

INTRAPERITONEAL CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE VERSUS INTRAVENOUS CISPLATIN PLUS INTRAVENOUS CYCLOPHOSPHAMIDE FOR STAGE III OVARIAN CANCER

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ABSTRACT

Background Intravenous platinum-based chemotherapy is the standard primary therapy for advanced ovarian cancer. We conducted a phase 3 trial to compare the effects of intraperitoneal and intravenous cisplatin on the survival of women with previously untreated, stage III, epithelial ovarian cancer.

Methods The patients underwent an initial exploratory laparotomy and resection of all tumor masses larger than 2 cm. Within four weeks after surgery, six courses of intravenous cyclophosphamide (600 mg per square meter of body-surface area per course) plus either intraperitoneal cisplatin (100 mg per square meter) or intravenous cisplatin (100 mg per square meter) were administered at three-week intervals.

Results Of 654 randomized patients, 546 were eligible for the study. The estimated median survival was significantly longer in the group receiving intraperitoneal cisplatin (49 months; 95 percent confidence interval, 42 to 56) than in the group receiving intravenous cisplatin (41 months; 95 percent confidence interval, 34 to 47). The risk of death was lower in the intraperitoneal group than in the intravenous group (hazard ratio, 0.76; 95 percent confidence interval, 0.61 to 0.96; $P=0.02$). Moderate-to-severe tinnitus, clinical hearing loss, and neuromuscular toxic effects were significantly more frequent in the intravenous group.

Conclusions As compared with intravenous cisplatin, intraperitoneal cisplatin significantly improves survival and has significantly fewer toxic effects in patients with stage III ovarian cancer and residual tumor masses of 2 cm or less. (N Engl J Med 1996;335:1950-5.)

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O VARIAN cancer, the leading cause of death from gynecologic cancer in the United States, is one of the few solid tumors in which the five-year survival rate for patients has improved in recent years.^{1,2} Nevertheless, most women with advanced ovarian cancer die of the disease. Even those with stage III cancer and minimal residual intraperitoneal masses (≤ 2 cm in the greatest dimension) have a median survival of only about 40 months.^{3,4}

Standard chemotherapy for advanced ovarian cancer includes a platinum analogue (either cisplatin or carboplatin). In an attempt to maximize its activity

against ovarian cancer, cisplatin has been administered directly into the peritoneal cavity in investigational studies.⁵ This route yields an intraperitoneal concentration of cisplatin that is 12 to 15 times greater than the plasma concentration.^{6,7} Some phase 2 studies have suggested that survival is prolonged in patients with small residual masses (<1 cm) who receive salvage intraperitoneal chemotherapy after initial chemotherapy and second-look surgery.^{8,9} The present phase 3 trial compares cisplatin administered intraperitoneally with cisplatin administered intravenously in patients with previously untreated stage III ovarian cancer and residual masses no larger than 2 cm in the greatest dimension.

METHODS

Patients

Within four weeks before enrollment, patients underwent an initial exploratory laparotomy with at least bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy, and debulking of all tumor nodules to a size of 2 cm or less in the greatest dimension. The Southwest Oncology Group's Gynecologic Surgical Review Board reviewed the surgical results to confirm eligibility for enrollment. Only patients with a histologic diagnosis of epithelial-type ovarian cancer were eligible.

Eligible patients had stage III disease, a performance status of 0 to 2 (according to criteria established by the Southwest Oncology Group), normal blood counts, and adequate renal function (serum creatinine, ≤ 1.5 mg per deciliter [$130 \mu\text{mol}$ per liter]; creatinine clearance, ≥ 40 ml per minute). All patients gave informed consent according to institutional and federal guidelines before enrollment.

Treatment Plan

Patients were randomly assigned to receive intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin plus intravenous cyclophosphamide. The randomization procedure incorporated stratification according to the amount of residual tumor (≤ 0.5 cm vs. >0.5 cm to 2 cm), performance status (0 or 1 vs. 2), the timing of enrollment (during vs. after surgery),

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and the cooperative group (Southwest Oncology Group vs. Gynecologic Oncology Group vs. Eastern Cooperative Oncology Group).

