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ORIGINAL REPORT

Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study

Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda, and David Cella

From the University of California, Irvine, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chao Family Comprehensive Cancer Center, Orange, CA; Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute; Department of Biostatistics, University at Buffalo, Buffalo, NY; University of Oklahoma, Oklahoma City, OK; The Ohio State University, Columbus, OH; M. D. Anderson Cancer Center, Houston, TX; Virginia Commonwealth University, Richmond, VA; University of Iowa, Iowa City, IA; Center on Outcomes, Research and Education, Evanston Northwestern Healthcare, Evanston; and Northwestern University Feinberg School of Medicine, Chicago, IL.

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Corresponding author: Bradley J. Monk, MD, University of California, Irvine Medical Center, Building 56, Room 262, 101 The City Dr, Orange, CA 92868; e-mail: bjmonk@uci.edu.

The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Assess toxicity and efficacy of cisplatin (Cis) doublet combinations in advanced and recurrent cervical carcinoma.

Patients and Methods
Patients were randomly assigned to paclitaxel 135 mg/m^2 over 24 hours plus Cis 50 mg/m^2 day 2 every 3 weeks (PC, reference arm); vinorelbine 30 mg/m^2 days 1 and 8 plus Cis 50 mg/m^2 day 1 every 3 weeks (VC); gemcitabine 1,000 mg/m^2 day 1 and 8 plus Cis 50 mg/m^2 day 1 every 3 weeks (GC); or topotecan 0.75 mg/m^2 days 1, 2, and 3 plus Cis 50 mg/m^2 day 1 every 3 weeks (TC). Survival was the primary end point with a 33% improvement relative to PC considered important (85% power, alpha = 5%). Quality-of-life data were prospectively collected.

Results
A total of 513 patients were enrolled when a planned interim analysis recommended early closure for futility. The experimental-to-PC hazard ratios of death were 1.15 (95% CI, 0.79 to 1.67) for VC, 1.32 (95% CI, 0.91 to 1.92) for GC, and 1.26 (95% CI, 0.86 to 1.82) for TC. The hazard ratios for progression-free survival (PFS) were 1.36 (95% CI, 0.97 to 1.90) for VC, 1.39 (95% CI, 0.99 to 1.96) for GC, and 1.27 (95% CI, 0.90 to 1.78) for TC. Response rates (RRs) for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection, and alopecia.

Conclusion
VC, GC, and TC are not superior to PC in terms of overall survival (OS). However, the trend in RR, PFS, and OS favors PC. Differences in chemotherapy scheduling, pre-existing morbidity, and toxicity are important in individualizing therapy.

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INTRODUCTION

Parkin et al[1] reported that cervical cancer affected 493,243 women worldwide in 2002, thereby making it the second most common cancer in women. Even in the United States, it remains a serious health threat with an estimated incidence and mortality of 11,070 and 3,870 in 2008, respectively.[2] Cervical cancer is preventable and generally curable if detected early.[3] Treatment paradigms in the primary management of cervical cancer are well established, with early lesions being treated surgically and locally advanced lesions being managed with concurrent cisplatin chemotherapy and pelvic radiation.[4,5] Metastatic disease or recurrent lesions not amenable to radical local excision or regional radiation are treated with palliative chemotherapy. The Gynecologic Oncology Group (GOG) has reported on seven randomized phase III trials in this setting with only one regimen being superior to single-agent cisplatin administered intravenously at 50 mg/m^2 every 3 weeks.[6] When added to cisplatin, topotecan at 0.75 mg/m^2 on the first 3 days of a 21-day cycle prolonged the median survival by 2.9 months (range, 6.5 to 9.4 months; $P = .017$) with an unadjusted relative risk estimate for survival of 0.76 (95% CI, 0.593 to 0.979; one-tailed $P = .017$).[7] Although the topotecan-cisplatin (TC) doublet was associated with more marrow suppression compared with cisplatin alone, there was no associated decrement in quality of life (QOL) associated with the combination.[8]

In addition to phase III trials, the GOG conducts phase II trials of compounds among women with recurrent cervical carcinoma.[6] Two recent phase II trials had shown promising activity of the

combinations of vinorelbine plus cisplatin (VC) and gemcitabine plus cisplatin (GC), and they were thus incorporated into the current trial.[9,10] This phase III trial began as a two-arm study comparing paclitaxel plus cisplatin (PC, reference arm) to VC, with GC and TC being added as third and fourth arms when the GC phase II data and the TC phase III data discussed above became available. Overall survival (OS) was chosen for the primary analysis because it was thought to be the most important metric of activity with response rate (RR), progression-free survival (PFS), toxicity, and QOL (to be reported in a future publication) being secondary objectives.

