CYCLOPHOSPHAMIDE AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN IN PATIENTS WITH STAGE III AND STAGE IV OVARIAN CANCER

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Abstract *Background.* Chemotherapy combinations that include an alkylating agent and a platinum coordination complex have high response rates in women with advanced ovarian cancer. Such combinations provide long-term control of disease in few patients, however. We compared two combinations, cisplatin and cyclophosphamide and cisplatin and paclitaxel, in women with ovarian cancer.

Methods. We randomly assigned 410 women with advanced ovarian cancer and residual masses larger than 1 cm after initial surgery to receive cisplatin (75 mg per square meter of body-surface area) with either cyclophosphamide (750 mg per square meter) or paclitaxel (135 mg per square meter over a period of 24 hours).

Results. Three hundred eighty-six women met all the eligibility criteria. Known prognostic factors were similar in the two treatment groups. Alopecia, neutropenia, fever, and allergic reactions were reported more frequently in the cisplatin–paclitaxel group. Among 216 women with measurable disease, 73 percent in the cisplatin–paclitaxel group responded to therapy, as compared with 60 percent in the cisplatin–cyclophosphamide group (P=0.01). The frequency of surgically verified complete response was similar in the two groups. Progression-free survival was significantly longer (P<0.001) in the cisplatin–paclitaxel group than in the cisplatin–cyclophosphamide group (median, 18 vs. 13 months). Survival was also significantly longer (P<0.001) in the cisplatin–paclitaxel group (median, 38 vs. 24 months).

Conclusions. Incorporating paclitaxel into first-line therapy improves the duration of progression-free survival and of overall survival in women with incompletely resected stage III and stage IV ovarian cancer. (N Engl J Med 1996;334:1-6.)

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A STANDARD therapy for women with advanced epithelial ovarian cancer in the United States is an alkylating agent plus cisplatin. Cisplatin-based combination therapy has been found to be more effective than alkylating agents alone[1] or combinations without cisplatin,[2,3] when measured by clinical response rates and progression-free intervals. However, the evidence of benefit in overall survival is less compelling.[4] When alkylating agents or combinations not containing plati-

num were used in advanced ovarian cancer, the anticipated average response rate was 40 to 50 percent (10 to 20 percent complete pathological response), with a median survival of 12 to 15 months. In women treated with cisplatin combinations as primary therapy, the response rates are 60 to 80 percent, with complete responses being most common in women who have had adequate surgical therapy.[5]

The only large prospective, randomized study comparing cisplatin with a cisplatin-containing combination in advanced ovarian cancer suggested that cisplatin by itself is as effective as platinum-based combinations[6] and is less toxic and less likely to lead to secondary tumors. Nevertheless, an overview of randomized therapeutic trials suggested that platinum-containing combinations are better than cisplatin alone.[7] In patients with advanced ovarian cancer, a combination of cisplatin and cyclophosphamide is now standard treatment. Unfortunately, long-term disease control with this regimen occurs in less than 10 percent of women with incompletely resected stage III disease and less than 5 percent of women with stage IV disease.[8]

After cisplatin emerged as an active drug in epithelial ovarian cancer, over a decade passed before another

drug was developed that could elicit responses in women with platinum-refractory disease. In 1989, paclitaxel was reported to produce a response rate of 24 percent in women with platinum-resistant ovarian cancer (30 percent overall response rate).[9] The activity of the drug was confirmed in a less heavily pretreated group of women who received a higher starting dose.[10] The response rate in these women was 37 percent, which made paclitaxel the most active single drug ever evaluated by the Gynecologic Oncology Group in a phase 2 study of ovarian cancer. Subsequently, a phase 1 trial of the paclitaxel and cisplatin combination demonstrated that the two drugs could be safely combined, with the paclitaxel administered first as a 24-hour infusion, followed immediately thereafter by cisplatin.[11] The use of paclitaxel in epithelial ovarian cancer has recently been reviewed.[12,13]

The reproducible activity of paclitaxel as salvage therapy, the ability to combine it easily and safely with cisplatin, and the poor long-term results of standard therapy led the Gynecologic Oncology Group to initiate a prospective, randomized phase 3 trial to compare cisplatin plus paclitaxel with standard therapy in women with incompletely resected stage III or any stage IV ovarian cancer.

