Systematic Review and Network Meta-Analysis of Bevacizumab Plus First-Line Topotecan-Paclitaxel or Cisplatin-Paclitaxel Versus Non–Bevacizumab-Containing Therapies in Persistent, Recurrent, or Metastatic Cervical Cancer

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Objective: Despite advances in cervical cancer prevention and diagnosis, outcomes for patients given a diagnosis of advanced and recurrent disease are poor. In the GOG240 trial, the addition of bevacizumab to paclitaxel-topotecan or paclitaxel-cisplatin has been shown to prolong survival compared with paclitaxel-topotecan or paclitaxel-cisplatin in patients with persistent, recurrent, or metastatic disease. However, standards of care vary between regions and countries. The purpose of this systematic review and network meta-analysis was to enable a comparison between bevacizumab + chemotherapy with multiple monotherapy or combination chemotherapy regimens in the treatment for women with advanced, recurrent, or persistent cervical cancer.

Methods/Materials: A systematic literature review was conducted to identify randomized or nonrandomized controlled trials of patients with recurrent, persistent, or metastatic cervical cancer published in English from 1999 to 2015. A feasibility study was performed to assess the heterogeneity of the trials, and a network meta-analysis was conducted. Fixed- and random-effects models were fitted to calculate the hazard ratio for overall survival (OS) for all pairwise comparisons and ranking of all interventions.

Results: Twenty-three studies (19 trials) met inclusion criteria and were included in the review. Sample sizes ranged from 69 to 452, and median patient age ranged from 45 to 53 years. There was a trend toward prolonged OS with cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab compared with all non–bevacizumab-containing therapies. Cisplatin-paclitaxel-bevacizumab had the highest probability of being the most efficacious compared with all regimens (68.1%), and cisplatin monotherapy had the lowest (0%).

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Conclusions: The results of this network meta-analysis show that bevacizumab in combination with paclitaxel-topotecan or paclitaxel-cisplatin is likely to prolong OS over other non–bevacizumab-containing chemotherapies (eg, paclitaxel-carboplatin), which were not included in the GOG240 trial. In patients with advanced, persistent, and recurrent cervical cancer, cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab showed the highest efficacy in all regimens investigated in this analysis.

Key Words: Cervical cancer, Angiogenesis inhibitors, Network meta-analysis

Worldwide, cervical cancer represents the fourth most common cancer in women, behind lung, breast, and colorectal cancer.[1] The World Health Organization estimates that 528,000 new cervical cancer cases were diagnosed in 2012.[2] Of these, approximately 85% occur in less developed regions, where cervical cancer is the second most common cancer in women[3] and accounts for nearly 12% of all female cancers.[4] The global burden of cervical cancer results primarily from difficulty implementing cytology-based screening programs due to economic, infrastructural, social, religious, cultural, and political barriers.[5] Mortality rates vary considerably across global regions based on economic development, with rates ranging from less than 2 per 100,000 (Western Asia, Western Europe, Australia/New Zealand) to 27.6 per 100,000 (Eastern Africa).[4]

Despite advances in cervical cancer prevention and diagnosis, outcomes for patients given a diagnosis of advanced and recurrent disease are poor. In the United States, the 5-year survival rate for locally advanced cervical cancer is 57%; for International Federation of Gynecology and Obstetrics stage IV disease, 16% or less[6]; and for recurrent disease, less than 5%.[7] In the setting of metastatic or recurrent disease, treatment is palliative, aiming to prolong survival and maintain or improve quality of life. Various combinations of cisplatin, paclitaxel, bevacizumab, carboplatin, topotecan, and gemcitabine are recommended as first-line therapies.[8] The European Society for Medical Oncology and National Institute for Health and Care Excellence guidelines highlight cisplatin-topotecan combination therapy as a favorable treatment option for women with recurrent or stage IVB cervical cancer, whereas paclitaxel-carboplatin and other chemotherapy combinations are standards of care in some countries.[9,10] A recent systematic literature review found carboplatin-paclitaxel to be equally effective and less toxic than cisplatin-paclitaxel as the first-line therapy for metastatic cervical cancer.[11] However, despite advances in standard chemotherapy, overall survival (OS) times have remained short, indicating the chemoresistant nature of cervical cancer relative to other gynecologic malignancies.[12]