PATIENTS AND METHODS

Eligibility

Eligible patients were women with advanced (stage IVB), recurrent, or persistent cervical cancer. Histologic types included squamous, adenosquamous, and adenocarcinoma. Measurable disease was required. While histologic documentation of the primary cervical cancer was required, biopsy confirmation of metastatic disease was not required for lesions identified by computed tomographic/magnetic resonance imaging if the lesion was more than 3 cm in diameter. In patients with small-volume metastatic disease ($<$ 3 cm), biopsy of at least one lesion was required. All diagnoses were verified by the GOG Pathology Committee. Patients were required to have a GOG performance status (PS) of zero or 1, have recovered from the effects of recent surgery or radiotherapy, and be free of clinically significant infection. Participating institutional review boards approved the protocol, and all patients provided written informed consent. Ineligible patients included those with an absolute neutrophil count less than 1,500/μL, platelet counts less than 100,000/μL, bilirubin more than 1.5$\times$ institutional normal, AST level more than 3$\times$ institutional normal, alkaline phosphatase level more than 3$\times$ institutional normal, or a serum creatinine level more than 1.2 mg/dL. Patients with serum creatinine level of more than 1.2 mg/dL but less than 1.5 mg/dL were eligible if a creatinine clearance determination was more than 50 mL/min. Other ineligible patients included those who had received prior chemotherapy for metastatic disease, had concurrent or past malignancy, had CNS metastasis, or had bilateral hydronephrosis that could not be alleviated by ureteral stents or percutaneous nephrostomy.

Treatment

Chemotherapy administration was as follows: paclitaxel 135 mg/m^2 over 24 hours plus cisplatin 50 mg/m^2 on day 2 every 3 weeks; vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; gemcitabine 1,000 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; topotecan 0.75 mg/m^{2}on days 1, 2, and 3 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks. All regimens were to be administered for a maximum of six cycles for nonresponders, including those with stable disease. Patients who achieved a partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond six cycles after discussion with the study chair.

The National Cancer Institute Common Toxicity Criteria, version 2.0, was used for characterizing adverse events and dose modifications.[11] All patients were required to have an absolute neutrophil count more than 1,500/μL and platelet count more than 100,000/μL on the day of re-treatment. The cisplatin dose was decreased by 50% for grade 2 renal toxicity and held for the present cycle for grade 3 to 4 renal toxicity on the scheduled day of re-treatment. The non–cisplatin component of the regimen was reduced by 20% for grade 3 nonhematologic adverse events or for grade 4 interval thrombocytopenia and grade 4 complicated (febrile) neutropenia for the entire course of therapy. No dose reductions were allowed for grade 1 or 2 interval hematologic toxicity or for uncomplicated (absence of sepsis or fever) grade 3 or 4 neutropenia. Patients were permitted to receive granulocyte growth factors during subsequent cycles of therapy if febrile neutropenia occurred after dose modification for hematologic toxicity during the previous cycle of therapy. Response was defined according to the criteria adopted by the Response Evaluation Criteria in Solid Tumors (RECIST).[12] Survival was defined as the time from random assignment until death or the date of last contact. PFS was defined as the time from random assignment until the date of last contact, disease progression, or death, whichever came first.

QOL Assessments

QOL was assessed before random assignment (baseline), before cycles 2 and 5, and 9 months post study entry. QOL measures included the Functional Assessment of Cancer Therapy–Cervix Trial Outcome Index (FACT-Cx TOI), the FACT/GOG-Neurotoxicity four-item scale (FACT/GOG-NTX), and the Brief Pain Inventory (BPI) zero to 10 pain intensity item.[8]

Statistical Considerations

The random assignment of the treatment regimen was balanced at registration for disease status (recurrent, persistent, or advanced stage IVB primary) and PS (zero or 1). The primary analysis consisted of three pairwise comparisons of the experimental arms (VC, GC, and TC) to the reference arm (PC) with a log-rank test of equivalency in OS. A decrease in the death rate of 33% was important to detect. This difference required the observation of 232 deaths in the two treatment groups to be detected with 84.5% power while keeping the pairwise probability of a type I error at 0.019 (one-sided). The family-wise error rate for the three comparisons was controlled to 5% (using Dunnett's method).[13] Because the number of events for PFS is at least as large as the number of events for survival, the operating characteristics for testing the equivalency of the three experimental treatments to the reference arm was maintained.