METHODS

Women with pathologically verified stage III epithelial ovarian cancer (borderline tumors excluded) who had undergone a surgical procedure and were left with residual disease (>1 cm residual mass) or stage IV disease were eligible for study. They could have clinically measurable or unmeasurable (but able to be evaluated) disease. Other eligibility criteria included having undergone no previous chemotherapy; having given informed consent; having a Gynecologic Oncology Group performance-status score[14] of 0, 1, or 2; and having a white-cell count of at least 3000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a serum creatinine level of 2.0 mg per deciliter (177 μmol per liter) or less, and serum bilirubin and serum aspartate aminotransferase values of no more than twice the upper level of normal for the institution. Patients had to enter the study within six weeks after the surgical procedure, and could have had no previous chemotherapy or radiation for the ovarian cancer nor any previous cancer other than nonmelanoma skin cancer. Women with a history of cardiac arrhythmia or who were currently taking an antiarrhythmic medication were excluded. Pathological material was centrally reviewed to verify that it conformed with acceptable diagnoses. Similarly, each case was reviewed for adequacy of the initial surgical procedure, and one of us reviewed all the operative and pathology reports to assess the volume of tumors before and after surgery as well as to record the findings at second-look surgery.

On entry into the study, the women underwent a review of their history, physical examination, and laboratory procedures. Appropriate imaging procedures to measure the extent of disease were performed before and after every other course of therapy.

The women in the standard-therapy group received cyclophosphamide (750 mg per square meter of body-surface area intravenously) and cisplatin (75 mg per square meter intravenously at the rate of 1 mg per minute) every three weeks for a total of six courses. The women in the experimental-therapy group received paclitaxel (135 mg per square meter intravenously as a 24-hour continuous infusion) and cisplatin (75 mg per square meter intravenously at a rate of 1 mg per minute) every three weeks for a total of six courses. The women assigned to the experimental group were premedicated with dexamethasone (20 mg orally or intravenously 14 and 7 hours before the

start of the paclitaxel infusion). Both diphenhydramine (50 mg) and any histamine H_2 antagonist were administered intravenously 30 minutes before the paclitaxel infusion.

Treatments were randomly assigned by the Statistical Office of the Gynecologic Oncology Group, with equal probability after stratification according to institution and the clinical measurability of disease. Women with clinically measurable disease formed the basis of the determination of the clinical response. Those without measurable disease and those with measurable disease and complete clinical responses at the end of their assigned treatment were required to have a reassessment laparotomy to determine the pathological response.

All adverse effects were graded according to the toxicity criteria of the Gynecologic Oncology Group.[14] The women had to have a white-cell count of at least 3000 per cubic millimeter and a platelet count of at least 100,000 per cubic millimeter before the next course could be administered. Courses were delayed week by week until these counts were achieved. If this delay exceeded three weeks, the woman was withdrawn from the study. No delay in the subsequent courses was allowed for any gastrointestinal toxicity, peripheral neurotoxicity of grade 1 or 2, mild renal toxicity (serum creatinine level of ≤2 mg per deciliter [177 μmol per liter] or creatinine clearance of ≥50 ml per minute), or mild ototoxicity (a reduction of ≤10 dB in high-frequency discrimination). More severe neurologic, otic, or renal toxic effects that had not resolved by the time of the next scheduled dose required withdrawal of the woman from the study but with continued follow-up. Cardiac toxic effects (except asymptomatic sinus bradycardia) were reported to the study chairman and were considered a cause for discontinuing therapy. A severe allergic reaction (bronchospasm, hypotension, or diffuse urticaria) during the infusion of paclitaxel was an indication for immediate discontinuation of the infusion and withdrawal of the woman from study treatment. Dose reductions of cyclophosphamide or paclitaxel (no reduction in the cisplatin dose was allowed) in subsequent courses were based on nadir counts from the

Table 1. Patients' Characteristics According to Treatment Group.