Patients in both treatment groups received cyclophosphamide (600 mg per square meter of body-surface area in 150 ml of diluent) administered in a 60-to-90-minute intravenous infusion on day 1. Patients in the intravenous group received cisplatin (100 mg per square meter in 500 to 1000 ml of normal saline) administered intravenously at a rate of 1 mg per minute, followed by at least 1 liter of normal saline with 3 g of magnesium sulfate and 40 g of mannitol over a period of one to two hours on day 1. Patients in the intraperitoneal group received cisplatin (100 mg per square meter in 2 liters of normal saline) warmed to body temperature and instilled into the peritoneal cavity as rapidly as possible. Concurrently, these patients received at least 1 liter of normal saline with 3 g of magnesium sulfate and 40 g of mannitol intravenously.

Courses of cyclophosphamide and cisplatin were repeated every three weeks for a total of six cycles, provided the serum creatinine concentration was less than or equal to 1.9 mg per deciliter (170 μ mol per liter), the white-cell count was higher than 3000 per cubic millimeter, and the platelet count was higher than 100,000 per cubic millimeter. Therapy could be delayed for a maximum of two weeks to allow for the resolution of toxic effects. Cisplatin was permanently discontinued and the dose of cyclophosphamide increased to 1 g per square meter (in the absence of grade 3 or 4 myelosuppression) if peripheral neuropathy of grade 2 or higher developed or the serum creatinine concentration rose above 1.9 mg per deciliter. Therapy was discontinued altogether if the serum creatinine level remained higher than 1.9 mg per deciliter for eight weeks.

Clinical and Pathological Assessments

At base line and after six courses of therapy, a physical examination was performed, with a complete blood count, serum CA-125 and blood chemical measurements, and chest radiography. In addition, before each cycle, a physical examination was performed, with a complete blood count and measurement of serum CA-125 and creatinine concentrations. Blood chemical measurements were performed at the start of every other course. At the completion of therapy, patients without clinical evidence of ovarian cancer (excluding an elevated serum CA-125 value) underwent a second-look laparotomy to determine whether there had been a pathological response.

A complete pathological response was defined as no pathological evidence of disease on second-look surgery and biopsy of the upper abdomen and the para-aortic and retroperitoneal lymph nodes, as well as any other site previously involved with tumor.

Statistical Analysis

In the original study design (before the protocol was amended to increase enrollment), it was assumed that 215 eligible patients would be randomly assigned to each treatment group. At a two-sided P value of 0.05, with the use of a Pearson chi-square approximation, the estimated power was 0.85 to detect a difference of 55 percent versus 40 percent in pathological-response rates in the intraperitoneal and intravenous groups, respectively. The power was 0.93 (two-sided log-rank test, $\alpha=0.05$) to detect a difference if the underlying risk of death (hazard ratio) in the intraperitoneal group, as compared with the intravenous group, was 0.67. Survival was defined as the time from randomization to death from any cause.

Provisions for subgroup analysis were not included in the original study design. During the study, however, a consensus emerged among gynecologic oncologists that the patients most likely to benefit from intraperitoneal chemotherapy were those with a tumor mass that was no larger than 0.5 cm in the greatest dimension. Therefore, in January 1991, with no knowledge of subgroup data, we extended accrual for an additional year to achieve a sufficiently large sample for a separate analysis of data from patients with residual tumors that were no larger than 0.5

cm. All previously eligible patients were included in the extended sample, which was planned to include 560 eligible patients overall and 390 eligible patients with residual tumors no larger than 0.5 cm. In the analysis of this subgroup, if the hazard ratio was 0.67 for the patients receiving intraperitoneal treatment, the power to detect a difference was 0.88.

The treatment group, size of residual tumor (microscopical vs. ≤ 0.5 cm vs. >0.5 cm to 2 cm), age, performance status (0 or 1 vs. 2), race (white vs. other), tumor type (clear cell or mucinous vs. other), tumor grade, participating group (Southwest Oncology Group vs. Gynecologic Oncology Group vs. Eastern Cooperative Oncology Group), and timing of enrollment (during vs. after surgery) were included as covariates in Cox regression analyses.¹⁰ Two-sided Fisher's exact tests were used for comparisons of toxic effects in the two treatment groups. All eligible patients who received chemotherapy were included in the analysis of toxicity.