The targeted accrual for the entire study was 600 eligible patients (150 per arm). The statistical power for detecting an odds ratio of approximately two for response (partial and complete) in the experimental treatment to the reference arm was 80% (using Fisher's exact test) when keeping the pairwise probability of a type I error rate to 0.019.

An interim analysis was triggered after 232 events were observed in the entire study (approximately 58 deaths per arm or at one half the planned information time). A futility analysis was to be conducted for each experimental regimen. The degree of risk was assessed through the numerator of the log-rank test before squaring (ie, $O_e - E_e$). If this value was greater than zero, then the experimental regimen was closed.[14] Alternatively, the control arm was considered for closure if there was a dramatic improvement in survival as assessed by the z-score associated with the log-rank test. The alpha spending function was provided by Lan and DeMets[15] based on the function $\alpha(t) = \alpha\, t^{1.5}$. If the interim analysis occurred at exactly one half the planned information time, the one-sided critical values in terms of z-scores would be 2.472 ($t = 0.5$) and 2.172 ($t = 1.0$), which maintained the overall pairwise type I error rate at 0.019.

Patient data were captured for each adverse event as the worst toxicity experienced by the patient during the course of therapy. Potential dependencies of the severity of adverse events on the regimen administered were explored by dichotomizing the adverse event into two categories (severe or fatal versus none, mild, or moderate) and calculating exact χ^2 statistics.[16] A 5% level of significance was used to identify possible differences between regimens.

The potential significance of prognostic factors was chiefly explored with Cox proportional hazards (PH) models (OS and PFS end points)[17] or logistic modeling (response end points).[18] Where feasible, model building techniques were used (eg, best subset selection approaches) to help uncover possible relationships. In other cases, certain variables were examined because of the level of interest given a priori to the study (eg, prior cisplatin therapy in conjunction with radiation therapy [CCRT]). The factors considered were disease status (recurrent, persistent, or advance stage, including time from primary diagnosis to first recurrence), location of target lesions (whether any tumors were within a previously irradiated zone or not), prior CCRT, age, PS, ethnicity (Hispanic or not), and race (black or not).

RESULTS

Patient Characteristics

From May 2003 through April 2007, 513 patients were enrolled when the planned interim analysis recommended early closure for futility. Until January 2004, this study consisted of only two arms comparing PC to VC (Fig 1). The primary analyses excluded these 41 patients. Thirty-eight patients were later found to be ineligible making 434 evaluable for efficacy. An additional nine patients were never treated, leaving 425 patients assessable for toxicity (Fig 1). Of all patients on the PC arm, 56.3% completed six cycles of therapy compared with 41.7%, 42.9%, and 47.8% on the VC, GC, and TC regimens, respectively. Other patient characteristics were well balanced among arms and are summarized in Table 1.