CHARACTERISTIC	CISPLATIN + CYCLOPHOSPHA-MIDE (N = 202)	CISPLATIN + PACLITAXEL (N = 184)
Age (yr)		
Median	60	59
Range	27–80	20–84
	number (percent)	
Gynecologic Oncology Group performance status*		
0	55 (27)	56 (30)
1	109 (54)	97 (53)
2	38 (19)	31 (17)
Cell type		
Serous adenocarcinoma	130 (64)	140 (76)
Endometrioid adenocarcinoma	26 (13)	15 (8)
Mucinous adenocarcinoma	10 (5)	4 (2)
Clear-cell adenocarcinoma	5 (2)	3 (2)
Other	31 (15)	22 (12)
Tumor grade		
1	15 (7)	7 (4)
2	82 (41)	82 (45)
3	105 (52)	93 (51)
Measurable disease		
Yes	116 (57)	100 (54)
No	86 (43)	84 (46)
Stage		
III	129 (64)	123 (67)
IV	73 (36)	61 (33)
Ascites (>100 ml)		
No	29 (14)	21 (11)
Yes	173 (86)	163 (89)

*See Blessing for an explanation of possible scores.[14]

previous course. A nadir hematologic toxicity of grade 4 (characterized by a white-cell count of ≤1000 per cubic millimeter, an absolute neutrophil count of ≤500 per cubic millimeter, or a platelet count of ≤25,000 per cubic millimeter) required the reduction of the cyclophosphamide dose to 500 mg per square meter or of the paclitaxel dose to 110 mg per square meter in the subsequent course, with reescalation in later cycles if nadir counts were not of grade 4.

The clinical response was assessed only in patients with clinically measurable disease, according to previously defined criteria.[15] In the women who underwent reassessment laparotomy, a pathological response was determined and assigned to one of three categories: complete response, partial response with microscopic disease only, and persistent disease. Women who were not surgically reassessed because they either had clinically persistent disease or had progressed before their second-look laparotomy were classified as having persistent disease.

Overall and progression-free survival was measured from the date of randomization. The duration of survival was measured up to the date of death or the date of last contact if the woman was alive at the time of the last contact. The duration of progression-free survival was the minimal amount of time until the onset of clinical progression, death, or the last contact. All eligible cases were included in the analysis of survival and progression-free survival unless otherwise specified. All causes of death were used to calculate survival, and the estimates of the cumulative proportion surviving were based on Kaplan–Meier procedures.[16] The independence of progression-free survival, overall survival, and randomized treatment was assessed with a two-tailed log-rank test,[17] stratified according to the measurability of disease. Linear proportional-hazards analysis was used to provide estimates of relative risk adjusted for other pretreatment factors.[18] Finally, proportional-hazards analysis with an interaction term was used to assess the homogeneity of the treatment effect across prognostic groups.

Only eligible women who received at least one course of treatment were included in the assessment of toxicity. One woman received no treatment. A Kruskal–Wallis rank test[19] adjusted for tied ranks was used to test the independence of the severity of toxicity with regard to the assigned treatment. Pearson's chi-square test[20] was used to test the independence of response and treatment. Twelve women, six in each treatment group, could only be partially evaluated and were classified as having no clinical response for the intention-to-treat

Table 3. Occurrence of Adverse Effects According to Severity and Treatment Group.*

ADVERSE EFFECT	CISPLATIN + CYCLOPHOSPHAMIDE						CISPLATIN + PACLITAXEL					
	GRADE OF SEVERITY					NO. OF WOMEN	GRADE OF SEVERITY					NO. OF WOMEN
	0	1	2	3	4		0	1	2	3	4	
	percent						*percent*					
Reduction in white cells or neutrophils†	3	4	9	22	61	197	2	2	4	14	78	179
Reduction in platelets	50	39	7	1	2	198	47	45	4	3	0	180
Anemia	38	17	36	8	0	200	33	15	43	8	<1	182
Gastrointestinal symptoms	29	18	42	8	3	201	28	14	42	12	3	184
Fever†	88	3	8	0	0	201	80	5	11	3	<1	184
Alopecia†‡	63	10	27	—	—	201	37	9	54	—	—	184
Renal symptoms	93	3	2	1	<1	201	96	2	1	<1	0	184
Neurologic symptoms	79	13	3	3	1	201	72	15	9	4	0	184
Allergic reaction†	99	0	1	0	0	201	92	2	2	2	2	184

*Results of repeated white-cell or granulocyte counts were not available for nine women, results of repeated platelet counts were not available for seven women, and results of repeated hemoglobin or hematocrit measurements were not available for three women. Because of rounding, not all percentages total 100.

†A Kruskal–Wallis rank test indicated that this effect was more severe in the cisplatin–paclitaxel group (P≤0.05).

