Randomized Trial of Bleomycin, Etoposide, and Cisplatin Compared With Bleomycin, Etoposide, and Carboplatin in Good-Prognosis Metastatic Nonseminomatous Germ Cell Cancer: A Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial

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Purpose: This prospective randomized multicenter trial was designed to evaluate the efficacy of carboplatin plus etoposide and bleomycin (CEB) versus cisplatin plus etoposide and bleomycin (BEP) in first-line chemotherapy of patients with good-risk nonseminomatous germ cell tumors.

Patients and Methods: Between September 1989 and May 1993, a total of 598 patients with good-risk nonseminomatous germ cell tumors were randomized to receive four cycles of either BEP or CEB. In each cycle, the etoposide dose was 120 mg/m^2 on days 1, 2, and 3, and the bleomycin dose was 30 U on day 2. BEP patients received cisplatin at 20 mg/m^2/d on days 1 to 5 or 50 mg/m^2 on days 1 and 2. For CEB patients, the carboplatin dose was calculated from the glomerular filtration rate to achieve a serum concentration × time of 5 mg/mL × minutes. Chemotherapy was recycled at 21-day intervals to a total of four cycles.

Results: Of patients assessable for response, 253 of 268 (94.4%) of those allocated to receive BEP achieved a complete response, compared with 227 of 260 (87.3%) allocated to receive CEB ($P = .009$). There were 30 treatment failures in the 300 patients allocated to BEP and 79 in the 298 allocated to CEB (log-rank $\chi^2 = 26.9$; $P < .001$), which led to failure-free rates at 1 year of 91% (95% confidence interval [CI], 88% to 94%) and 77% (95% CI, 72% to 82%), respectively. There were 10 deaths in patients allocated to BEP and 27 in patients allocated to CEB (log-rank $\chi^2 = 8.77$; $P = .003$), which led to 3-year survival rates of 97% (95% CI, 95% to 99%) and 90% (95% CI, 86% to 94%), respectively.

Conclusion: With these drug doses and schedules, combination chemotherapy based on carboplatin was inferior to that based on cisplatin. This BEP regimen that contains moderate doses of etoposide and bleomycin is effective in the treatment of patients with good-prognosis metastatic nonseminoma.

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CISPLATIN-BASED chemotherapy combinations are highly effective in the management of metastatic nonseminomatous germ cell tumors and a variety of such combinations are associated with long-term disease-free survival and presumed cure in approximately 85% of patients.[1-5] The prognosis has been found to be better in patients with less extensive metastatic disease defined in a number of ways by different groups. For the purposes of this trial, the definition of eligibility was derived from an analysis of 795 patients treated for metastatic disease between 1982 and 1986.[2] This showed that a good-prognosis group could be defined as those who did not have metastases in liver, bone, or brain; who had relatively low tumor markers (human chorionic gonadotropin [HCG] < 10,000 IU/L and alfa fetoprotein [AFP] < 1,000 KU/L); who had ≤ 20 lung masses; and whose maximum diameter of metastatic disease was 10 cm in the abdomen or 5 cm in the mediastinum or supraclavicular fossa. The predicted 3-year survival rate in this group was 94%.[2]

In view of the reduced toxicity of carboplatin compared with cisplatin with respect to gastrointestinal symptoms, renal damage, high-tone auditory loss, and peripheral neuropathy, this drug was introduced into the management of patients with germ cell tumors.[6-8] Results of pilot studies were promising. Of 121 patients with good-prognosis metastatic nonseminomatous disease treated with carboplatin, etoposide, and bleomycin (CEB) at the Royal Marsden Hospital between 1984 and 1990, there were only nine treatment failures and the cause-specific survival rate was 98% with a median follow-up duration of 36 months.[9] However, the prognosis was substantially worse in patients with more advanced categories of metastatic disease,[8] and in view of the curability of this tumor in good-prognosis patients, it was felt that the efficacy of carboplatin combinations required rigorous evaluation before being generally accepted as the standard of care. Therefore, the United Kingdom Medical Research Coun-

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cil (MRC) Testicular Tumour Working Party designed a prospective randomized trial, which was launched in 1989. The Genitourinary Group of the European Organization for Research and Treatment of Cancer (EORTC) joined the trial in January 1991.

The trial design was informed by results of studies available at that time suggesting that bleomycin may not be an essential component of the combination chemotherapy of patients with good-prognosis germ cell tumors,[3,10,11] and for this reason, together with the aim to reduce toxicity further, the dose of bleomycin in both arms of the trial was reduced to 30 U per cycle.