RESULTS

Patients

Between June 1986 and July 1992, 654 women were randomly assigned to a study group: 295 from the Southwest Oncology Group, 298 from the Gynecologic Oncology Group, and 61 from the Eastern Cooperative Oncology Group. A total of 108 patients were ineligible (52 in the intravenous group and 56 in the intraperitoneal group) for the following reasons: inadequate surgery (in 54), pathological findings that did not meet the study criteria (31), insufficient documentation (20), and miscellaneous

TABLE 1. CHARACTERISTICS OF 546 ELIGIBLE PATIENTS WITH STAGE III OVARIAN CANCER WHO WERE ASSIGNED TO TREATMENT WITH INTRAVENOUS OR INTRAPERITONEAL CISPLATIN.*

CHARACTERISTIC	INTRAVENOUS GROUP (N=279)	INTRAPERITONEAL GROUP (N=267)
Age (yr)		
Median	56	59
Range	21-85	24-84
	% of patients	
White race	92	93
Minimal residual disease (≤ 0.5 cm)	72	73
No gross disease after initial surgery	26	25
Performance status of 0 or 1	86	85
Type of tumor		
Serous	66	67
Endometrioid	9	10
Mixed cell	6	6
Undifferentiated	11	11
Clear cell	2	2
Mucinous	3	1
Unknown	3	3
Tumor grade		
1	13	11
2	30	31
3	57	58
Postsurgical enrollment	94	94

*Of the 654 patients randomly assigned to treatment with intravenous cisplatin (331 patients) or intraperitoneal cisplatin (323), 108 were ineligible for the study (52 in the intravenous group and 56 in the intraperitoneal group).

TABLE 2. PERCENTAGES OF ELIGIBLE PATIENTS RECEIVING CISPLATIN AND THE DOSE RECEIVED DURING EACH COURSE OF TREATMENT.

TREAT- MENT COURSE	PATIENTS RECEIVING CISPLATIN		CISPLATIN DOSE RECEIVED	
	INTRAVENOUS GROUP	INTRAPERITO- NEAL GROUP	INTRAVENOUS GROUP	INTRAPERITO- NEAL GROUP
	% of patients		% of initial dose	
1	99	93	100	100
2	96	87	102	100
3	92	81	98	98
4	84	75	97	99
5	73	67	99	98
6	58	58	96	97

clinical factors that did not meet the study criteria (3). Table 1 shows the characteristics of the eligible patients. There were no significant differences between the study groups with respect to important prognostic factors.

Of the 279 eligible patients in the intravenous group, 2 died before treatment, and 1 refused treatment after randomization. There were 20 major protocol violations among the 267 eligible patients in the intraperitoneal group: 3 patients died before treatment was started, 6 withdrew consent after randomization, 8 did not receive the assigned treatment for other reasons (5 because of complications related to intraperitoneal catheterization and 3 because of errors by the local pathologist), 2 received treatment for only one day, and 1 erroneously received intravenous carboplatin during cycles 2 through 6. All 546 eligible patients were included in the efficacy analyses (according to the intention-to-treat princi-

ple), regardless of whether they completed the assigned treatment. The 20 patients in both groups who did not receive any treatment were excluded from the toxicity analysis.

Intensity of Cisplatin Dose

In both the intravenous and intraperitoneal groups, 58 percent of all eligible patients completed six courses of cisplatin therapy (Table 2). Among these patients, the average proportion of the initial cisplatin dose administered during cycle 6 (the course with the maximal dose reduction) was 96 percent in the intravenous group and 97 percent in the intraperitoneal group. Cisplatin was discontinued because of toxic effects (with a concomitant increase in the cyclophosphamide dose) in 40 patients in the intravenous group and 22 in the intraperitoneal group.

Complete Pathological Responses

Of the 546 eligible patients, 20 never received any study treatment, 81 did not complete therapy, and 45 had tumors that progressed before the completion of therapy. Second-look surgery was not required in these patients. In 103 of the remaining 400 patients, surgery was contraindicated or the patient refused it (70 patients), or the procedure was performed but deemed inadequate by the Gynecologic Surgical Review Board (33). Because of the bias associated with this group of 103 patients who had no clinical evidence of disease at the completion of therapy but did not undergo second-look surgery or had inadequate surgery, the rates of pathological responses are given without statistical comparisons.