Targeting angiogenesis has emerged as an important therapeutic strategy in the management of advanced cervical cancer. Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor, the central mediator of tumor angiogenesis.[13] In the first phase III randomized trial of bevacizumab for advanced cervical cancer (GOG240), the addition of bevacizumab to paclitaxel-topotecan or paclitaxel-cisplatin significantly prolonged survival compared with paclitaxel-topotecan or paclitaxel-cisplatin in patients with persistent, recurrent, or metastatic disease.[12] Bevacizumab is approved in the United States, the European Union, and other countries (eg, Brazil) for the treatment of cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.[14]

Given that the standards of care in some countries are different from the comparator arms in the GOG240 trial, there is an interest for physicians and payers to evaluate the effect of bevacizumab in combination with paclitaxel-topotecan or paclitaxel-cisplatin compared with the standard of care in their countries or regions. In the absence of head-to-head comparison, an indirect estimate for the relative effect could be obtained via a common comparator, as suggested by Bucher et al.[15] Network meta-analyses (NMAs) combine evidence from both direct and indirect comparisons. An NMA provides estimates of relative effect of all pairwise comparisons and builds a hierarchy of all available treatments.[16] Furthermore, the outputs of NMA-based relative effect can be used in a full economic appraisal of competing interventions to assess cost-effectiveness. We therefore performed this systematic review and NMA to enable comparisons among all available therapies in the treatment for women with advanced, recurrent, or persistent cervical cancer.

MATERIALS AND METHODS

Systematic Review

A systematic review of the literature, using PubMed/MEDLINE, The Cochrane Library, and EMBASE, was conducted to identify relevant studies meeting prespecified inclusion criteria. Using the PICOS framework,[17] a clinical trials search strategy was designed to identify randomized controlled trials (RCTs) or controlled nonrandomized trials involving patients with recurrent, persistent, or metastatic cervical cancer and published in English from 1999 to 2014. The year 1999 was chosen because the standard of care in this disease area changed in this year. Trials conducted after 1999 are considered more homogeneous to the GOG240 study. Controlled nonrandomized trials were included to provide a comprehensive representation of all available treatments in this disease area. The quantitative analyses will be performed

using RCTs only. In the event of an insufficient number of RCTs, controlled nonrandomized trials could be used to fill the potential gaps. Standard operational definitions of "recurrent," "persistent," "refractory," and "metastatic cervical cancer" were used. The complete search strategies, including key words and search terms, are provided in tabular format in Supplemental Digital Content, http://links.lww.com/IGC/A480. The search for clinical trials was implemented first in PubMed/MEDLINE and then later translated for EMBASE and the Cochrane Library because of differences in indexing terminology. In addition, searches were conducted in the 3 databases for systematic reviews regarding advanced, recurrent, persistent, or metastatic cervical cancer published between 2011 and 2014 to identify clinical trials that might have been missed in the clinical trials searches. Conference Web site and article bibliographies were also searched. Finally, a search for clinical trials registered between 2011 and 2014 was performed using the following databases: ClinicalTrials.gov, the International Clinical Trial Registry Platform, European Union Clinical Trials Register, and Klinische Prüfungen PharmNet.Bund (see Supplemental Digital Content, http://links.lww.com/IGC/A480). A subsequent update of the systematic review was conducted in May 2015.

Article Screening and Data Abstraction

In a 2-step process, 2 reviewers independently determined whether the studies met inclusion criteria. Discrepancies were resolved by consensus, and a third reviewer adjudicated unresolved disputes. Information that was abstracted from the final set of articles included study design and methodology, patient characteristics, disease status and tumor stage, treatments, outcome analyses, and efficacy outcomes. Two independent reviewers assessed the final set of articles for study design quality, and discrepancies were resolved by consensus. The NICE and CONSORT checklists were used to assess the quality of RCTs.[18,19]

Feasibility Assessment for NMA

A feasibility assessment was performed to assess the heterogeneity of the clinical trials identified by the systematic review and to determine the extent to which the study results could be combined into an NMA. This assessment was based on the inclusion/exclusion criteria used in the literature review. An article was excluded if it did not report OS as an efficacy outcome and/or if it only investigated treatments that were not evaluated in other articles. Trials that included the same treatment arm were compared with regard to patient characteristics, previous platinum exposure, disease stage, inclusion/exclusion criteria, and treatment regimen. The data from the studies meeting these more stringent NMA inclusion criteria were analyzed with respect to the therapeutic efficacy of different drug combinations for prolonging OS, allowing construction of the OS-specific network.