‡Severity of alopecia is graded as 0, 1, or 2.

analysis. Generally, these women received one or two courses of treatment, experienced toxic effects, and then received alternative therapy or refused any further treatment before having any objective response.

RESULTS

Characteristics of the Patients

Four hundred ten women with epithelial ovarian cancer entered the trial. Twenty-four women were ineligible — 3 because their cancer was of an inappropriate stage, 13 because they had the wrong primary tumor, 3 because they had the wrong cell type, 4 because they had a history of cancer, and 1 because she had had the wrong kind of surgery. The remaining 386 eligible women were randomly assigned to either the cisplatin–cyclophosphamide group or the cisplatin–paclitaxel group. The two groups were balanced for several prognostic factors (Table 1).

Dose Delivered and Drug Tolerance

The planned total dose of cisplatin was the same (450 mg per square meter) for both treatment groups. The 25th, 50th, and 75th percentiles of the actual cisplatin dose delivered were 410, 442, and 450 mg per square meter, respectively, for the women in the cisplatin–cyclophosphamide group and 425, 441, and 449 mg per square meter, respectively, for those in the cisplatin–paclitaxel group. There was no difference between the groups in the total delivered dose of cisplatin.

Table 2 shows the number of women treated at each cycle of treatment and the interval between consecutive cycles. More women completed the paclitaxel-based regimen (160 of 184 [87 percent]) than the standard (cisplatin–cyclophosphamide) regimen (158 of 202 [78

Table 2. Number of Courses Completed and Timing, According to Treatment Group.

COURSE	CISPLATIN + CYCLOPHOSPHAMIDE*		CISPLATIN + PACLITAXEL†	
	NO. OF WOMEN TREATED	MEDIAN NO. OF DAYS BETWEEN COURSES	NO. OF WOMEN TREATED	MEDIAN NO. OF DAYS BETWEEN COURSES
1	201‡	—	184	—
2	196	21	175	21
3	187	25	168	21
4	175	27	166	21
5	166	28	163	21
6	158	28	160	21

*The median total dose was 442 mg of cisplatin per square meter and 4176 mg of cyclophosphamide per square meter.

†The median total dose was 441 mg of cisplatin per square meter and 751 mg of paclitaxel per square meter.

‡One woman was not treated.

percent]). Twenty-three women (11 percent) in the standard-regimen group and nine (5 percent) in the paclitaxel group did not complete all six cycles of therapy because of disease progression or death. Twenty-one women in the standard-regimen group (10 percent) and 15 in the paclitaxel group (8 percent) did not complete six cycles of therapy, either because of toxicity or because they declined to do so.

Toxicity

The frequency of adverse effects for the 385 eligible women who received at least one course of treatment is shown in Table 3. The severity of neutropenia, febrile neutropenia, alopecia, and peripheral neurotoxicity was significantly different in the two treatment groups (P≤0.05), with more toxicity in the cisplatin–paclitaxel group. Although neutropenia of grade 3 or 4 developed in the majority of women in the cisplatin–paclitaxel group, the incidence of febrile neutropenia was low and was consistent with the brevity of paclitaxel-induced myelosuppression. Peripheral neurotoxicity was more common in the paclitaxel group but overall was very mild. In 10 women death was at least partly attributed to treatment — 6 in the cisplatin–cyclophosphamide group and 4 in the cisplatin–paclitaxel group. Since bradyarrhythmias with atrioventricular block and ventricular irritability have been reported in patients receiving paclitaxel therapy,[21] the initial phase of this study required all women in the cisplatin–paclitaxel group to undergo cardiac monitoring. However, only seven women in the paclitaxel group had cardiac episodes of grade 2 or higher, such as first-degree heart block or ischemic events without other symptoms and without infarction. Therefore, the requirement of cardiac monitoring was suspended near the end of the study.

Response

Response was assessed in the 216 women who entered the study with clinically measurable disease (Table 4). The overall response rate in the cisplatin–cyclophosphamide group was 60 percent, and it was 73 percent in the cisplatin–paclitaxel group. Complete clinical responses were more frequent among women treated with cisplatin and paclitaxel (51 percent) than

Table 4. Clinical Response According to Treatment Group.

CLINICAL RESPONSE	CISPLATIN + CYCLOPHOSPHAMIDE (N = 116)	CISPLATIN + PACLITAXEL (N = 100)
	*number (percent)**	
Complete	36 (31)	51 (51)
Partial	34 (29)	22 (22)
None	46 (40)	27 (27)

*Values are the numbers and percentages of women with clinically measurable disease.