A total of 297 patients with no clinical evidence of disease at the end of chemotherapy underwent adequate second-look surgery. The rate of complete pathological responses was 36 percent in the intravenous group (complete responses in 57 of 158 pa-

TABLE 3. SURVIVAL OF ALL ELIGIBLE PATIENTS, ELIGIBLE PATIENTS WITH MINIMAL RESIDUAL DISEASE, AND ALL RANDOMIZED PATIENTS.*

SURVIVAL	ALL ELIGIBLE PATIENTS		ELIGIBLE PATIENTS WITH MINIMAL RESIDUAL DISEASE		ALL RANDOMIZED PATIENTS	
	INTRAVENOUS GROUP (N = 279)	INTRAPERITONEAL GROUP (N = 267)	INTRAVENOUS GROUP (N = 202)	INTRAPERITONEAL GROUP (N = 195)	INTRAVENOUS GROUP (N = 331)	INTRAPERITONEAL GROUP (N = 323)
	Survival (mo)					
Median	41	49	46	51	40	48
95% confidence interval	34-47	42-56	37-57	44-67	34-45	42-54
Hazard ratio	0.76†		0.80‡		0.77†	

*Minimal residual disease was defined as a residual tumor mass that was less than or equal to 0.5 cm in the greatest dimension.

†The hazard ratio is for the intraperitoneal group as compared with the intravenous group (P=0.02).

‡The hazard ratio is for the intraperitoneal group as compared with the intravenous group (P=0.10).

tients) and 47 percent in the intraperitoneal group (complete responses in 66 of 139).

Survival

All eligible patients were included in the primary analysis regardless of whether they completed the assigned treatment. Covariates associated with improved survival included the absence of gross disease at enrollment ($P < 0.001$), a younger age ($P < 0.001$), a type of tumor other than clear cell or mucinous ($P < 0.001$), and enrollment after surgery ($P < 0.001$). The final Cox model included these four factors and performance status (which was retained in the model because of its established prognostic importance).

The results after adjustment for these five factors are shown in Table 3, along with unadjusted median survival in the two groups. The hazard ratio for the risk of death in the intraperitoneal group, as compared with the intravenous group, was 0.76 (95 percent confidence interval, 0.61 to 0.96; $P = 0.02$). The median survival was 41 months (95 percent confidence interval, 34 to 47) in the intravenous group and 49 months (95 percent confidence interval, 42 to 56) in the intraperitoneal group (Fig. 1).

Figure 2 shows the survival curves for all eligible patients according to the extent of residual intraperitoneal disease. The effect of the treatment (intravenous or intraperitoneal cisplatin) was not influenced by the extent of residual disease ($P = 0.93$ for the interaction of treatment and residual disease). Table 3 shows the results of a separate analysis for the subgroup of patients with residual tumors no larger than 0.5 cm. The analysis was repeated for all 654 randomized patients, including those who were ineligible. The results were equivalent to those of the primary analysis (Table 3).

Toxic Effects

Two treatment-related deaths occurred in the intraperitoneal group. One patient died of respiratory failure of unknown cause 41 days after the second cycle of chemotherapy (blood counts were adequate at the time of death). The second patient died of bronchopneumonia during a period of chemotherapy-associated leukopenia 13 days after the third cycle. No treatment-related deaths occurred in the intravenous group.

Significantly more patients in the intravenous group than in the intraperitoneal group had grade 3 or higher granulocytopenia ($P = 0.002$) and leukopenia ($P = 0.04$) (Table 4). Table 5 shows the frequency of other toxic effects (grade 2 or higher) during any treatment cycle. Moderate-to-severe tinnitus and hearing loss were more frequent in patients receiving intravenous cisplatin than in those receiving intraperitoneal cisplatin. In addition, significantly more patients in the intravenous group had grade 2 or 3 neuromuscular toxic effects at the

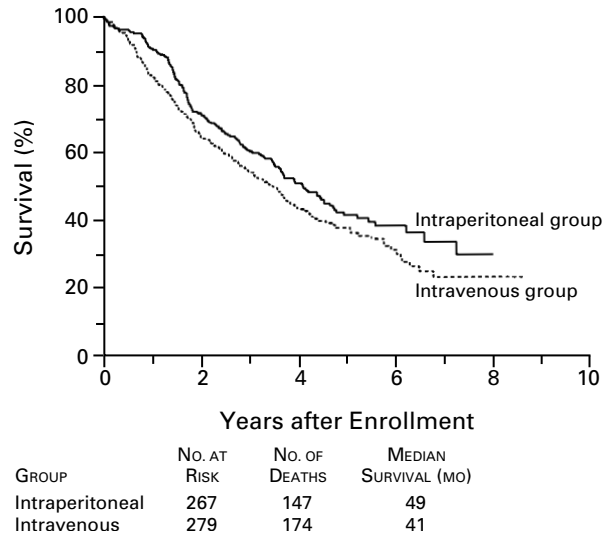


Figure 1. Survival of 546 Eligible Patients with Stage III Ovarian Cancer Who Were Randomly Assigned to Treatment with Intravenous or Intraperitoneal Cisplatin.