A synchronous trial was performed by the Memorial Sloan-Kettering Cancer Center and the Southwestern Oncology Group (SWOG) based on 270 patients whose treatment was randomized between four cycles of etoposide plus cisplatin (EP) or four cycles of etoposide plus carboplatin (EC). In this trial, EC was given on a 28-day cycle and the carboplatin dose in 108 of 130 patients allocated to receive EC was 500 mg/m^2 on day 1 of each cycle.[12] This trial showed that the carboplatin-based combination led to inferior relapse free-survival, but no difference in overall survival was detected.

PATIENTS AND METHODS

Eligibility

Patients with histologically confirmed nonseminomatous germ cell tumors, or seminoma with unequivocally raised AFP levels, were eligible if they satisfied all of the following criteria, which were derived from prognostic factor analyses by the MRC[2] and EORTC and defined a group that consisted of two thirds of patients with metastatic nonseminoma who had an expected progression-free survival rate at 1 year of 90%. All patients had had testicular primary tumors and had adequate renal function (glomerular filtration rate [GFR] > 50 mL/min). Criteria for entry were abdominal mass at most 10 cm in maximum transverse diameter; supraclavicular and mediastinal masses at most 5 cm in diameter; less than 20 lung metastases; no liver, bone, or brain metastases; and AFP level less than 1,000 KU/L and HCG level less than 10,000 IU/L.

Patients were randomized through the MRC Cancer Trials Office (CTO) in Cambridge and the EORTC Data Center in Brussels. Randomization was stratified by participating center. Data management was performed in both randomizing centers, and the data were transferred to the MRC CTO for interim and final analyses.

Treatment

Chemotherapy consisted of four cycles at 21-day intervals of either bleomycin, etoposide, and cisplatin (BEP) or CEB. The BEP schedule gave etoposide 120 mg/m^2 on days 1, 2, and 3 and bleomycin 30 U on day 2 only; cisplatin was given to a total dose of 100 mg/m^2 divided over 2 or 5 days. The CEB schedule was identical, except for the replacement of cisplatin by carboplatin. The initial carboplatin dose was that required to achieve an area under the concentration-time curve (AUC) of 5 mg/mL × minutes.[9,13] Thus, for GFR based on EDTA clearance, the recommended dose was 5 × (GFR + 25) mg; for GFR based on creatinine clearance, the dose was 10% lower. Carboplatin dose was escalated through successive cycles when the day 16 platelet count was more than 150 × 10^9/L and WBC count greater than 1.5 × 10^9/L. Following chemotherapy, excision of residual masses greater than 2 cm was considered in patients with normal markers, with smaller masses being watched and excised only if persistent. Treatment on relapse was at the clinician's discretion.

Statistical Considerations

The main end point of the trial was failure-free survival, with failure being defined by serial rising markers, the finding of residual undifferentiated malignancy in the resected surgical specimen, the appearance of new metastases or the noncystic enlargement of existent masses, or death. Response to chemotherapy and overall survival were also recorded.

The trial was designed as an equivalence trial. Given the anticipated toxicity savings with carboplatin-based therapy and the assumption that most CEB failures would respond favorably to cisplatin-based salvage therapy, some reduction in the failure-free rate was considered acceptable. The target accrual was a minimum of 450 patients to enable an 8% to 10% difference in failure-free rate to be excluded reliably (90% power) assuming a failure-free rate at 1 year on BEP of 90%. An independent data-monitoring committee (DMC) reviewed the data after this target had been reached to advise on further continuation of the trial to detect smaller differences in the failure rate. They recommended against further accrual and the trial was formally closed in May 1993.

Failure-free survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Treatment effects are summarized via the hazards ratio (HR); an HR greater than 1 indicates benefit to BEP. Categorical data were analyzed using standard χ^2 tests with tests for trend across ordered categories where appropriate.

RESULTS

Randomization began via the MRC in September 1989, and the EORTC joined in January 1991. The rapid accrual meant that few events were observed while the trial was open. The final decision to close the trial was made in May 1993, when a total of 598 patients had been randomized: 300 allocated to receive BEP and 298 allocated to receive CEB. Patients were entered from 46 centers in 10 countries. The median follow-up time of surviving patients is approximately 3 years. Eighty percent of patients in each treatment group have been monitored for at least 2 years.

Pretreatment characteristics are listed in Table 1, and are well balanced between the treatments. Overall, 13% of patients had raised markers as the only sign of disease and a further 53% had disease confined to the paraaortic nodes.

