain the top priorities for large-scale public health initiatives. Cost-effective studies are needed to better understand the relationship between prolonged survival in countries where cervical cancer is a leading cause of cancer-related death in women and the societal burden associated with making expensive novel therapies available to those have the greatest need. If bevacizumab is not accessible to resource-poor and developing countries, hundreds of thousands of women will be denied the longevity that women who can afford the treatment will gain from it and this will only contribute to increasing healthcare disparities worldwide, which is obviously very concerning and unethical [29].

On the other hand, what are the risks associated with angiogenesis blockade? Adverse events associated with bevacizumab are very serious. Fortunately, the rate of serious adverse events in GOG 240 was < 10% [10]. Patient selection and the strict confines of a clinical trial may be responsible for this low rate but thankfully none of the toxicities related to bevacizumab were life-threatening. However, whereas it is important to ensure that all women who may benefit from anti-angiogenesis drugs are afforded the opportunity all cancer care providers need education to ensure appropriate patient selection and careful monitoring for adverse events as described earlier (Section 4.4). Expeditious management of toxicity and adherence to the strict eligibility criteria of GOG 240 will optimize efficacy without compromising patient safety. In clinical practice, gynecologic oncologists have the opportunity to use their clinical judgment in counseling patients about the risk-benefit ratio of adding bevacizumab to standard chemotherapy on an individual patient basis. For example, hypertension, proteinuria, bleeding, and fistula represent more common risks associated with bevacizumab that do not occur in isolation; detriments to a particular patient's health are often weighed against the oncologic benefits (response) individual patients are receiving from the drug. The balance achieved through the art of medicine is not as black and white as clinical trial protocols and for well-informed patients and healthcare providers clinical decision making is a shared responsibility.

We should emphasize that in an incurable situation perhaps one of the most important implications of this work is time. Currently, the intent of chemotherapy in this setting is palliative but by gaining nearly 4 months of survivorship has untold benefits to those patients without compromising quality of life. The definition of clinically meaningful advances in survival is in the eye of the beholder. From the standpoint of drug development and efficacy in oncology, OS advantage is

the gold standard and an OS benefit of 3.7 months in GOG 240 meets an important benchmark in the field. This represents valuable time that may allow patients to receive other promising novel therapies including other types of angiogenesis treatment or immunotherapy to take advantage of what the forefront of translational research has to offer. Additionally in GOG 240, validation of the Moore criteria for identification of patients with poor prognostic factors not likely to respond to cisplatin-based regimens demonstrated that the highest risk patients benefit the most from angiogenesis inhibition with bevacizumab [31,32].

Unfortunately, despite the proven efficacy of anti-angiogenesis therapy in cervical cancer the majority of women diagnosed with locally advanced or metastatic cervical cancer will experience disease recurrence. To move anti-angiogenesis therapy forward in advanced cervical cancer the Phase III clinical trials that will replace GOG 240 should include multifactorial study designs combining conventional chemotherapy backbones (triplet or quadruplet therapies) with known active biologic agents (e.g., carboplatin or cisplatin/paclitaxel/bevacizumab with or without cediranib and/or pazopanib). Researchers are also working on identifying biomarkers that may be able to predict which patients will benefit the most from angiogenesis blockade. Furthermore, if we continue to extend the survival of these patients with anti-angiogenesis therapy there will be an increasing demand for novel therapies in the future. Other molecularly targeted agents and methods of immunotherapy are being developed to exploit other relevant signal transductions pathways and the host immune response that will lead to the next major advance in invasive cervical cancer.

Declaration of interest

KS Tewari has been a consultant for Genetech/Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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