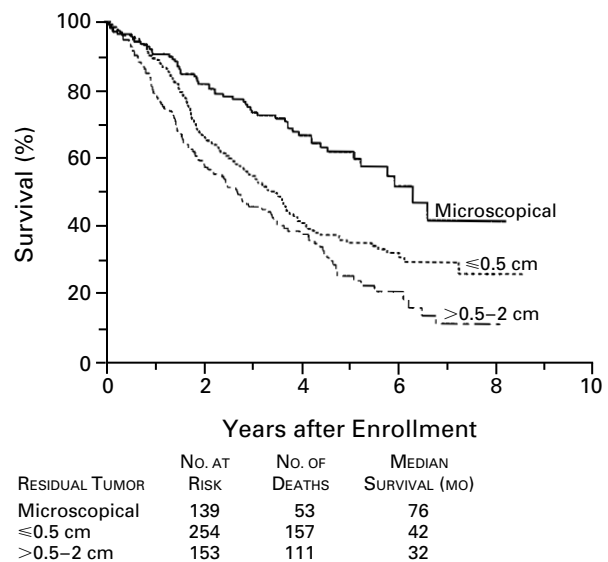


Figure 2. Survival of Eligible Patients According to the Extent of Residual Disease at Enrollment.

completion of chemotherapy (25 percent, vs. 15 percent in the intraperitoneal group; $P = 0.02$).

As expected, abdominal pain of grade 2 or higher was more common in the intraperitoneal group ($P < 0.001$); however, the pain usually resolved within 24 hours and was controlled with nonopioid or only weak opioid drugs. One patient had grade 4 abdominal pain. Transient dyspnea was infrequent but occurred in a significantly larger proportion of pa-

TABLE 4. FREQUENCY OF HEMATOLOGIC TOXIC EFFECTS (\geq GRADE 3) DURING ANY COURSE OF TREATMENT.

TOXIC EFFECT	INTRAVENOUS GROUP	INTRAPERITONEAL GROUP	P VALUE
	(N=276)	(N=250)	
	% of patients		
Anemia (<8.0 g of hemoglobin/dl)	25	26	0.84
Granulocytopenia (<1000 granulocytes/mm ³)	69	56	0.002
Leukopenia (<2000 white cells/mm ³)	50	40	0.04
Thrombocytopenia (<50,000 platelets/mm ³)	9	8	0.64

TABLE 5. FREQUENCY OF OTHER TOXIC EFFECTS (\geq GRADE 2) DURING ANY COURSE OF TREATMENT.

TOXIC EFFECT*	INTRAVENOUS GROUP	INTRAPERITONEAL GROUP	P VALUE
	(N=276)	(N=250)	
	% of patients		
Abdominal pain	2	18	<0.001
Fever	5	6	0.45
Tinnitus	14	7	0.01
Hearing loss	15	5	<0.001
Neuromuscular effects	21	16	0.18
Neuromuscular effects at end of treatment†	25	15	0.02
Pulmonary effects	0.4	3	0.002

*Grade 2 toxic effects were defined as follows: abdominal pain was pain relieved by oral opioids; fever, a temperature higher than 38°C; tinnitus, moderate symptoms of tinnitus; hearing loss, the ability to hear normal voice and sound levels but not whispered sounds; neuromuscular effects, an absence of deep-tendon reflexes, weakness, and peripheral-nerve pain; and pulmonary effects, transient dyspnea on mild exertion.

†A total of 201 patients in the intravenous group and 175 in the intraperitoneal group completed five or six courses of treatment.

tients in the intraperitoneal group (3 percent, vs. 0.4 percent in the intravenous group; $P=0.002$). In the patients receiving intraperitoneal cisplatin, dyspnea probably resulted from compression of the base of the lung by the fluid-filled intraperitoneal cavity.

DISCUSSION

In this study we compared intraperitoneal with intravenous cisplatin in women with advanced ovarian cancer. All the patients had undergone debulking surgery and received intravenous cyclophosphamide concomitantly with the cisplatin. The median survival of the patients treated intraperitoneally was 8 months longer than that of the patients given intravenous cisplatin (49 vs. 41 months), and the haz-

ard ratio in the intraperitoneal group was 0.76 ($P=0.02$). These results represent a 20 percent improvement in median survival and a 24 percent reduction in the risk of death during the entire follow-up period among the eligible patients in the intraperitoneal group.