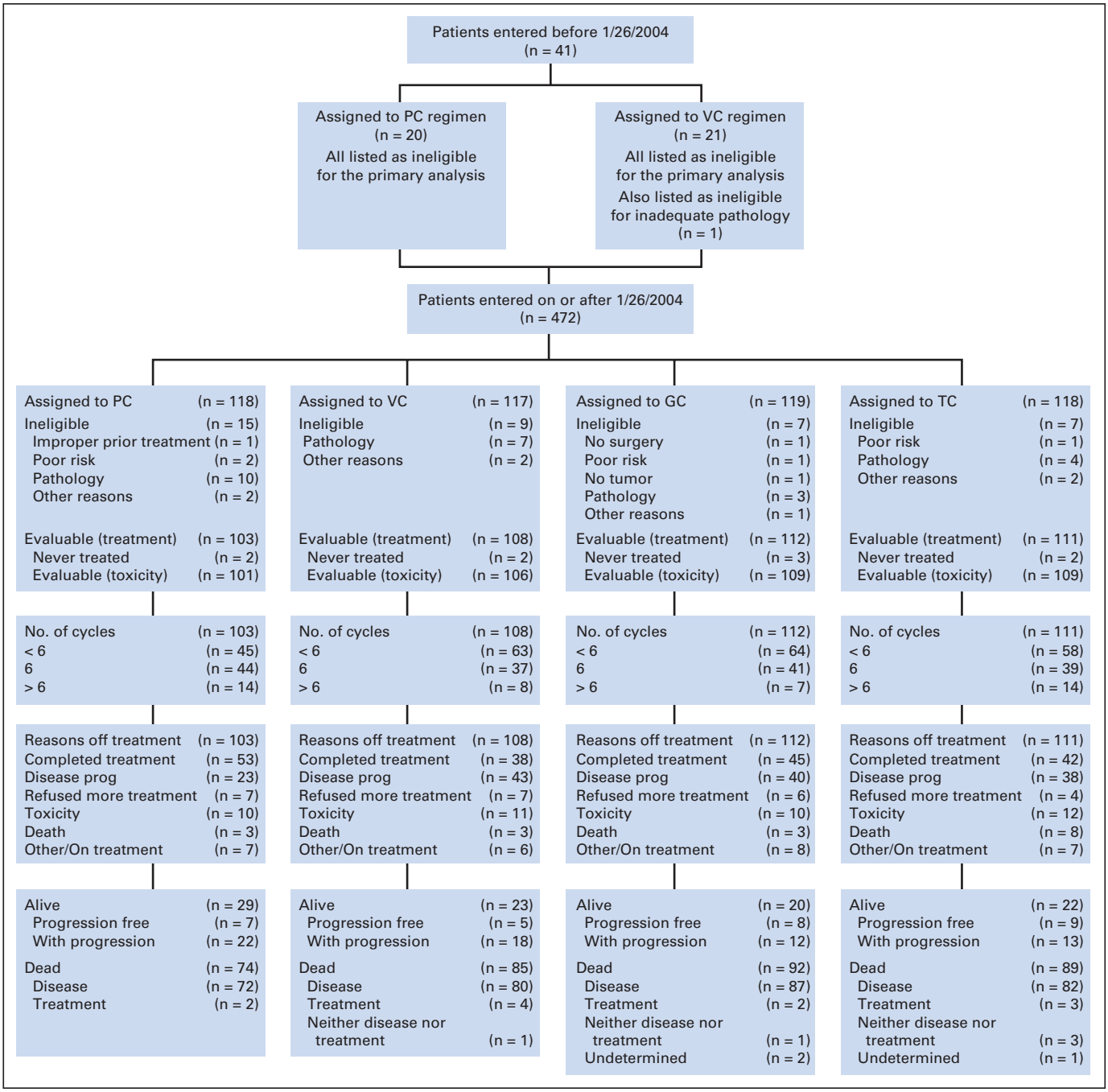

Fig 1. CONSORT flow diagram. Initially, 41 patients were registered onto a randomized phase III trial comparing two arms, paclitaxel + cisplatin (PC) versus vinorelbine + cisplatin (VC). On January 26, 2004, the trial was amended to include two additional arms: gemcitabine + cisplatin (GC) and topotecan + cisplatin (TC). The initial 41 patients were excluded from the primary analysis. Additional analyses with these patients and with all of the ineligible patients yielded the same qualitative conclusions with regard to treatment efficacy. prog, progression.

Table 1. Patient Characteristics

Characteristic	Cis+Pac (n = 103)	Cis+Vin (n = 108)	Cis+Gem (n = 112)	Cis+Top (n = 111)
Age, years				
Median	50	49	45	48
Range	29-81	24-76	20-89	25-75
Median time from diagnosis to first recurrence, months*	16.9	17.1	14.0	18.6
No. of cycles of protocol therapy				
Median	6	5	4	5
Number not treated	2	2	3	2
Race				
White	75	79	80	82
Black	19	20	23	17
Asian/Pacific	4	6	3	4
American Indian	2	1	1	1
Unspecified	3	2	5	7
Ethnicity				
Hispanic	16	10	20	19
Non-Hispanic	75	90	86	78
Unknown	12	8	6	14
Performance status				
0	57	57	55	59
1	46	51	57	52
Tumor grade†				
1	5	8	4	6
2	49	54	57	55
3	48	46	51	50
Prior primary cisplatin and radiation	70	79	72	81
Target lesion in radiated field	41	30	39	37
Cell type				
Squamous	81	80	88	86
Adenosquamous	8	8	6	14
Adenocarcinoma	13	14	15	10
Mucinous adenocarcinoma	0	3	1	1
Clear cell	0	0	0	0
Endometrioid	1	2	1	0
Villoglandular	0	0	0	0
Undifferentiated carcinoma	0	1	1	0
Stage				
IVB	17	17	20	20
Persistent	12	14	12	14
Recurrent	74	77	80	77

Abbreviations: Cis+Pac, cisplatin + paclitaxel; Cis+Vin, cisplain + vinorelbine; Cis+Gem, cisplatin + gemcitabine; Cis+Top, cisplatin + topotecan.
*Among patients with recurrent disease.
†One person in the reference arm had a cell type that was not graded.