Table 5. Results of Reassessment Laparotomy According to Treatment Group.

REASSESSMENT RESULT	CISPLATIN + CYCLOPHOSPHAMIDE*	CISPLATIN + PACLITAXEL†
Negative	35 (20)	42 (26)
Microscopically positive	7 (4)	23 (14)
Persistent disease‡	136 (76)	95 (59)
Procedure contraindicated or refused	24	24
Total	202	184

*Values in parentheses are percentages of evaluated cases. Percentages do not include the 24 women in this treatment group who declined second-look surgery.

†Percentages do not sum to 100 because of rounding.

‡This category includes clinically persistent and gross surgical disease.

among those treated with cisplatin and cyclophosphamide (31 percent) (P = 0.01, χ^2_2).

Women who had complete clinical responses or who did not have measurable disease on entering the study and had not had interval progression were required by the protocol to undergo a reassessment laparotomy. Of the 386 women, 48 (24 in each treatment group) did not undergo the procedure because of refusal or contraindication (Table 5). There was no significant difference in the proportion of negative reassessment laparotomies between the two treatment groups (20 percent vs. 26 percent).

Figures 1 and 2 show the progression-free and overall survival curves for all the eligible women. The median duration of follow-up for women alive at last contact was 37 months (range, 5 to 56). There was a statistically significant difference between the treatment groups in both these comparisons. The median progression-free survival in the cisplatin–cyclophosphamide group was 13 months (95 percent confidence interval, 11 to 15); in the cisplatin–paclitaxel group it was 18 months (95 percent confidence interval, 16 to 21) (relative risk, 0.7; 95 percent confidence interval, 0.5 to 0.8; P<0.001). The median survival of women treated with cisplatin and cyclophosphamide was 24 months (95 percent confidence interval, 21 to 30), and for women treated with cisplatin and paclitaxel it was 38 months (95 percent confidence interval, 32 to 44) (relative risk, 0.6; 95 percent confidence interval, 0.5 to 0.8; P<0.001). Including the 24 women who were deemed ineligible for this study did not appreciably alter these results.

The overall survival of women with and without clinically measurable disease in each treatment group and the overall survival according to the stage of disease were also assessed (data not shown). There was no evidence that the combination of cisplatin and paclitaxel was less effective than cisplatin and cyclophosphamide within those prognostic groupings.

Previous studies conducted by the Gynecologic Oncology Group that included women with incompletely resected stage III or IV disease suggested that those

with either mucinous or clear-cell adenocarcinoma tended to have a poor prognosis.[22] Removal of such cases from the comparison of progression-free survival and overall survival did not alter the results.

DISCUSSION

The results of this trial provide strong evidence that the cisplatin–paclitaxel regimen we used is more effective than cisplatin and cyclophosphamide for women with advanced ovarian cancer. There was a good balance of known prognostic factors between the two treatment groups, and random sampling was unlikely to explain the differences in survival, progression-free survival, and complete response rate.

The results we obtained are similar to those of the predecessor to this trial — a study that included a similar sample of women who were treated with similar doses of cisplatin and paclitaxel.[23] It appears that the relative benefit of paclitaxel in our trial was not due to a poorer-than-anticipated outcome among the women receiving standard therapy. There is no evidence that the benefit of cisplatin and paclitaxel was limited to women with measurable disease or to those with stage III disease. The toxicity of the drugs was clinically manageable.

When an active new drug enters clinical use, its effect on survival may be blunted because of the crossover of patients from the old standard to the new drug. There may be a similar but less profound effect on progression-free survival when crossover occurs before clinical progression — for example, after a positive reassessment laparotomy. Such a situation occurred when cisplatin, already commercially available, was incorporated into primary tumor therapy.[3] This may explain why the effect on survival was not more profound when
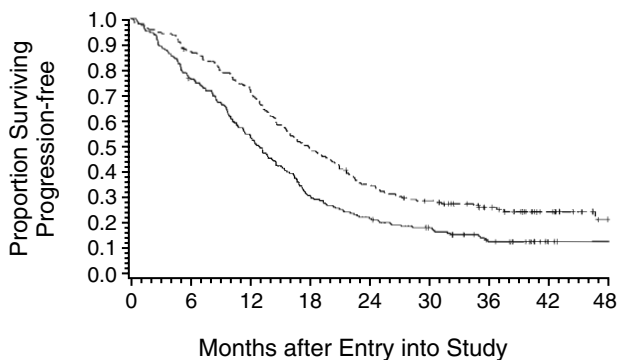
Figure 2. Survival According to Treatment Group.