Treatment Received

Of 300 patients allocated to receive BEP, full treatment data are available on 297, of whom 271 (91%) received the full four cycles of BEP. Of the 26 who did not, one

Table 1. Pretreatment Characteristics by Treatment Allocated

Characteristic	Allocated Treatment: BEP No.	BEP %	CEB No.	CEB %
Age, years				
< 20	18	6	26	9
20-29	135	45	135	46
30-39	111	37	102	34
≥ 40	34	11	33	11
Primary histology				
MTI	100	33	97	33
MTT	23	8	16	5
MTU	120	40	124	42
TD	22	7	29	10
Other	31	10	29	10
AFP level (IU/L)				
< 100	227	77	225	76
100-499	40	14	52	18
500-999	21	7	12	4
≥ 1,000	7	2	7	2
β-HCG level (IU/L)				
< 100	215	3	200	68
100-999	53	18	71	24
1,000-4,999	21	7	22	7
5,000-9,999	5	2	1	0
≥ 10,000	2	1	1	0
Maximum diameter of abdominal mass (cm)				
None	79	27	78	27
< 2	44	15	44	15
2-5	153	52	149	51
5-10	18	6	23	8
> 10	3	1	0	0
Maximum diameter of mediastinal mass (cm)				
None	277	93	271	92
< 2	10	3	9	3
2-5	12	4	15	5
Maximum diameter of neck mass (cm)				
None	293	98	281	95
< 2	1	0	4	1
2-5	5	2	10	3
No. of lung metastases				
None	201	68	205	70
1-4	71	24	58	20
5-19	22	8	30	10
≥ 20	2	1	1	0
Royal Marsden Stage*				
IM	36	12	37	13
II	151	51	154	53
III	14	5	13	4
IV	95	32	89	30
Indiana Classification*†				
Minimal disease				
1	36	12	37	13
2	4	1	4	1
3				
(a) < 3 in maximum transverse diameter	90	30	81	28
(b) ≥ 3 cm in maximum transverse diameter	59	20	72	25
4	61	21	58	20
Subtotal	250	84	262	86
Moderate disease				
5	2	1	1	0
6	34	11	34	12
Subtotal	36	12	35	12
Advanced disease				
7	7	2	5	2
8	3	1	1	0
9	0	0	0	0
Subtotal	10	3	6	2
Total	300	100	298	100

* Nine patients (4 BEP, 5 CEB) were not classifiable on the Royal Marsden or Indiana University staging systems.

† Only total lung metastases were recorded, so they have been translated for the Indiana University Classification[20] as follows: ≤ 9, equivalent to < 5 per lung field; 10-20, equivalent to 5-10 per lung field; > 20, equivalent to > 10 per lung field.

patient failed to attend and received no chemotherapy; six stopped after three cycles and went for early surgery; two stopped after three cycles having achieved a rapid response; nine changed to CEB because of renal, cardiac, or ototoxicity; one received CEB in cycle 1 in error; one died after the first cycle from a small bowel infarction; two switched to more intensive treatment because of lack of marker response; and four received alternative treatment throughout—two of these received CEB, one through patient choice and one through administrative error.

Of 298 patients allocated to receive CEB, full data are available on 295, of whom 277 (94%) received the full four cycles of CEB. Of the 18 who did not, six patients stopped after three cycles and received no further chemotherapy—three of these patients went for early surgery, two had achieved a rapid response, and one patient failed to attend for the fourth cycle. Seven patients switched to more intensive treatment because of lack of marker response, and one patient died after the first cycle with the postmortem examination unable to establish the cause. One received BEP in cycle 2 in error, and three patients

Table 2. Response

Response	Allocated Treatment			
	BEP		CEB	
	No.	%	No.	%
Complete response	253	87.2	227	78.3
To ch alone	180	62.0	171	59.0
To ch + S	73	25.2	56	19.3
Incomplete response	15	5.2	33	11.4
Undiff cancer resected	11	3.8	29	8.2
Inadequate marker response	4	1.4	9	3.1
Not assessable (PMNM)	22	7.6	30	10.3
Unknown	10		8	
Total	300		298	

Abbreviations: ch, chemotherapy; S, surgery; Undiff, undifferentiated; PMNM, persisting mass(es) with normal markers.

received alternative treatment throughout—one of these received BEP by patient request.

Response

Responses to chemotherapy with or without surgery are listed in Table 2. Complete response is defined as either complete remission on chemotherapy alone or complete resection of residual masses that contain only necrosis/fibrosis or mature (differentiated) teratoma. Patients with raised markers, viable (undifferentiated) tumor in the resected mass, or death while on treatment are considered incomplete responders. Of those patients assessable for response (ie, excluding those patients in whom residual masses were not excised), 94.4% of patients allocated to receive BEP and 87.3% of patients allocated to receive CEB achieved a complete response as described earlier, a difference that is statistically significant ($P = .009$).

Failure-Free Survival

The failure-free survival curves for all randomized patients according to allocated treatment are given in Fig 1. The HR of 2.75 (95% confidence interval [CI], 1.88 to 4.03) corresponds to an absolute difference in failure-free rates at 1 year of 14%, with a 95% CI of 8% to 25%. There were 30 treatment failures in the 300 patients allocated to receive BEP and 79 in the 298 patients allocated to receive CEB (log-rank $\chi^2 = 26.9$; $P < .001$), which led to failure-free rates at 1 year of 91% (95% CI, 88% to 94%) and 77% (95% CI, 72% to 82%), respectively.