Neutropenia, tinnitus, hearing loss, and neuromuscular toxic effects were significantly less frequent in the intraperitoneal group than in the intravenous group. Abdominal pain was more common in the intraperitoneal group, but in most cases it was transient and not severe (i.e., grade 3 or higher in only 5 percent of the patients).

Previous reports have summarized the toxic effects of intraperitoneal cisplatin at doses ranging from 50 to 100 mg per square meter.¹¹⁻¹³ Chronic, low-grade inflammation from repeated intraperitoneal administration may cause mild-to-severe abdominal pain and intraabdominal adhesions. These reports have generally focused on patients who had undergone two exploratory laparotomies before the administration of intraperitoneal cisplatin. In our study, all the patients had undergone only one definitive exploratory laparotomy within four weeks before the start of chemotherapy. Thus, our patients were probably less susceptible to the local toxic effects of intraperitoneal cisplatin.

Howell et al. reported that after second-line therapy with intraperitoneal cisplatin, rates of surgically established complete responses were significantly higher among patients with smaller residual intraperitoneal tumor masses (≤ 0.5 cm) than among those with larger masses (>0.5 cm to 2 cm).⁸ Consistent with this finding was the 80 percent rate of a complete pathological response among our patients with no gross residual disease who received intraperitoneal cisplatin (32 of 40 patients), as compared with a rate of 56 percent among those with no gross residual disease who received intravenous cisplatin (24 of 43). Such results reflect the fact that the penetration of intraperitoneal cisplatin is limited to a depth of 0.1 to 1 mm from the surface of the peritoneal tumor.¹⁴

We found that intraperitoneal cisplatin was associated with a longer survival than was intravenous cisplatin, whether residual intraperitoneal tumor masses were 0.5 cm or less or more than 0.5 cm in the greatest dimension. We do not know the reason for this result, but several explanations are possible. All previous investigations of intraperitoneal cisplatin therapy have been phase 2 studies, which included mainly patients who had already received intravenous cisplatin. Our patients had never before received chemotherapy, and their tumors may therefore have been highly sensitive to cisplatin. Moreover, the precision in measuring intraperitoneal tumor masses during an initial exploratory laparotomy is limited, and the total volume of the mass may

have more prognostic value than the maximal dimension.

The combination of intravenous paclitaxel plus intraperitoneal cisplatin may prove to be more effective than intravenous cyclophosphamide plus intraperitoneal cisplatin in patients with stage III ovarian cancer and minimal residual disease. The Gynecologic Oncology Group recently reported that paclitaxel plus cisplatin significantly increased survival (median, 38 months, vs. 24 months with cyclophosphamide plus cisplatin) when administered as primary chemotherapy in women with incompletely resected stage III or IV ovarian cancer.¹⁵ Ongoing phase 3 studies by the Gynecologic Oncology Group and the Southwest Oncology Group will further define the role of intraperitoneal cisplatin (and intravenous paclitaxel) in the treatment of stage III ovarian cancer that has been optimally resected.

Supported in part by grants from the National Cancer Institute (CA38926, CA32102, CA45450, CA04920, CA42028, CA46441, CA45560, CA13612, CA20319, CA35119, CA35090, CA35281, CA58686, CA28862, CA35431, CA35200, CA45377, CA58861, CA45807, CA35261, CA12644, CA35192, CA37981, CA42777, CA16385, CA12213, CA35128, CA04919, CA35178, CA35176, CA35262, CA32734, CA46282, and CA58415) and Bristol-Myers Squibb.

We are indebted to Drs. Renzo Canetta and Mace Rothenberg for scientific advice; to the individual investigators for their participation and support (especially Drs. Ronald Alvarez, Albert Bonebrake, Eric Jenison, William Creasman, Nicola Spirtos, Matthew Burrell, and Mark Crozier); to Dava Garcia for assistance with study coordination and manuscript preparation; to Janet O'Sullivan, M.S., for assistance with the statistical analysis; to Dana Sparks, M.A.T., for protocol coordination; to Janet Quade, Nancy Mason-Liddil, and Dianna Garcia for assistance with data management; and to Lois Loescher, R.N., M.S., for editorial assistance.

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