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ORIGINAL REPORT

Randomized Phase III Study Comparing Paclitaxel–Bleomycin, Etoposide, and Cisplatin (BEP) to Standard BEP in Intermediate-Prognosis Germ-Cell Cancer: Intergroup Study EORTC 30983

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ABSTRACT

Purpose
To compare the efficacy of four cycles of paclitaxel–bleomycin, etoposide, and cisplatin (T-BEP) to four cycles of bleomycin, etoposide, and cisplatin (BEP) in previously untreated patients with intermediate-prognosis germ-cell cancer (GCC).

Patients and Methods
Patients were randomly assigned to receive either T-BEP or standard BEP. Patients assigned to the T-BEP group received paclitaxel 175 mg/m^2 in a 3-hour infusion. Patients who were administered T-BEP received primary granulocyte colony-stimulating factor (G-CSF) prophylaxis. The study was designed as a randomized open-label phase II/III study. To show a 10% improvement in 3-year progression-free survival (PFS), the study aimed to recruit 498 patients but closed with 337 patients as a result of slow accrual.

Results
Accrual was from November 1998 to April 2009. A total of 169patients were administered BEP, and 168 patients were administered T-BEP. Thirteen patients in both arms were ineligible, mainly as a result of a good prognosis of GCC (eight patients administered BEP; six patients administered T-BEP) or a poor prognosis of GCC (one patient administered BEP; four patients administered T-BEP). PFS at 3 years (intent to treat) was 79.4% in the T-BEP group versus 71.1% in the BEP group (hazard ratio [HR], 0.73; CI, 0.47 to 1.13; *P* [log-rank test] = 0.153). PFS at 3 years in all eligible patients was 82.7% versus 70.1%, respectively (HR, 0.60; CI: 0.37 to 0.97) and was statistically significant (*P* = 0.03). Overall survival was not statistically different.

Conclusion
T-BEP administered with G-CSF seems to be a safe and effective treatment regimen for patients with intermediate-prognosis GCC. However, the study recruited a smaller-than-planned number of patients and included 7.7% ineligible patients. The primary analysis of the trial could not demonstrate statistical superiority of T-BEP for PFS. When ineligible patients were excluded, the analysis of all eligible patients demonstrated a 12% superior 3-year PFS with T-BEP, which was statistically significant.

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INTRODUCTION

The treatment of metastatic germ-cell cancer (GCC) with cisplatin-etoposide based chemotherapy results in the cure of the majority of patients.[1] In the current consensus classification for nonseminoma and seminoma, the following three prognostic categories are defined; a good-prognosis group with a 5-year disease-free survival (DFS) of 90%, an intermediate-prognosis group with a 5-year DFS of 70%, and a poor-prognosis group with a 5-year DFS of 45%.[2] For all three prognostic groups, the administration of bleomycin, etoposide, and cisplatin (BEP) is the standard treatment.

Three decades of chemotherapy studies that tested shortened intervals between chemotherapy cycles, the concept of alternating or sequential chemotherapy, and recent studies of high-dose chemotherapy plus autologous peripheral stem-cell support have not proven to be superior to the gold standard of BEP.[3-5]

An alternative strategy could be the incorporation of a new effective agent in the BEP regimen. Paclitaxel has demonstrated activity in two phase II studies in patients with platinum-refractory cancer.[6,7] Therefore, the European Organisation for Research and Treatment of Cancer (EORTC) decided to investigate the addition of paclitaxel to BEP. In a formal paclitaxel (Taxol; Bristol-Myers Squibb International, Brussels, Belgium)–bleomycin, etoposide, and cisplatin (T-BEP) dose-finding study, paclitaxel was administered at dose levels of 75, 125, 175, and 200 mg/m^2 in a 3-hour infusion on day 1 before the start of BEP.[8] Primary granulocyte colony-stimulating factor (G-CSF) prophylaxis was applied. A dose of paclitaxel 175 mg/m^2 was feasible with full-dose BEP, and this regimen was chosen for the intended randomized multicenter study.