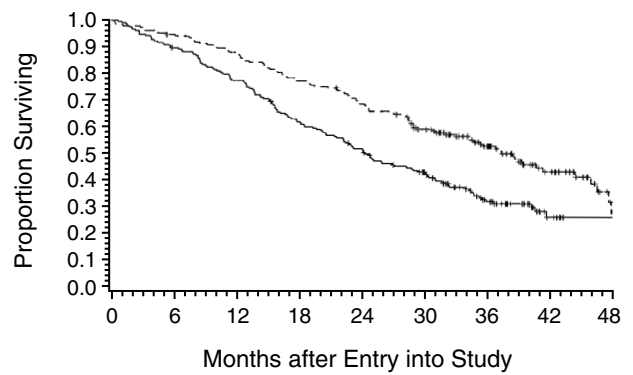| Treatment	No. Alive	No. Dead	Total	Median Survival (mo)
—— Cisplatin + cyclophosphamide	65	137	202	24
- - - Cisplatin + paclitaxel	86	98	184	38

cisplatin was first incorporated into primary tumor therapy. Crossover may have affected our trial, but to a smaller degree than usual, because paclitaxel was in limited supply during the early accrual phase of the study and the women in the cisplatin–cyclophosphamide group were often prevented from receiving paclitaxel until after they had received third-line or fourth-line therapy.

The results of this study are encouraging, but we are concerned that variants of the cisplatin–paclitaxel regimen are being adopted without proper evaluation. Some clinicians have substituted carboplatin for cisplatin, even though the carboplatin–paclitaxel combination is still in a phase 1 evaluation.[24]

Of even greater concern to us is the reduction in the length of paclitaxel infusion to three hours or less. This practice is based largely on a trial of paclitaxel alone as second- and third-line therapy that showed similar efficacy for 3-hour and 24-hour infusions and less hematologic toxicity with the shorter infusion.[25] This approach may be preferred by patients and may have financial advantages, but the efficacy of a three-hour infusion of paclitaxel has not been verified. Our concern about this is pertinent because in vitro data show that the duration of exposure to paclitaxel is much more important than the peak level of exposure.[26]

APPENDIX

The following Gynecologic Oncology Group institutions participated in this study: Oregon Health Sciences Center, Johns Hopkins Oncology Center, University of Alabama at Birmingham, Duke University Medical Center, Colorado Foundation for Medical Care, Bowman Gray School of Medicine of Wake Forest University, Temple University Health Science Center Hospital, University of Minnesota Medical School, University of Mississippi Medical Center, University of California Medical Center at Irvine, Walter Reed Army Medical Center, University of Iowa Hospitals and Clinics, University of Kentucky, Pennsylvania Hospital, Washington University School of Medicine, Cooper Hospital University Medical Center, Cleveland Clinic

Treatment	No. Progression-free	No. with Treatment Failure	Total	Median Progression-free Survival (mo)
—— Cisplatin + cyclophosphamide	28	174	202	13
- - - Cisplatin + paclitaxel	45	139	184	18

Figure 1. Progression-free Survival, According to Treatment Group.

Foundation, University of Texas, M.D. Anderson Cancer Center, Georgetown University Hospital, University of Rochester Medical Center, University of Southern California Medical Center at Los Angeles, Tufts–New England Medical Center, Columbus Cancer Council, University of Cincinnati College of Medicine, Albany Medical College of Union University, Illinois Cancer Council, Wayne State University School of Medicine, Milton S. Hershey School of Medicine of Pennsylvania State University, University of California Medical Center at Los Angeles, University of North Carolina School of Medicine, University of Massachusetts Medical Center, Medical University of South Carolina, Women's Cancer Center of Northern California, University of Oklahoma Health Science Center, Fox Chase Cancer Center, University of Miami School of Medicine, University of Texas Health Science Center at Dallas, State University of New York Downstate Medical Center, Eastern Virginia Medical School, and State University of New York at Stony Brook.

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