Statistics

The NMA analysis was conducted within a Bayesian framework using WinBUGS code[20] for the fixed- and random-effects models. A natural logarithm of the hazard ratio (lnHR) was used to estimate within-trial treatment differences in OS.[20] Estimates of the mean and standard error for the lnHR from each trial, as well as the variance of the reference treatment, were in accordance with Woods et al.[21] The natural logarithm of the HR was obtained from the midpoint between the lower and upper limits of the 95% confidence interval (CI). A natural logarithm of the HR less than 0 was indicative of shorter mean OS times in the comparator arm; lnHR of greater than 0 was identified as a longer OS. Overall survival was selected for the NMA because it is the most relevant end point for this disease.

The NMAs were fitted by Markov chain Monte Carlo techniques and implemented in WinBUGS.[22] The first 50,000 iterations were discarded as a burn-in period to lessen the influence of the starting values and wait for the chains to converge to the target distribution. Models were run using 3 chains. A thinning of 10 was applied to reduce the autocorrelation of the series. The chains were run long enough to collect 50,000 values for each chain.

An informative prior for the lnHR was applied in the random-effects model because of the fact that each comparison is informed by only 1 trial. It was assumed that the prior distribution for the lnHR followed a normal distribution with a mean (SD) of 0 (0.7) (corresponding to HRs between 0.25 and 3.94). As the range of HRs corresponding to the standard deviations were large enough and cover the HRs that were reported in all of the publications for this analysis, the informative priors are considered reasonable. An adjustment for the correlation in multiarm trials was also incorporated by following the approach of Dias et al.[20]

The NMA results were reported as median posterior HRs with corresponding 95% credible intervals (CrIs). Furthermore, posterior probabilities of being each possible ranking (first best, second best, etc) were obtained as the proportion of all iterations.

RESULTS

Systematic Review and Included Studies

Twenty-three articles (19 trials) met inclusion criteria and were included in the review. Seven eligible systematic reviews encompassing 145 clinical trials were identified; all of these had already been included in the literature search. No additional publications of unique clinical trials were identified by the registry searches.

The PRISMA flow diagram in Figure 1 provides details regarding screening, eligibility assessment, and reasons for article exclusions for the systematic review. These further exclusions were necessary for preparation of the NMA. Three articles were excluded because they reported results for health-related quality of life only.[23–25] Eight additional articles were excluded because the treatment regimens could not be linked to other studies in the network.[26–33] The remaining 12 articles,[12,34–44] representing 11 different trials, were evaluated for heterogeneity, including potential differences in definitions and staging. Trials including the following treatment regimens were compared for heterogeneity: cisplatin,[34,38,39,41,44] cisplatin-paclitaxel,[12,36,37,40,41] cisplatin-topotecan,[35,38–40,43] paclitaxel-topotecan,[12,43] and paclitaxel-carboplatin.[36,42]
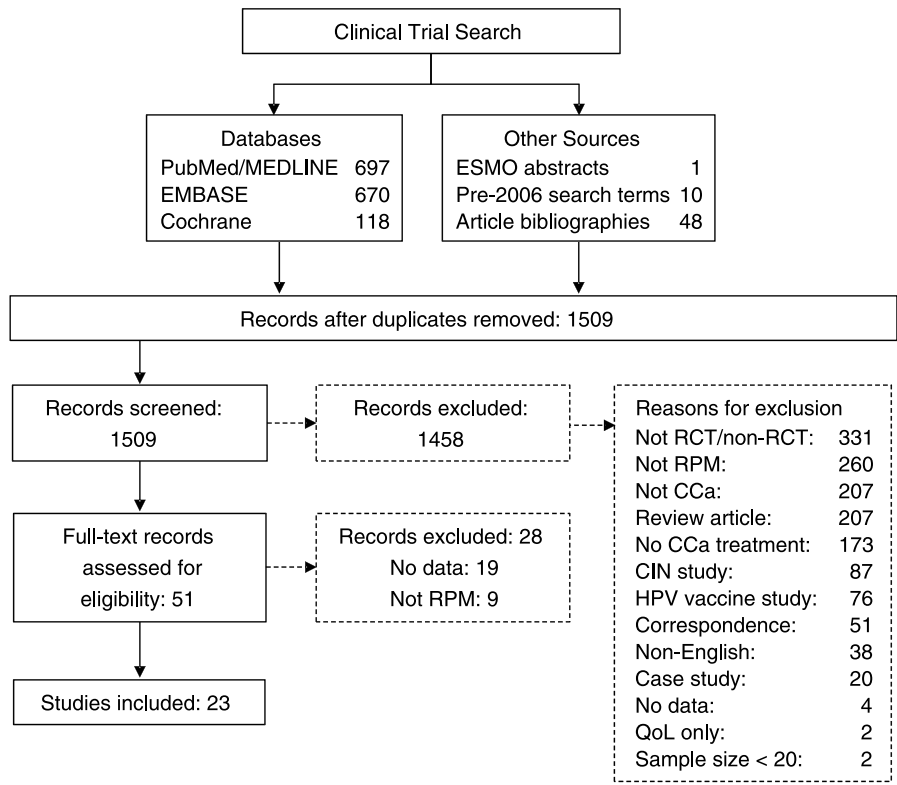
FIGURE 1. PRISMA flow diagram: clinical trials.