The difference in failure-free survival was more marked in patients with stage III or IV disease than in patients with stage I marker-positive or stage II disease. A formal test of heterogeneity of treatment effect by stage was not significant ($\chi^2 = 2.74$; $P = .09$), although there were 21 failures among 191 patients with stage IM or II allocated to receive BEP, compared with 46 failures among 196 allocated to receive CEB (HR = 2.3; 95% CI, 1.3 to 3.4). In stage III/IV, there were nine failures among 109 patients allocated to receive BEP, compared with 33 failures among 102 allocated to receive CEB (HR = 4.2; 95% CI, 2.2 to 7.8).

Table 3 lists a summary of failure and salvage data. Approximately one third of patients who failed to respond to initial chemotherapy with either BEP or CEB were disease-free at the time of analysis; this proportion may decrease with longer follow-up evaluation.

Survival

Survival curves are given in Fig 2. A total of 10 deaths have been reported in patients allocated to receive BEP and 27 in patients allocated to receive CEB, a difference that is statistically significant (log-rank $\chi^2 = 8.77$; $P = .003$; HR = 2.65; 95% CI, 1.39 to 5.05). The 3-year survival rates were 97% (95% CI, 95% to 99%) and 90% (95% CI, 86% to 94%), respectively, a difference of 7% (95% CI, 1% to 11%).

Carboplatin Dose

The initial carboplatin dose given was, on average, 30 mg higher than that required according to the patient's GFR; this was largely due to an option to increase the prescribed dose in patients with a large surface area. Carboplatin dose escalations following assessment of first-course blood count nadirs were performed in just over half the patients. Thirty-one percent had just one dose escalation, 11% had two, and 10% had escalations throughout all three subsequent cycles.

In patients treated with CEB, the validity of carboplatin dose was investigated in a number of ways. In comparing treatment failures with patients continuously disease-free, the mean cycle 1 carboplatin dose per square meter was 378 mg versus 391 mg ($P = .14$). Fifty-three percent versus 51%, respectively, had dose escalations. The cycle 1 blood count nadirs were lower in patients who have not failed to respond (χ^2 [trend], $P = .03$ for platelets, .04 for WBCs) (Table 4). There were no significant differences in WBC and platelet nadirs in the first cycle of CEB comparing those whose carboplatin dose was calculated from a creatinine clearance or an EDTA clearance, and also there was no difference in failure rates (28% *v* 26.2%; $\chi^2 = 0.98$; $P = .75$). In summary, there was no evidence that CEB treatment failures were incorrectly dosed in comparison to those who did not fail to respond. There is some evidence that higher nadir counts were associated with increased failure rates, and the possibility that this relates