Toxicity

Adverse events are reported in Table 2 and Appendix Table A1 (online only) as the percentage of patients who had grade 3 or higher toxicity. There was evidence of a dependence of grade 3 or higher toxicity on the regimen administered for leucopenia ($P < .0001$), neutropenia ($P < .0001$), thrombocytopenia ($P < .0001$), anemia ($P = .02$), and infection ($P = .04$). The severe adverse event rate (grades 4 and 5) of leucopenia for the GC arm was about one half to one third the rates in the other three arms. The rate of severe neutropenia (grades 4 and 5) was approximately 50% in all of the arms except GC where it was approximately 15%. There were 11 grade 5 fatal adverse events in the study with attribution to therapy rated as at least possible (Table 3). A statistically significant association was not detected between the type of regimen administered and treatment-related deaths ($P = .84$). Finally, the rate of grade 2 alopecia (*v* grades zero or 1) was significantly higher in the PC arm (54%) than in the VC (9%), GC (7%), or TC (26%) arm ($P < .0001$).

Response and Survival

The RRs for the four treatment regimens along with the odds ratios are provided in Table 4. Figure 2A illustrates OS. The median OS for the reference arm (PC) was 12.87 months (95% CI, 10.02 to 16.76 months, unadjusted for multiplicity). Likewise, the median OS was 9.99 months (95% CI, 8.25 to 12.25 months) for VC, 10.28 months (95% CI, 7.62 to 11.60 months) for GC, and 10.25 months (95% CI, 8.61 to 11.66 months) for TC. When compared with PC, the OS hazard ratios were 1.15 (95% CI, 0.79 to 1.67) for VC, 1.32 (95% CI, 0.91 to 1.92) for GC, and 1.26 (95% CI, 0.86 to 1.82) for TC. The CIs for the hazard ratios were adjusted for multiplicity using Dunnett's procedure.[13] No statistically significant differences were detected

Table 2. Percentage of Patients Who Experienced Grade 3 or Above Adverse Events for the Specified Event by Treatment Regimen

Adverse Event	% of Patients			
	Cis+Pac	Cis+Vin	Cis+Gem	Cis+Top
Leucopenia*	63.4	67.9	43.1	70.6
Neutropenia*	78.2	78.3	42.2	82.6
Thrombocytopenia*	6.9	7.5	28.4	34.9
Anemia*	16.8	29.2	33.9	34.9
Other hematologic	35.6	48.1	50.5	51.4
Allergic reaction	5.0	0.9	0.9	2.8
Inner ear/hearing	0.0	0.0	0.9	0.9
Other auditory	0.0	0.9	0.0	0.0
Thrombosis embolism	5.0	5.7	0.0	5.5
Cardiac left ventricular function	0.0	0.0	0.9	0.9
Other cardiovascular	5.0	3.8	1.8	2.8
Fatigue	16.8	17.0	23.9	20.2
Other constitutional	1.0	0.9	0.0	0.9
Alopecia	0.0	0.0	0.0	0.0
Dermatologic	0.0	1.9	0.9	0.0
Nausea	13.9	12.3	5.5	8.3
Vomiting	19.8	13.2	10.1	8.3
Stomatitis	1.0	0.9	0.0	0.0
Other GI	15.8	13.2	10.1	10.1
Creatinine	1.0	3.8	2.8	2.8
Other genitourinary/renal	3.0	2.8	1.8	5.5
Hemorrhage	1.0	1.9	5.5	1.8
Hepatic	0.0	0.0	0.9	0.0
Febrile with neutropenia	12.9	14.2	6.4	10.1
Infection without neutropenia	12.9	7.5	9.2	4.6
Other infection/fever*	8.9	12.3	1.8	9.2
Lymphatics	0.0	0.0	0.0	0.0
Metabolic	17.8	16.0	16.5	17.4
Musculoskeletal	2.0	3.8	3.7	4.6
Peripheral neuropathy	2.0	2.8	0.9	4.6
Other neurological	3.0	4.7	5.5	1.8
Ocular/visual	1.0	0.9	0.0	0.0
Myalgia	2.0	0.0	0.0	0.0
Other pain	9.9	10.4	12.8	6.4
Pulmonary	3.0	1.9	3.7	5.5

Abbreviations: Cis+Pac, cisplatin + paclitaxel; Cis+Vin, cisplain + vinorelbine; Cis+Gem, cisplatin + gemcitabine; Cis+Top, cisplatin + topotecan.
*There was evidence for a dependence of the proportion who experienced grade 3 or above adverse events involving leucopenia, neutropenia, thrombocytopenia, and infection on the regimen administered.

using a log-rank test to compare the experimental regimens with the reference arm. The one-sided *P* values associated with VC, GC, and TC were .71, .90, and .89, respectively, adjusting for multiplicity with Dunnett's procedure.[13] Results are summarized in Appendix Table A2 (online only).