Of these 11 trials, only those that reported HRs or reported data that could be used to estimate HRs for OS were included in the NMA. Under these criteria, the OS-specific network (Fig. 2) included 11 treatment combinations from 5 trials published in 6 articles. The 11 treatment combinations included 7 doublets, 3 triplets, and 1 quadruplet regimen. Sample sizes ranged from 69 to 452,[12,42] and median patient age ranged from 45 to 53 years.[12,36,40] Tewari et al[12] (GOG240) enrolled the smallest percentages of platinum-naive patients (25%); Long et al[38,39] (GOG179) and Kitagawa et al[36] (JCOG0505) enrolled the largest percentages of platinum-naive patients (42%–53%). Most study subjects (68%–81%) had recurrent disease. Table 1 summarizes the key features of each trial, including treatment arms and regimens (dose and
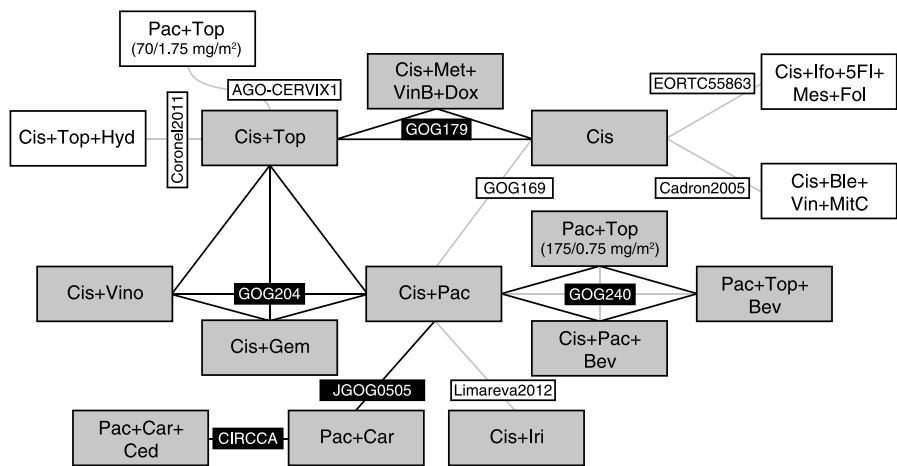

FIGURE 2. Overall survival–specific network. Overall survival–specific network includes only those trials that reported HRs or provided data from which HRs could be estimated. Treatments/trials from the general network subsequently removed from the OS-specific network are shown in the gray boxes.