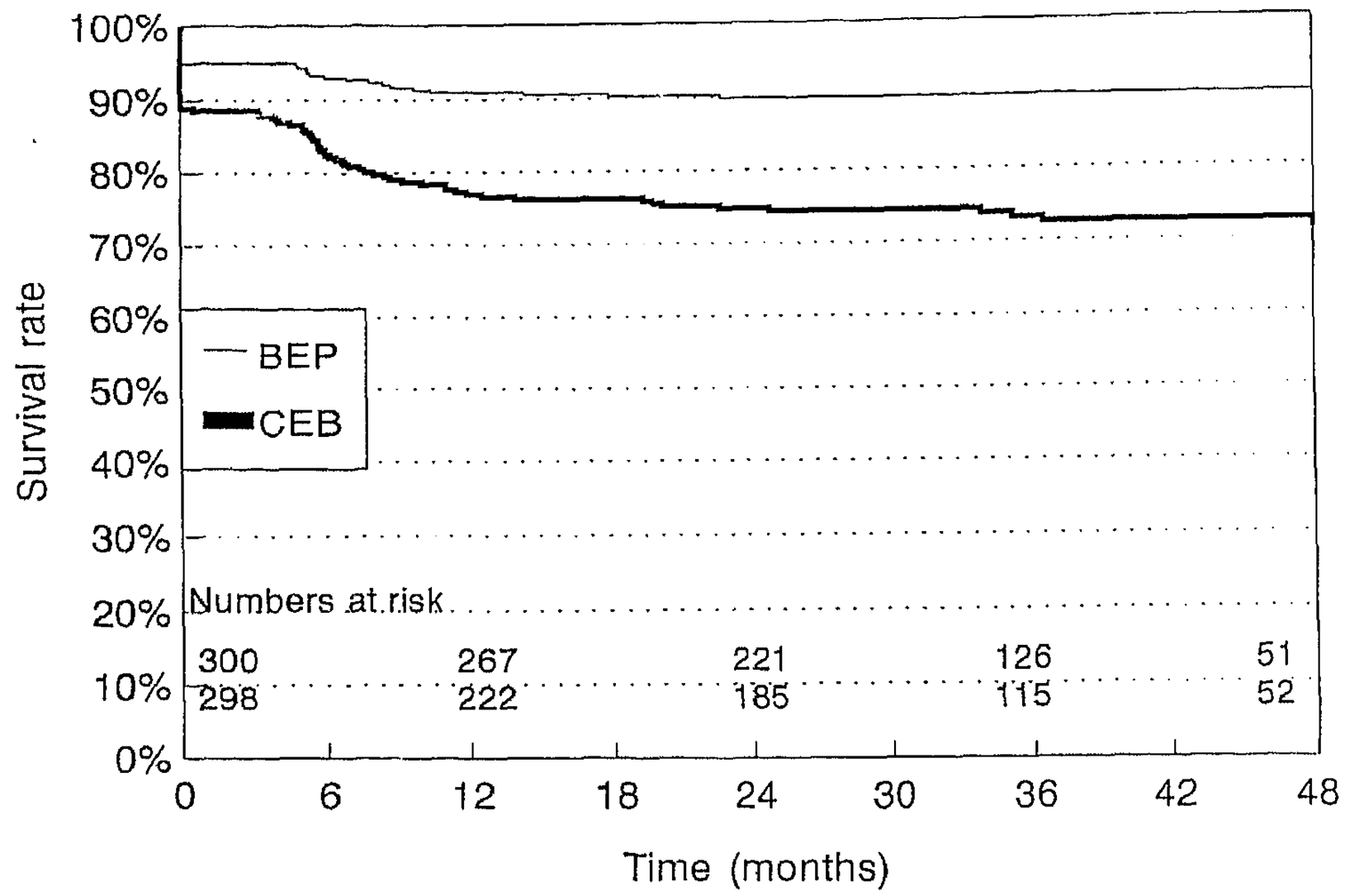

Fig 1. TE09/30896. Failure-free survival by treatment allocated.

also to BEP patients cannot be excluded in view of the small number of BEP failures.

To assess carboplatin dose-response, patients were split into three groups of approximately equal size; there was no consistent trend in failure rates (Table 5).

Toxicity

Toxicity on treatment is listed in Table 6. Thrombocytopenia was more pronounced in CEB patients (χ^2 [trend], $P < .0001$). Mild mucosal toxicity was more common in BEP patients (χ^2 [trend], $P = .07$); however, there was no difference in the incidence of "clinically distressing" mucosal toxicity. Sensory deficit was also more common with BEP (χ^2 [trend], $P = .001$), but was mainly mild. Audiometry was performed in only a small subset of MRC patients; some degree of hearing loss was found in 11 of 39 BEP patients and two of 28 CEB patients ($P = .07$). As expected, CEB was associated with fewer days in hospital during the protocol chemotherapy; 88% of patients allocated CEB had fewer than 14 days in hospital compared with 41% of patients allocated to receive BEP.

Renal toxicity is listed in Table 7. GFR decreased from a median of 123 mL/min prechemotherapy to 110 mL/min approximately 4 weeks after completion of induction chemotherapy with BEP, and to 120 mL/min after completion of CEB, a statistically significant difference (Mann-Whitney $P = .02$). This difference appears to be maintained; taking the maximum GFR recorded at any time more than 12 months from randomization (9 months from completion of treatment), the median value for BEP was 109 mL/min and for CEB, 121 mL/min (Mann-Whitney $P = .05$).

Table 3. Current Status of Patients by Initial Chemotherapy Allocated

Status	Allocated Treatment	
	BEP	CEB
Total failures	30	79
Early death	1	1
Incomplete response to initial chemotherapy (lack of marker response)	3	8
Viable (undifferentiated) tumor resected	11	24
Relapse	15	46
Dead	10	26
Time from failure to death, months		
Median	8	11
Range	0-37	0-32
Alive	20	53
Time since failure, months		
Median	29	23
Range	3-69	0-62
Continuously disease-free	270	219
Total	300	298

DISCUSSION

This trial has demonstrated that combination chemotherapy based on BEP is superior to the combination of CEB in the doses and schedules used. Patients allocated