Figure 2B illustrates PFS. The median PFS for the reference arm (PC) was 5.82 months (95% CI, 4.53 to 7.59 months, unadjusted for multiplicity). Likewise, the median PFS was 3.98 months (95% CI, 3.19 to 5.16 months) for VC, 4.70 months (95% CI, 3.58 to 5.59 months) for GC, and 4.57 months (95% CI, 3.71 to 5.75 months) for TC. When compared with PC, the PFS hazard ratios were 1.36 (95% CI, 0.97 to 1.90) for VC, 1.39 (95% CI, 0.99 to 1.96) for GC, and 1.27 (95% CI, 0.90 to 1.78) for TC. The log-rank test, two-sided *P* values associated with VC, GC, and TC were .06, .04, and .19, respectively, adjusting for multiplicity with Dunnett's procedure.[13] PC had a significant advantage over GC, according to this analysis, which was similar to the Cox proportional hazards analysis. Results are summarized in Appendix Table A3 (online only).

Table 3. Cause of Death by Treatment Regimen

Cause of Death	Regimen				Total
	Cis+Pac	Cis+Vin	Cis+Gem	Cis+Top	
Treatment	2	4	2	3	11
Disease	72	80	87	82	321
Neither	0	1	1	3	5
Undetermined	0	0	2	1	3
Alive	29	23	20	22	94
Total	103	108	112	111	434

Abbreviations: Cis+Pac, cisplatin + paclitaxel; Cis+Vin, cisplain + vinorelbine; Cis+Gem, cisplatin + gemcitabine; Cis+Top, cisplatin + topotecan.

An analysis of all eligible patients on the PC and VC arms (including the initial 40 patients entered on or before January 25, 2004) yielded essentially the same results. A full intent-to-treat analysis including ineligible patients also gave similar results.

QOL

After adjustment for the baseline scores, patients' age, and performance status at random assignment, there was no statistical evidence indicating that the observed mean differences between any of the experimental arms and control arm were associated with the treatment assignments in terms of the FACT-Cx TOI, FACT/GOG-NTX or BPI.

Prognostic Factors

The prognostic significance of race/ethnicity, prior CCRT, PS, site of target lesions (in or out of a radiated field), and disease status was examined. Appendix Tables A4 and A5 (online only) present treatment-adjusted results for factors added to a Cox PH model singly (univariate analysis) and jointly (multivariate analysis) for OS and PFS, respectively. CIs for selected variables are displayed in Figure 3 for the analysis of OS.

Table 4. Objective Response by Treatment Regimen

Tumor Response	Cis+Pac		Cis+Vin		Cis+Gem		Cis+Top		Total
	No.	%	No.	%	No.	%	No.	%	
Responders	30	29.1	28	25.9	25	22.3	26	23.4	109
Complete	3	2.9	8	7.4	1	0.9	2	1.8	14
Partial	27	26.2	20	18.5	24	21.4	24	21.6	95
Stable disease	50	48.4	46	42.6	54	48.2	53	47.8	203
Progressive disease/ other	23	22.3	34	31.5	33	29.5	32	28.8	122
Total	103		108		112		111		434
Odds ratio*	—		1.17		1.43		1.34		
95% CI†	—		0.54 to 2.58		0.65 to 3.19		0.61 to 2.98		

Abbreviations: Cis+Pac, cisplatin + paclitaxel; Cis+Vin, cisplain + vinorelbine; Cis+Gem, cisplatin + gemcitabine; Cis+Top, cisplatin + topotecan.
*Odds ratios for response are provided for the reference arm, Cis+Pac, to the experimental therapies.
†CIs are adjusted with a Bonferroni correction.