The randomized phase II/III study of T-BEP versus BEP in patients with intermediate-prognosis GCC reported in this article was conducted in the framework of EORTC, the German Testicular Cancer Study Group/Association of Urologic Oncology, the Medical Research Council (Testis Cancer study 21)/United Kingdom National Cancer Research Institute Testicular Cancer Clinical Study Group, and the Spanish Germ-Cell Cancer Group.

PATIENTS AND METHODS

Patients

Patients were eligible for the study if they had intermediate-prognosis metastatic GCC according to International Germ Cell Cancer Concensus as follows: for nonseminoma, all of (1) a testis or retroperitoneal primary tumor, (2) α-fetoprotein (AFP) $\geq$ 1,000 but $\leq$ 10,000 U/L, human chorionic gonadotropin $\geq$ 5,000 U/L (1,000 ng/mL) but $\leq$ 50,000 U/L (10,000 ng/mL), or lactate dehydrogenase $\geq$ 1.5$\times$ but $\leq$ 10$\times$ the upper limit of normal, and (3) no liver, bone, brain, or other nonpulmonary visceral metastases; and for pure seminoma, (1) any primary site, (2) any lactate dehydrogenase and any human chorionic gonadotropin, (3) nonpulmonary visceral metastases present, and (4) AFP within the normal range. Patients were not accepted if they had previously received chemotherapy, had a creatinine clearance less than 40 mL/min, or were less than 16 or greater than 50 years of age. All patients provided ethics board– approved written informed consent.

Treatment

Standard BEP consisted of cisplatin 20 mg/m^2 days 1 through 5 and etoposide 100 mg/m^2 administered days 1 through 5 for four cycles. Bleomycin was administered at a dose of 30 mg weekly for 12 weeks (total dose of bleomycin, 360 mg). Patients administered T-BEP received paclitaxel 175 mg/m^2 given as a 3-hour infusion on day 1, before starting standard BEP, for four cycles. Paclitaxel was supplied by Bristol-Myers Squibb International. G-CSF (filgrastim and later pegfilgrastim) was used for primary prophylaxes in patients allocated to the T-BEP group. In patients who received BEP, G-CSF was used only as secondary prophylaxis.

Chemotherapy dose modifications for hematologic toxicity are presented in detail in Appendix Tables A1 and A2 (online only).

After grade 3 or 4 mucosal toxicity or diarrhea, the following cycle of chemotherapy was delayed until recovery. For patients allocated to the T-BEP group, the dose of paclitaxel was reduced by 25% for all remaining cycles. For clinically significant hypersensitivity reactions during paclitaxel administration, the infusion was discontinued, and patients were treated with antihistamines and epinephrine and were retreated at the discretion of the investigator.

The actual dose-intensity was calculated as follows for all drugs except bleomycin for which the total dose in milligrams was used.

$$\mathrm{DI}_{\mathrm{observed}}(\mathrm{mg/m^2 \times week}) = \frac{\text{Total dose}(\mathrm{mg/m^2})}{\text{Actual total treatment duration (week)}}$$

The relative dose intensity (RDI) was the ratio of the observed dose intensity to the weekly dose planned per protocol and expressed as a percentage. The average RDI for BEP or T-BEP was obtained by averaging the RDI of the individual components of each regimen.

Response Assessment

After completion of chemotherapy, patients with normal tumor marker levels and no clinical or radiologic evidence of residual masses were classified as complete responders and were monitored without additional therapy. Patients in whom markers normalized but who showed evidence of residual tumor mass underwent debulking surgery unless the initial histologic diagnosis was pure seminoma. The protocol advised complete macroscopic resection of all tumor remnants. These patients were classified as complete responders if the histologic examination showed no viable cancer. If viable malignancy had been resected completely, patients were classified as having been rendered disease free by chemotherapy plus surgery. Patients in whom the surgical resection of residual viable cancer was incomplete, patients who had a continuing increase of tumor markers, or patients who had disease progression while receiving chemotherapy or within 2 months after the completion of chemotherapy were classified as incomplete responders. Rising tumor markers or an increase in tumor volume (unless this was caused by mature teratoma that was completely resectable) was considered progression of disease. Patients with residual masses who did not undergo complete debulking surgery were classified as nonassessable for response and included in progression-free survival (PFS) and survival analyses. Events in the PFS analysis were incomplete response, progression of disease, and death.