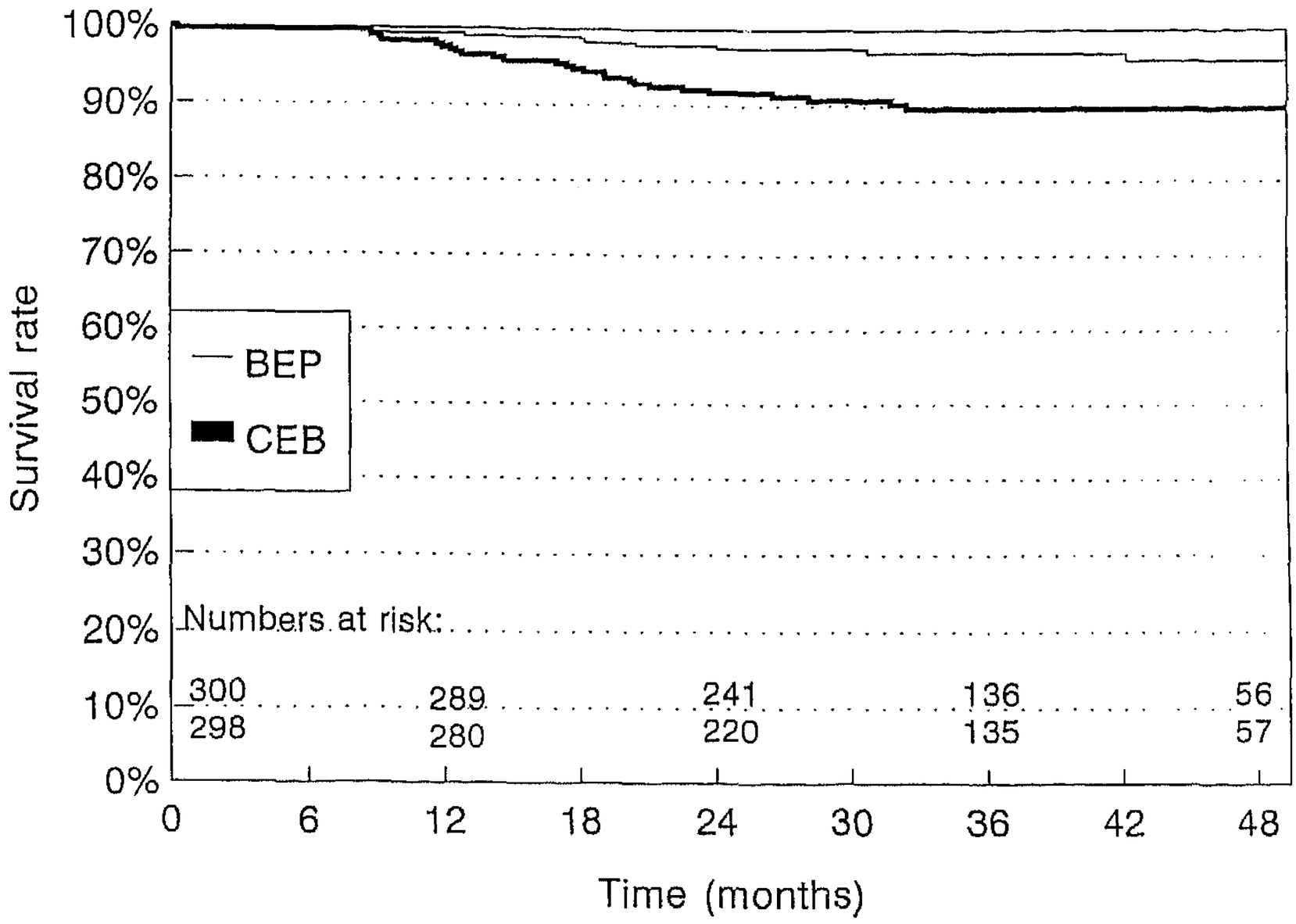

Fig 2. TE09/30896. Overall survival by treatment allocated.

to receive CEB had significantly worse failure-free and overall survival and, additionally, nadir thrombocytopenia was more pronounced. The mild mucosal toxicity, peripheral sensory neuropathy, and audiometric evidence of hearing loss were more marked in patients who received cisplatin. These toxicities were all mild in severity. Renal toxicity was more marked in patients allocated to receive cisplatin; however, there was only a minor decrease in the median GFR assessed at 1 month and again more than 9 months after the completion of cisplatin-based chemotherapy.

The inferior failure-free survival in patients treated with CEB is consistent with the results of a multicenter randomized phase III clinical trial that compared EC with EP.[12] This trial was based on 270 patients with good-risk germ cell tumors randomized to receive four cycles of either EP or EC with an etoposide dose in all patients of 100 mg/m^2 on days 1 through 5, cisplatin 20 mg/m^2 on days 1 through 5, and carboplatin at a fixed dose of 500 mg/m^2 on day 1. In this trial, the EC recycling interval was 28 days, whereas the EP recycling interval was 21 days. One interpretation of the inferior results in the car-