TABLE 1. Summary of study characteristics for articles included in the OS NMA

Citation	Trial	N	Treatment	Dose	Duration (Cycle)	Patient Age, y	Previous Platinum Therapy	Stage
Long et al,[38] 2005*	GOG179	146	Ci	Ci 50 mg/m²	6 × 3 wk	27–48–76	Naive, 64; experienced, 82	IVB, 17; P, 11; R, 118
		147	Ci + T	Ci 50 mg/m², T 0.75 mg/m²	6 × 3 wk	22–46–84	Naive, 62 Experienced, 85	IVB, 18; P, 17; R, 112
Long et al,[39] 2006*		60	Ci	Ci 50 mg/m²	6 × 3 wk	≤40, 13 (21%); 41–50, 17 (28%); 51–60, 19 (32%); >61, 11 (18%)	Naive, 31; experienced, 29	IVB, 10; P, 8; R, 42
		63	Ci + T	Ci 50 mg/m², T 0.75 mg/m²	6 × 3 wk	≤40, 15 (24%); 41–50, 26 (41%); 51–60, 12 (19%); >61, 10 (16%)	Naive, 29; experienced, 34	IVB, 7; P, 10; R, 46
		63	Ci + M + Vb + D	Ci 70 mg/m², d2; M 30 mg/m², d1, d15, d22; Vb 3 mg/m², d2, d15, d22; D 30 mg/m², d2	6 × 4 wk	≤40, 14 (22%); 41–50, 30 (48%); 51–60, 10 (16%); >61, 9 (15%)	Naive, 27; experienced, 36	IVB, 5; P, 7; R, 51
Monk et al,[40] 2009	GOG204	103	Ci + Pa	Pa 135 mg/m², 24 h; Ci 50 mg/m², d2	6 × 3 wk	29–50–81	Naive, 33; experienced, 70	IVB, 17; P, 12; R, 74
		108	Ci + Vr	Vr 30 mg/m², Ci 50 mg/m²	6 × 3 wk	24–49–76	Naive, 29; experienced, 79	IVB, 17; P, 14; R, 77
		112	Ci + G	G 1000 mg/m², Ci 50 mg/m²	6 × 3 wk	20–45–89	Naive, 40; experienced, 72	IVB, 20; P, 12; R, 80
		111	Ci + T	T 0.75 mg/m², Ci 50 mg/m²	6 × 3 wk	25–48–75	Naive, 30; experienced, 81	IVB, 20; P, 14; R, 77
Kitagawa et al,[36] 2015	JCOG0505	121	Pa + Ca	Pa 175 mg/m², 3 h, d1; Ca AUC5, 1 h d1	6 × 3 wk	30–50–74†	Naive, 64; experienced, 59	IVB, 27; R, 37†
		123	Ci + Pa	Ci 50 mg/m², 2 h d2; Pa 135 mg/m², 24 h d1	6 × 3 wk	31–53–72†	Naive, 53; experienced, 68	IVB, 24; R, 29†
Symonds et al,[42] 2014	CIRCCa	35	Pa + Ca	Pa 175 mg/m², Ca AUC5	6 × 3 wk	NR	Any, 57	NR
		34	Pa + Ca + Ce	Pa 175 mg/m², Ca AUC5, Ce 20 mg daily	6 × 3 wk	NR		NR

(Continued on next page)

TABLE 1. (Continued)

Citation	Trial	N	Treatment	Dose	Duration (Cycle)	Patient Age, y	Previous Platinum Therapy	Stage
Tewari et al,[12] 2014	GOG240	114	Ci + Pa	Ci 50 mg/m², d1; Pa 135 or 175 mg/m²	3 wk	20-45-83	Naïve, 29; experienced, 85	Advanced, 18; P, 7; R, 89
		115	Ci + Pa + B	Ci 50 mg/m², d; Pa 135 or 175 mg/m²; B 15 mg/kg, d1	3 wk	26-47-85	Naïve, 27; experienced, 88	Advanced, 19; P, 14; R, 82
		111	Pa + T	Pa 175 mg/m², d1; T 0.75 mg/m², d1–d3	3 wk	28-48-82	Naïve, 30; experienced, 81	Advanced, 19; P, 16; R, 76
		112	Pa + T + B	Pa 175 mg/m², d1; T 2.25 mg/m², d1–d3; B 15 mg/kg, d1	3 wk	22-49-74	Naïve, 29; experienced, 83	Advanced, 20; P, 14; R, 78

*Data are different outcomes from the same trial.
†Without previous platinum therapy.
B, bevacizumab; Ca, carboplatin; Ce, cediranib; Ci, cisplatin; D, doxorubicin; G, gemcitabine; M, methotrexate; NR, not reported; P, persistent; Pa, paclitaxel; R, recurrent; T, topotecan; Vb, vinblastine; Vr, vinorelbine.

duration) and patient characteristics, including age, disease stage, and previous exposure to platinum-based therapies; all trials included in the OS network were RCTs.

The HRs and lnHRs from these 5 included trials are provided in Table 2, which shows data extracted from each article. Additional HRs of pairwise comparisons from the GOG240 trial were provided by Roche (Roche, data on file). For the GOG179 trial, HRs for cisplatin-topotecan versus cisplatin monotherapy were estimated from the final report,[38] and HRs for cisplatin-methotrexate-vinblastine-doxorubicin versus cisplatin monotherapy were taken from the interim report.[39] These are the input data to the NMA.

Network meta-analysis of OS

Table 3 depicts the posterior median HRs and CrIs of all pairwise comparisons among each of the 11 interventions from the fixed-effects NMA. The HRs are displayed as treatments listed in columns comparing treatments listed in rows. Hazard ratio of less than 1 means a favorite treatment effect for the treatment listed in the column. For example, the median HR of cisplatin-paclitaxel-bevacizumab compared with paclitaxel-carboplatin is 0.75 with CrI of 0.50 to 1.13. Forest plots of HR (95% CI) showing comparisons with paclitaxel-carboplatin and with cisplatin monotherapy, respectively, are shown in Supplemental Digital Content Figure 1, http://links.lww.com/IGC/A481.