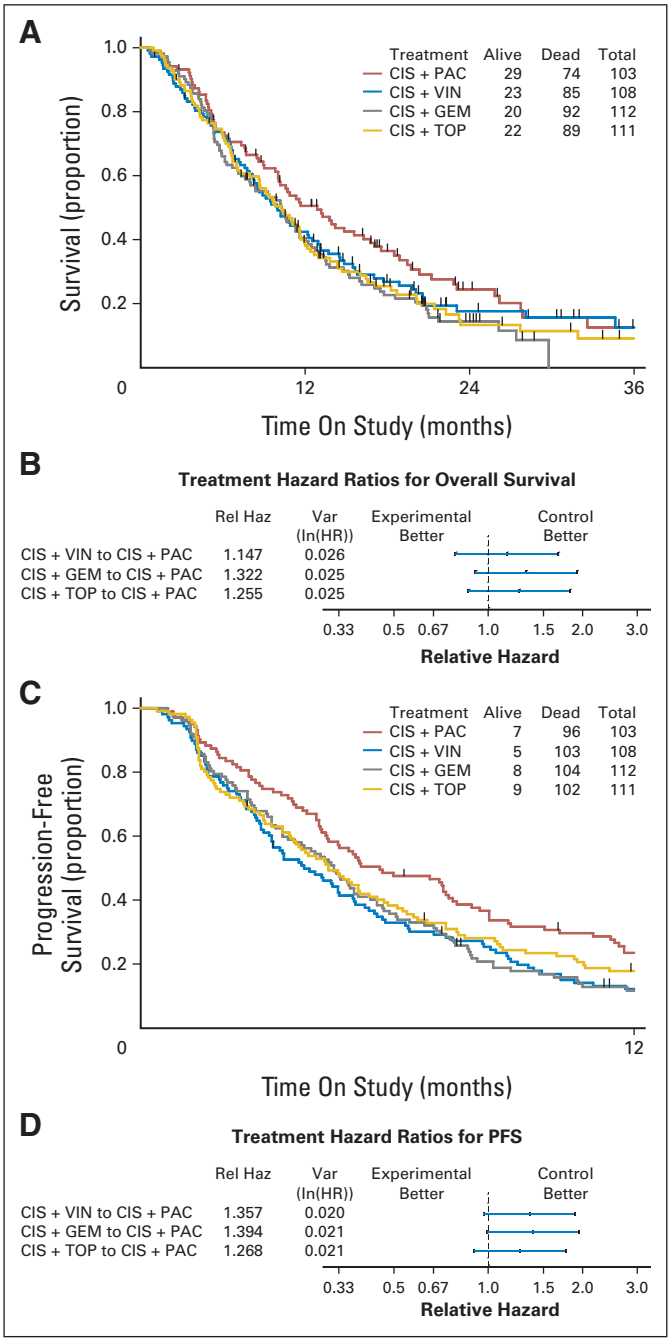

Fig 2. (A) Overall survival Kaplan-Meier plots for the 434 patients in the study sample and (B) hazard ratios with 95% CIs adjusted for multiplicity, using Dunnett's procedure.[13] (C) Progression-free survival Kaplan-Meier plots for the 434 patients in the study sample and (D) hazard ratios with 95% CIs adjusted for multiplicity, using Dunnett's procedure.[13] Cis + Pac, cisplatin + paclitaxel; Cis + Vin, cisplatin + vinorelbine; Cis + Gem, cisplatin + gemcitabine; Cis + Top, cisplatin + topotecan; Rel Haz, relative hazard; Var, Variance; ln, natural logarithm; HR, hazard ratio.