Table 4. Treatment Effect and Myelosuppression

	Treatment Failures			
	No		Yes	
Cycle 1 Nadirs	No.	%	No.	%
CEB patients				
Platelets (× 10^9/L)				
> 150	109	53	43	61
90-150	54	17	23	33
< 90	41	20	4	6
WBC (× 10^9/L)				
> 2.0	160	79	63	90
≤ 2.0	42	21	7	10
BEP patients				
Platelets (× 10^9/L)				
> 150	183	78	21	81
90-150	41	18	5	19
< 90	10	4	0	0
WBC (× 10^9/L)				
> 2.0	209	89	25	86
≤ 2.0	25	11	1	4

Table 5. Carboplatin Dose-Response

Carboplatin Dose	No. of Failures/ Patients	Crude Failure Rate (%)	Test Statistic
Cycle 1 dose received (mg)			
< 700	18/69	26	χ^2 (trend) = 0.75
700-800	28/85	33	P = .39
> 800	15/75	20	
Cycle 1 dose received (mg/m^2)			
< 350	18/58	31	χ^2 (trend) = 0.44
350–400	20/81	25	P = .51
> 400	23/67	26	

Table 6. Toxicity During Treatment

During Treatment	Allocated Treatment			
	BEP		CEB	
	No.	%	No.	%
Nadir WBC (× 10^9/L)				
> 2	154	75	137	65
1.0-2.0	47	23	72	34
< 1.0	3	1	1	0
< 1.0 + sepsis	1	0	0	0
Nadir platelets (× 10^9/L)				
> 150	142	69	75	36
90-150	43	21	68	32
50-89	18	9	42	20
< 50	2	1	25	12
Swelling of hands/feet				
None	205	95	209	95
Minor	8	4	8	4
Clinically distressing	2	1	3	1
Mucosal				
None	169	79	190	87
Minor	42	20	24	11
Clinically distressing	4	2	5	2
Motor				
None	204	95	211	97
Minor	9	4	7	3
Clinically distressing	1	0	0	0
Sensory				
None	179	84	205	94
Minor	30	14	12	6
Clinically distressing	4	2	1	0
Audiometry				
Normal hearing	28	72	27	93
High tone loss, 8 kHz	9	23	1	3
High tone loss, 2 kHz	2	5	1	3
Total (MRC patients only)	236		236	472

boplatin arm was this was due to the long intercycle interval. The trial demonstrated that 24% of patients who received carboplatin experienced an incomplete response or relapse, compared with 13% of those allocated to receive cisplatin ($P = .02$). No difference in overall survival was evident at the time of the report.[12]

The etoposide dose was higher at 2,000 mg/m^2 per cycle in the Memorial Sloan-Kettering/SWOG trial of EP versus EC than in the MRC/EORTC trial (1,440 mg/m^2); however, there is no clear evidence that this had an impact on response. Before response rates are compared, it should be emphasized that the Memorial/SWOG report included within the definition of complete response those patients who had complete resection of undifferentiated cancer postchemotherapy (classified as incomplete response by the MRC/EORTC). Also, in our report on the MRC/EORTC trial, almost 10% of patients were classified as not assessable for response because of persisting masses with normal markers (PMNM). Table 2 classifies subcategories of response to allow a comparison between the trials. Using the Memorial/SWOG definition, the MRC/EORTC complete response rates were 91% (264 of 290) for BEP and 87% (251 of 290) for CEB if nonassessable (PMNM) patients were included in the denominator. Complete response rates were 98.5% (264 of 268) for BEP and 96.5% (252 of 260) for CEB in assessable patients, compared with 90% for EP and 88% for EC in the Memorial/SWOG report. However, as shown in Table 1, our use of primary chemotherapy for many patients with small-volume retroperitoneal metastases led to a higher proportion of those in the MRC/EORTC trial having minimal disease on the Indiana University classification (85% *v* 58% in the Memorial/SWOG trial), which might also influence the response rates.

The results appear in contrast to the pilot study of carboplatin-based therapy in germ cell tumors.[9,14] The major differences between the pilot study and the randomized trial are that the pilot study was performed within a single institution by a specialized unit and was based on a higher bleomycin dose and dose-intensity, namely, 30 U/wk to a total of 360 U. There is evidence for improved survival of patients with germ cell tumors treated in specialized centers[15]; however, all centers that contributed to this trial had experience and expertise in the chemotherapy of germ cell tumors. When this trial was designed, evidence was suggesting that bleomycin had little role in the combination chemotherapy of patients with good-prognosis germ cell tumors.[3,10,16] Subsequent studies have emphasized the importance of bleomycin, especially in the context of modifications of the standard four cycles of BEP, such as the use of vinblastine rather than etoposide[17] or a reduction in the total number of treatment cycles.[18] It is conceivable therefore that the inferior efficacy of CEB found by the randomized trial was compensated for in the pilot study by the use of full-dose weekly bleomycin.