The NMA results suggest that cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab were likely to prolong OS compared with all non–bevacizumab-containing therapies (range of median HR, 0.45–0.75, for cisplatin-paclitaxel-bevacizumab; range of median HR, 0.55–0.90, topotecan-paclitaxel-bevacizumab). For most other comparisons, results are uncertain because CrIs included a value of 1. The large CrIs are a result of a couple of factors: the number of trials included in the NMA is small, each comparison is informed by only 1 trial, and the number of OS events is relatively small across trials. Results from the random-effects model were similar, although the CrIs were even larger as a result of incorporating both within- and between-study heterogeneity (data not shown).

By ranking of therapies, cisplatin-paclitaxel-bevacizumab had the highest probability of being the most efficacious compared with all other regimens (68.1%; median rank, 1; CrI, 1–4), and cisplatin monotherapy had the lowest (0%; median rank, 11; CrI, 7–11) (Table 4). Other rankings showed high variability, with topotecan-paclitaxel-bevacizumab scores having the third highest probability of being the most efficacious treatment, cisplatin-paclitaxel having the fifth highest probability of being the most efficacious, and cisplatin-topotecan having the eighth highest probability of being the most efficacious.

DISCUSSION

The results of this systematic review and NMA show that cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab have the highest probability of being efficacious and demonstrate a trend toward improved OS compared with carboplatin-paclitaxel and other non–bevacizumab-containing therapies. In contrast, cisplatin monotherapy has the lowest probability of improved OS. The equivalent effects of carboplatin-paclitaxel and cisplatin-paclitaxel suggest that the use of bevacizumab in combination with carboplatin-paclitaxel

TABLE 2. Hazard ratios for the OS-specific network

Citation	Study	Treatment	Comparator	HR (95% CI)	lnHR (SE)
Monk et al,[40] 2009	GOG204	Ci + G	Ci + Pa	1.322 (0.91–1.92)	0.279 (0.190)
		Ci + Vr	Ci + Pa	1.147 (0.79–1.67)	0.139 (0.191)
		Ci + T	Ci + Pa	1.255 (0.86–1.82)	0.224 (0.191)
Tewari et al,[12] 2014	GOG240	Pa + T + B	Ci + Pa + B	1.150 (0.85–1.56)	0.141 (0.155)
		Ci + Pa + B	Ci + Pa	0.750 (0.55–1.01)	−0.294 (0.155)
		Pa + T	Ci + Pa	1.080 (0.80–1.45)	0.074 (0.152)
		Pa + T + B	Pa + T	0.790 (0.59–1.07)	−0.230 (0.152)
Kitagawa et al,[36] 2015	JCOG0505	Pa + Ca	Ci + Pa	0.990 (0.79–1.25)*	−0.006 (0.139)
Symonds et al,[42] 2014	CIRCCa	Pa + Ca	Pa + Ca + Ce	0.930 (0.64–1.36)†	−0.069 (0.294)
Long et al,[38] 2005	GOG179	Ci + T	Ci	0.760 (0.59–0.98)	−0.272 (0.128)
Long et al,[39] 2006		Ci + M + Vb + D	Ci	0.700 (0.48–1.01)	−0.362 (0.190)

*90% CI.
†80% CI.
B, bevacizumab; Ca, carboplatin; Ce, cediranib; Ci, cisplatin; D, doxorubicin; G, gemcitabine; ln, natural logarithm; Pa, paclitaxel; SE, standard error; T, topotecan; Vb, vinblastine; Vr, vinorelbine.

may also prolong OS, although further clinical studies and/or real-world data are needed to test this hypothesis. These findings support the large body of evidence demonstrating the survival benefit of bevacizumab when added to standard chemotherapy for advanced, persistent, and recurrent cervical cancer. The unique biologic suitability of antiangiogenic therapy in treating highly vascular neoplasms, its high clinical tolerability, and synergism with standard chemotherapeutic agents have led to its adoption of bevacizumab as the standard of care for patients with advanced cervical cancer.[45] To date, bevacizumab is the only antiangiogenesis agent with demonstrated significant activity against advanced and recurrent cervical cancer.[13]