Sample Size and Statistical Analysis

The study was designed as an open-label phase II/III trial. Phase II aimed at the exclusion of a complete-response (CR) rate of 65% (one-sided $\alpha = 0.10$; power, 95%) with a two-stage optimum Simon design. A maximum of 82 patients taking T-BEP were needed, with the assumption that the true CR rate was 80%. Phase III was planned to show an increase of the 3-year PFS from 75% to 85% with T-BEP (hazard ratio [HR], 0.56) with 80% power and am two-sided $\alpha = 0.05$. To this aim, 98 events were needed, and it was planned to recruit 498 patients. Randomization was by minimization to ensure the treatment arms were balanced with respect to histology (seminoma *v* nonseminoma or combined tumors) and the number of patients allocated in each hospital.[9,10]

The decision to continue the trial into phase III was taken by the EORTC independent data monitoring committee in March 2004. In December 2006, the EORTC independent data monitoring committee requested and reviewed an interim analysis of the phase III trial by using stopping rules for both futility (γ-family with $\gamma = -2$) and superiority (γ-family with $\gamma = -3$),[11] but the boundaries were not crossed, and the study continued. The trial eventually closed to accrual in August 2009 with 337 patients as a result of recruitment problems and difficulties with paclitaxel supply. An independent statistician advised to conduct the final analysis when a minimum of 2 years follow-up was reached for all patients entered before June 2008. With 85 events of PFS observed in the intent-to-treat population, the study had a power of 74% (instead of 80% as planned) to detect the hypothesized difference in PFS if it was present. The CIs of the 3-year PFS rates in both treatment groups were compatible with the hypothesized values (ie, 75% and 85%).

The primary analysis of the response rate was in all eligible patients; patients of PFS and overall survival were in the intent-to-treat population. Sensitivity analyses were conducted in eligible patients and eligible patients who started the allocated treatment (per-protocol population). Survival end points were described by Kaplan-Meier curves, and comparisons were analyzed by using the nonstratified log-rank test. Binary variables were compared by using the χ^2 test. The analysis was based on all available data as of January 3,