There was concern that the requirement for accurate assessment of GFR as a basis for carboplatin dosimetry might have led to inadvertent underdosing with carboplatin. Previous studies that analyzed carboplatin dose-response suggested the relevance of accurate dosimetry.[9]

Table 7. Renal Toxicity

Time	Allocated Treatment			
	BEP		CEB	
	Median	Range	Median	Range
Pretreatment	123	69-252	123	58-213
4 weeks postchemotherapy	110	45-182	120	75-198
> 9 months postchemotherapy	109	65-169	121	55-279

An analysis of 121 patients treated with CEB at the Royal Marsden Hospital demonstrated that at a carboplatin dose of ≥ 400 mg/m^2, two of 58 patients failed to respond to treatment, compared with seven of 63 patients who received a dose less than this. Similarly, if dose was based on GFR, a serum concentration × time of 5.0 mg/mL × minutes was associated with failure in two of 74 patients (2.7%), compared with seven of 47 patients (14.9%) treated to a serum concentration × time less than this ($P \leq .05$). The failure rate increased to 26% for doses less than 4.5 mg/mL × minutes. To seek evidence for carboplatin underdosing, we analyzed dose and extent of myelosuppression in patients treated with CEB, comparing those who failed to respond after chemotherapy with those who did not fail to respond (Table 5). There were no significant differences, which suggests that inadequate carboplatin dose was not the cause of the increased failure rate. Also, the complete response rate for CEB was not significantly different from that reported for EC (with carboplatin at 500 mg/m^2) in the Memorial/SWOG trial.[12] However, it is noteworthy that the overall level of myelosuppression that resulted from CEB was low (Table 6). In other tumor types, such as ovarian cancer, correlations between carboplatin-induced myelosuppression and treatment outcome have been noted,[19] and it is conceivable that a higher initial carboplatin dose might have been associated with improved efficacy of the combination. Additionally, it is conceivable that there is pharmacokinetic interaction between cisplatin and etoposide, with the renal effects of cisplatin influencing the excretion of etoposide. This has been shown not to occur with carboplatin.[19]

This trial confirms the efficacy of the combination of BEP, even when associated with the relatively low total doses of 120 U of bleomycin and 1,440 mg/m^2 of etoposide. This arm of the trial was associated with only 10 disease-related deaths among 300 allocated patients, a survival rate at 3 years of 97%, and with toxicities that were both uncommon and mild. Since bleomycin-induced pulmonary toxicity continues to be a problem in the management of testicular tumors, the efficacy of the BEP schedule that contains a total bleomycin dose of only 120 U is of interest. In good-prognosis patients with germ cell tumors defined using different criteria, four cycles of EP have also achieved high control rates and survival.[3,12,16] Thus, to define the optimal regimen for patients with good-prognosis metastatic germ cell tumors, key clinical trial results include the inferiority of carboplatin compared with cisplatin in this and a previous report[12] and the equivalence of EP and BEP when each are given to total of four cycles,[19] but the inferiority of EP compared with BEP when each is given to a total of only three cycles.[18] The MRC and the EORTC are now cooperating on a prospective randomized trial with the main aim to confirm the previous report[4] that three cycles of BEP chemotherapy are as effective as four cycles in good-prognosis patients. In this trial, all patients will receive bleomycin 30 U/wk for 9 cycles.

APPENDIX
Other Trial Participants

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	M.V. Williams	Addenbrooke's Hospital, Cambridge
	P. Harper	Guys Hospital, London
	N.J. Hodson	Royal Sussex County Hospital, Brighton
	F. Madden	Leicester Royal Infirmary, Leicester
	A. Benghiat	Derby Royal Infirmary
	A.L. Harris, P.A. Philip, D.J. Cole	Churchill Hospital, Oxford
	R.J. Grieve, D.A. Jones, A.D. Stockdale	Walsgrave Hospital, Coventry
France:	H. Bittard	Hopital Saint Jacques, Besançon
	J.P. Bergerat	Hopital Universitaire Hautpierre, Strasbourg
Germany:	G. Kaiser	Klinikum Nuremberg
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Netherlands:	H.P.T. Slee	St Antonius ZH, Nieuwegein
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	K.L. Roozendaal	OLV Gasthuis, Amsterdam
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	C. van de Beek	AZH Maastricht
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New Zealand:	C.H. Atkinson, B.M. Colls, B. Fitzharris, B. Robinson	Christchurch Hospital
	S.G. Allan	Palmerston North Hospital, Palmerston
Scotland:	G.W. Howard, M. Cornbleet	Western General Hospital, Edinburgh
	D. Whillis	Raigmore Hospital, Inverness
	H. Yosef	Western Infirmary, Glasgow
Switzerland:	J.A. Bauer	Centre Hosp. Univ. Vaudois, Lausanne
Wales:	H. Parry	Ysbyty Gwnedd, Bangor

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