Systematic reviews and meta-analyses of RCTs are considered an important component of evidence for informing clinical practice guidelines and standards of care. Network meta-analysis is an extension of meta-analysis and enables comparisons of interventions that have not been compared head-to-head for the same condition. The results of an NMA could be incorporated in the economic evaluation via cost-effectiveness analysis. Therefore, NMAs provide very useful information for clinical practice and reimbursement decision making. In a recent systematic literature review comparing standard chemotherapy regimens, carboplatin-paclitaxel was shown to be equally effective and less toxic than cisplatin-paclitaxel as the first-line therapy for metastatic cervical cancer.[11] The evidence supporting the use of bevacizumab in cervical cancer is well established, but its comparative effectiveness with chemotherapy regimens that were not included in the pivotal GOG240 trial has not been previously evaluated. The use of this NMA allows for indirect comparisons of bevacizumab plus chemotherapy treatments with chemotherapy regimens that have not previously been compared directly. To our knowledge, this study is the first one that applied NMA methodology to the treatment of

advanced and recurrent cervical cancer. This was a comprehensive systematic review with a low probability of missing any publication, thereby limiting publication bias. Through feasibility assessment, the network was limited to trials with a population similar to GOG240. Although the statistical heterogeneity could not be assessed, the clinical heterogeneity was reduced by including similar trials in the NMA. In this study, among all relevant comparators, treatment of advanced cervical cancer with cisplatin-paclitaxel-bevacizumab has the highest probability of efficacy, and cisplatin monotherapy has the lowest. Combined with existing evidence that bevacizumab added to chemotherapy improves outcomes without significant deterioration in health-related quality of life,[12] these results underscore the growing role of bevacizumab in the treatment of advanced cervical cancer.

The results of our NMA should be interpreted taking into account a number of limitations. A pertinent limitation of this study is the small number of trials in the network with many different treatment regimens. This was also experienced in the systematic review by Lorusso et al.[11] Many studies in our analysis did not report OS or had no common regimens to be linked with other studies, and we included studies with greater homogeneity. Therefore, only a small number of trials met inclusion criteria for this analysis. Because each comparison was informed by only 1 clinical study, a full statistical analysis of heterogeneity could not be performed. This limitation also precluded any sophisticated statistical analysis (eg, meta-regression). For the random-effects model, an informative prior had to be used; however, we believe the selection of this prior distribution was conducted in a reasonable manner because the ranges included all values reported in the literature and our base case analysis was the fixed-effects model. With regard to the assessment of study quality, many articles did not include important methodological details that would have allowed for a more comprehensive study

TABLE 3. Pairwise comparison of OS results (fixed-effects model)