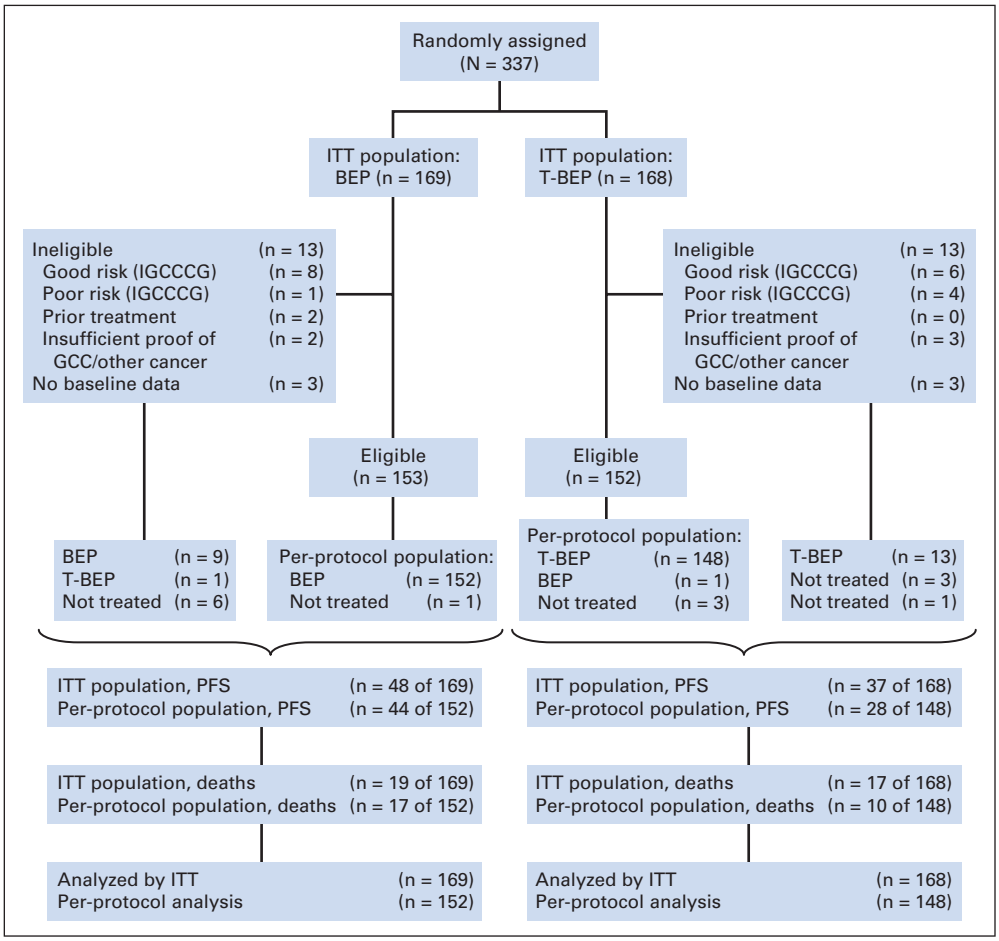

Fig 1. CONSORT diagram. BEP, bleomycin, etoposide, and cisplatin; GCC, germ-cell cancer; IGCCCG, International Germ Cell Cancer Collaborative Group; ITT, intent to treat; PFS, progression-free survival; T-BEP, paclitaxel–bleomycin, etoposide, and cisplatin.

2011. All tests were two-sided at the 5% significance level with adjustment for the interim analysis (nominal $\alpha = 0.0455$).

RESULTS

A total of 337 patients from 12 countries entered the trial between November 1998 and April 2009; 169 patients were allocated to the BEP group, and 168 patients were allocated to the T-BEP group.

Of these patients, 26 patients were found ineligible (mostly as a result of a different prognostic classification), and for six patients, the eligibility was not completely verifiable (Fig 1). Of importance, distributions of good-risk and poor-risk ineligible patients were uneven because there were numerically more good-risk patients (predestined for a better prognosis) in the standard BEP-treatment group, whereas four of five poor-risk patients (with the associated worse prognosis) had been allocated to the T-BEP group.

Besides the 26 ineligible patients, the following five additional patients were excluded from the per-protocol analysis: one patient in the T-BEP group who received BEP instead and four eligible patients without documented treatment (one patient taking BEP and three patients taking T-BEP).

As of the clinical cutoff date of January 3, 2011, the median follow-up of all patients was 5.3 years. There was no difference in follow-up between the two treatment groups.

The pretreatment characteristics of all patients are listed in Table 1. The two treatment arms were well balanced with respect to age, histology, and disease extent, with the exception of a higher median AFP in the T-BEP arm (499 IU/L in the T-BEP group *v* 156 IU/L in the BEP group; Kruskal-Wallis $P = .0350$).

Treatment Administered

In the intent-to-treat population, 92.3% of patients allocated to the BEP group completed four cycles of treatment; in patients allocated to the T-BEP group, 87.5% of patients completed four cycles of treatment. In the safety population (all patients who started the allocated treatment) these percentages were 96.3% and 91.3%, respectively. The reasons not to receive the allocated four cycles were mostly due to ineligibility, toxicity (including three patients with allergic reactions to paclitaxel), and refusal.