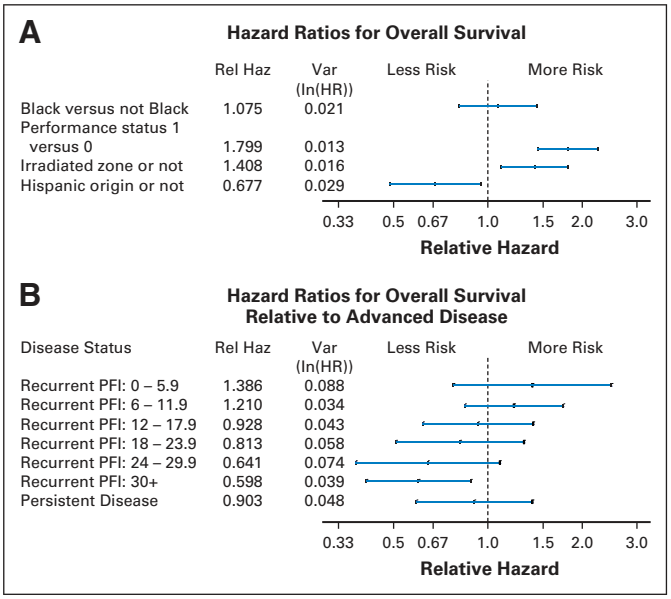

Fig 3. (A) Hazard ratios for overall survival with 95% CIs adjusted for treatment regimen and disease status, investigating the potential prognostic impact of race (black not statistically significant), performance status (patients with performance status = 1 indicate worse prognosis), disease site (patients with target lesion in a previously irradiated zone indicate worse prognosis), and ethnicity (patients of Hispanic origin indicate improved prognosis). (B) Hazard ratios of overall survival for disease status with 95% CIs, adjusted for treatment, race, ethnicity, performance status, and disease site. The status of disease was classified into three categories: advanced disease, recurrent disease, and persistent disease. Persistent disease was classified as evidence of disease following initial therapy. Recurrent disease was further broken down by the progression-free interval since the date of diagnosis. All hazard ratios are relative to patients with advanced disease. Rel Haz, relative hazard; Var, Variance; ln, natural logarithm; HR, hazard ratio; PFI, progression-free interval.

DISCUSSION

This trial was designed to be the definitive phase III trial to evaluate the optimal cisplatin doublet among women with advanced or recurrent cervical cancer. Four regimens were studied, including PC (reference arm), VC, GC, and TC. Although the current trial was stopped early at a planned interim analysis for futility, important information can be gained from this large study. First, VC, GC, and TC are not superior in terms of RR, OS, and PFS compared with PC. Although only the comparison of PC with GC for PFS was statistically significant, the difference in OS between PC (12.9 months) compared with the other three arms (10 to 10.3 months) is worth considering in treatment planning and future clinical trial design. Other issues such as toxicity, less marrow suppression with GC, and more alopecia with PC must also be taken into account. Differences in scheduling are also important in determining which regimen is best for an individual patient, but unfortunately, all four regimens require multiple days of therapy per cycle.

When evaluating the efficacy of PC in treating advanced and recurrent cervical cancer, the prior phase III GOG study reported by Moore et al[19] should also be considered. This trial showed that adding paclitaxel to cisplatin increased the objective RR from 19% (6% complete plus 13% partial) to 36% (15% complete plus 21% partial; $P = .002$). The median PFS was also increased from 2.8 months for cisplatin to 4.8 months for PC ($P < .001$). Interestingly, there was little difference in median OS (8.8 months *v* 9.7 months). Grade 3 to 4 anemia and neutropenia were more common in the combination arm. When evaluating both the Moore PC trial and this study, one must be aware that the Moore study was completed during the transition to CCRT and, unlike this study, included patients with a PS = 2, both of which negatively affect prognosis in the setting of recurrent cervical cancer.[20]

Analysis of prognostic factors showed that age was not significant in these data. PS appeared to be the strongest prognostic factor

detected for OS and PFS. Its association with these outcomes remained strong in the presence of additional cofactors in the model. Marginally, being black or having a target lesion in a previously irradiated zone was negatively prognostic for OS and PFS. In multivariate models, the cofactor for race lost significance whereas the cofactor for ethnicity became significant (indicating positive prognosis for those with Hispanic origin). The cofactor for site of target lesions was marginally significant and remained significant in the presence of other cofactors. The factor for disease status appeared significant, both marginally and in multivariate models; however, this factor was confounded with prior CCRT. This created a problem of redundancy of information in both variables, leading to difficulties in interpreting the significance of both variables jointly. Marginally, it appears that the risk of death decreases as the patients' progression-free interval increases. It is also possible that prior CCRT is associated with an increased risk of death (as indicated in other studies), but the relationship with prior CCRT does not appear to be as compelling in the current analysis.[7,8,20] This study is the first prospective analysis of the prognostic significance of site of measurable disease, and it indicated that target lesions in an irradiated field have a higher risk of death (HR, 1.41; 95% CI, 1.10 to 1.81). Similar to the meta-analysis reported by Plaxe et al[21], black patients were not at increased risk of disease progression or death. However, as shown previously, Hispanic women had a favorable prognosis.[22]

Although this study represents a significant step forward in defining optimal therapy for advanced and recurrent cervical cancer, the low RR and relatively short OS are disappointing. The need to study targeted and biologic therapies is obvious. Among biologic agents, only bevacizumab was deemed worthy of further investigation in a recent GOG phase II trial, and a phase III randomized study using this drug is planned.[23]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Bradley J. Monk, Michael W. Sill, David Cella
Provision of study materials or patients: Bradley J. Monk, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda
Collection and assembly of data: Bradley J. Monk, D. Scott McMeekin
Data analysis and interpretation: Bradley J. Monk, Michael W. Sill, David Cella
Manuscript writing: Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, David Cella
Final approval of manuscript: Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda, David Cella

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