| | | | | Median HR (95% CrI) | | | | | | | |
Reference	Pa + T + B	Pa + T	Ci	Ci + M + Vb + D	Pa + Ca	Pa + Ca + Ce	Ci + Pa + B	Ci + T	Ci + Vr	Ci + G	Ci + Pa
Pa + T + B	1.00	1.20 (0.90–1.60)	1.83 (1.07–3.13)	1.28 (0.72–2.26)	1.11 (0.74–1.65)	1.19 (0.59–2.41)	0.83 (0.62–1.11)	1.39 (0.87–2.24)	1.28 (0.80–2.06)	1.47 (0.92–2.37)	1.12 (0.83–1.49)
Pa + T	0.83 (0.63–1.11)	1.00	1.53 (0.89–2.62)	1.06 (0.60–1.88)	0.92 (0.62–1.38)	0.99 (0.49–2.01)	0.69 (0.51–0.93)	1.16 (0.72–1.87)	1.07 (0.66–1.72)	1.23 (0.76–1.98)	0.93 (0.69–1.25)
Ci	0.55 (0.32–0.94)	0.66 (0.38–1.13)	1.00	0.70 (0.48–1.01)	0.61 (0.36–1.03)	0.65 (0.30–1.43)	0.45 (0.26–0.78)	0.76 (0.59–0.98)	0.70 (0.45–1.09)	0.81 (0.52–1.25)	0.61 (0.39–0.96)
Ci + M + Vb + D	0.78 (0.44–1.39)	0.94 (0.53–1.68)	1.44 (0.99–2.08)	1.00	0.87 (0.50–1.53)	0.93 (0.42–2.09)	0.65 (0.37–1.17)	1.09 (0.79–1.50)	1.00 (0.62–1.64)	1.16 (0.71–1.88)	0.87 (0.54–1.44)
Pa + Ca	0.90 (0.61–1.34)	1.08 (0.72–1.62)	1.65 (0.97–2.79)	1.15 (0.65–2.01)	1.00	1.07 (0.60–1.91)	0.75 (0.50–1.13)	1.26 (0.79–2.00)	1.16 (0.73–1.83)	1.33 (0.84–2.11)	1.01 (0.77–1.32)
Pa + Ca + Ce	0.84 (0.42–1.69)	1.01 (0.50–2.03)	1.54 (0.70–3.36)	1.07 (0.48–2.39)	0.93 (0.52–1.66)	1.00	0.70 (0.34–1.41)	1.17 (0.56–2.45)	1.08 (0.51–2.25)	1.24 (0.59–2.59)	0.94 (0.50–1.77)
Ci + Pa + B	1.20 (0.90–1.61)	1.45 (1.07–1.95)	2.20 (1.27–3.79)	1.54 (0.86–2.73)	1.34 (0.89–2.01)	1.43 (0.71–2.91)	1.00	1.68 (1.04–2.72)	1.54 (0.95–2.49)	1.77 (1.10–2.87)	1.34 (0.99–1.82)
Ci + T	0.72 (0.45–1.15)	0.86 (0.53–1.39)	1.31 (1.02–1.69)	0.91 (0.67–1.26)	0.80 (0.50–1.27)	0.85 (0.41–1.79)	0.60 (0.37–0.97)	1.00	0.92 (0.64–1.33)	1.06 (0.73–1.52)	0.80 (0.55–1.16)
Ci + Vr	0.78 (0.49–1.25)	0.94 (0.58–1.51)	1.43 (0.91–2.22)	1.00 (0.61–1.62)	0.87 (0.55–1.38)	0.93 (0.44–1.95)	0.65 (0.40–1.05)	1.09 (0.75–1.57)	1.00	1.15 (0.80–1.65)	0.87 (0.60–1.26)
Ci + G	0.68 (0.42–1.09)	0.82 (0.50–1.32)	1.24 (0.80–1.94)	0.87 (0.53–1.40)	0.75 (0.47–1.20)	0.80 (0.39–1.70)	0.56 (0.35–0.91)	0.95 (0.66–1.36)	0.87 (0.61–1.25)	1.00	0.76 (0.52–1.10)
Ci + Pa	0.90 (0.67–1.20)	1.08 (0.80–1.45)	1.64 (1.04–2.57)	1.14 (0.70–1.87)	0.99 (0.76–1.31)	1.06 (0.57–2.02)	0.75 (0.55–1.01)	1.25 (0.86–1.82)	1.15 (0.79–1.66)	1.32 (0.91–1.92)	1.00

B, bevacizumab; Ca, carboplatin; Ce, cediranib; Ci, cisplatin; D, doxorubicin; G, gemcitabine; M, methotrexate; Pa, paclitaxel; T, topotecan; Vb, vinblastine; Vr, vinorelbine.

TABLE 4. OS ranking by treatment regimen

Outcome/ Treatment Regimen	Fixed-Effects Model	
	Probability Best	Median Rank (95% CrI)
Ci + Pa + B	0.681	1 (1–4)
Pa + Ca + Ce	0.138	6 (1–11)
Pa + T + B	0.068	3 (1–8)
Ci + M + Vb + D	0.050	7 (1–10)
Pa + Ca	0.036	4 (1–10)
Ci + Vr	0.018	7 (2–10)
Ci + Pa	0.004	5 (2–8)
Pa + T	0.002	6 (2–11)
Ci + G	0.002	9 (4–11)
Ci + T	0.002	8 (3–10)
Ci	0.000	11 (7–11)

B, bevacizumab; Ca, carboplatin; Ce, cediranib; Ci, cisplatin; D, doxorubicin; G, gemcitabine; M, methotrexate; Pa, paclitaxel; T, topotecan; Vb, vinoblastine; Vr, vinorelbine.

assessment. In addition, potential sources of bias included study-specific inclusion/exclusion criteria and proportions of platinum-naive patients, as well as publication bias inherent to the process of systematic literature review. All literature reviews are limited by publication bias with respect to the articles that are available and which studies may be more likely to report significant findings. In addition, articles included in this review were constrained to those published in English. However, despite these limitations, the review was systematic and comprehensive and included manual searches of clinical registries and conference Web sites in addition to the systematic searches of the MEDLINE, EMBASE, and Cochrane databases. Despite these limitations, this systematic review and NMA effectively synthesize clinical evidence in the published literature establishing the benefit of bevacizumab added to standard chemotherapy in recurrent, persistent, and metastatic cervical cancer.

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