In the safety population, the median average RDI achieved for all agents was 97.1% in the BEP group and 97.5% in the T-BEP group. Detailed information about the dose intensity and RDI for each component in the two study arms is shown in Appendix Tables A3 and A4 (online only). In patients treated with BEP, 26% of patients had at least one cycle postponed, mainly as a result of hematologic toxicity; in patients who received T-BEP, 16% of patients had at least one cycle postponed, likely as a result of the primary use of G-CSF, as per

Table 1. Patient and Disease Characteristics

Characteristic	Treatment: BEP (n = 169) No. of Patients	%	T-BEP (n = 168) No. of Patients	%
Patient characteristic				
Age, years				
Median	28		28	
Range	16-50		16-50	
Interquartile range	23-35		24-35	
Disease characteristic				
Histology				
Seminoma	14	8.3	15	8.9
Non seminoma	108	63.9	103	61.3
Combined seminoma and nonseminoma	44	26.0	46	27.4
Unknown/missing	3	1.8	4	2.4
Primary site				
Testis	156	92.3	155	92.3
Retroperitoneal	10	5.9	8	4.8
Mediastinal	1	0.6	2	1.2
Other/missing	2	1.2	3	1.8
Involved metastatic sites				
Abdominal lymph nodes	147	86.9	144	85.8
Mediastinal lymph nodes	46	27.3	52	30.9
Supraclavicular lymph nodes	25	14.8	22	13.1
Lung metastases	81	47.9	86	51.2
Liver metastases	3	1.8	4	2.4
Bone metastases	3	1.8	7	4.2
AFP, IU/L*				
< 1,000	117	69.2	91	54.2
1000 ≤ AFP < 10,000	50	29.6	74	44.0
> 10,000	0	0.0	1	0.6
Unknown/missing	2	1.2	2	1.2
Median	156.0		499.0	
Range	1.0-8,791.0		1.0-1,3448.0	
Q1-Q3	5.0-1,219.0		9.0-2,319.0	
HCG, IU/L				
< 5,000	119	70.4	116	69.0
5,000 ≤ HCG < 50,000	48	28.4	49	29.2
>50,000	0	0.0	1	0.6
Unknown/missing	2	1.2	2	1.2
Median	423.0		267.0	
Range	0.0-49,010.0		0.0-56,053.0	
Q1-Q3	10.0-5,710.0		8.0-7,999.0	
LDH, ×ULN				
< 1.5× ULN	44	26.0	57	33.9
1.5× ULN ≤ LDH < 10× ULN	121	71.6	107	63.7
> 10× ULN	2	1.2	2	1.2
Unknown/missing	2	1.2	2	1.2
Median	2.1		1.9	
Range	0.4-17.8		0.0-12.8	
Q1-Q3	1.3-3.9		1.2-3.4	

Abbreviations: AFP, α-fetoprotein; BEP, bleomycin, etoposide, and cisplatin; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; Q, quartile; T-BEP, paclitaxel–bleomycin, etoposide, and cisplatin; ULN, upper limit of normal.

*χ^2 test for different distribution of AFP (< 1,000 v ≥ 1000 ng/mL), P = .005; Kruskall-Wallis χ^2 test for difference in distribution of actual AFP values, P = .035.

Table 2. Toxicity

Toxicity	Treatment: BEP (N = 161) No. of Patients	%	T-BEP (N = 161) No. of Patients	%
Hematologic toxicity				
Leucocytes < 1.0 × 10 g/L	17	10.6	26	16.1
Leucocytopenic fever*	16	10	31	19.2
Platelets < 25 × 10 g/L	5	3.1	5	3.1
Nonhematologic toxicity				
Allergic reaction				
Grades 1-2†	15	9.3	30	18.6
Grades 3-4	0	0	9	5.5
Fatigue				
Grades 1-2	111	69	103	64
Grades 3-4	4	2.5	12	7.5
Stomatitis/mucocitis				
Grades 1-2	57	35.4	72	44.7
Grades 3-4	4	2.5	15	9.4
Diarrhea				
Grades 1-2	32	19.9	56	34.8
Grades 3-4	3	1.9	16	9.9
Sensory neuropathy				
Grades 1-2	46	28.5	57	35.4
Grades 3-4	2	1.2	0	0
Other neurotoxicity				
Grades 1-2	23	14.3	24	14.9
Grades 3-4	3	1.2	1	0.6
Nausea				
Grades 1-2	117	72.7	114	70.8
Grades 3-4	7	4.3	11	6.8

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; T-BEP, paclitaxel–bleomycin, etoposide, and cisplatin.

*Leucocytes < 2.0 × 10 g/L, temperature > 38°C.

†Denotes National Cancer Institute Common Toxicity Criteria version 2.0, worst toxicity reported over all cycles.

protocol. In patients who received BEP, G-CSF was applied during at least one cycle in 33% of patients.

Toxicity

Dose reductions were applied at least once in 15% of patients who received BEP and in 12% of patients who received T-BEP. However, 9.3% of patients who received BEP compared with 22% of patients who received T-BEP stopped one drug definitively (mostly bleomycin as a result of pulmonary toxicity [eight patients in each arm] or paclitaxel as a result of allergic reactions, refusal, or reclassification into good-prognosis disease). Grade 3 and 4 neutropenia was encountered more frequently during BEP treatment, which was most likely caused by the restrictive use of G-CSF for secondary prophylaxis only, whereas patients who received T-BEP received G-CSF for primary prophylaxis. However, there were numerically more neutropenic fevers in the T-BEP group than in the BEP group (19% versus 10%, respectively; Table 2). Grades 2 and 3 mucositis/stomatitis and diarrhea occurred more frequently in the T-BEP group. However, grade 4 toxicities were rare in both study arms (Table 2).

There were seven fatal adverse events. Of these, four events were possibly related to treatment; two patients (one patient who received T-BEP and one patient who received BEP) died of massive

pulmonary embolism between cycles 1 and 2, one patient who received T-BEP died from pulmonary fibrosis that was likely bleomycin related, and one patient developed diarrhea and fever during his first cycle of T-BEP, was admitted 2 days later at a nearby hospital, and died during the diagnostic workup from sudden cardiorespiratory failure. The remaining three fatal events were not treatment related.

Post-Treatment Evaluations and Surgery

After chemotherapy, the majority of patients in both treatment arms had residual lesions (135 patients [80.4%] who received T-BEP versus 134patients (79.3%) who received BEP). Reasons not to resect all lesions, as reported by the investigators on the forms, were mostly due to either multiple lesions or lesions resected at one site that contained no vital cancer, and the decision was made not to resect additional lesions (detailed information is listed in Appendix Tables A5 to A7; online only). Histology was obtained from 119 patients with nonseminoma or mixed seminoma/nonseminoma histologies who received T-BEP and from 116 patients who received BEP. Complete resection of all remnants was possible in 50.8% of the patients who received T-BEP and underwent surgery and in 48.8% of patients who received BEP. Viable cancer was found in nine patients (7%) who received T-BEP and in 15 patients (12.9%) who received BEP.

Response to Treatment

Responses to chemotherapy, with or without surgery, were computed primarily in eligible patients. Because 4.5% of eligible patients did not start the allocated treatment, a computation was also made for eligible patients who started allocated treatment (per-protocol analysis). Analyses of intent to treat, all eligible patients, and per-protocol are listed in Table 3. In the eligible patient population, the rate of CR/no evidence of disease after chemotherapy plus surgery rate was 70.4% in the T-BEP group versus 59.5% in the BEP group ($P = .0549$).

Table 3. Response to Treatment

	Treatment					
	BEP		T-BEP		Total	
Response to Treatment	No. of Patients	%	No. of Patients	%	No. of Patients	%
Intent-to-treat analysis						
No. of patients	169		168		337	
Response to treatment						
CR to chemotherapy only	84	49.7	100	59.5	184	54.6
NED, CR after chemotherapy and surgery	11	6.5	8	4.8	19	5.6
Treatment failure	17	10.1	7	4.2	24	7.1
Not evaluable	56	33.1	47	28.0	103	30.6
Early death as a result of disease	1	0.6	2	1.2	3	0.9
Early death as a result of toxicity	0	0.0	2	1.2	2	0.6
Early death as a result of other reason	0	0.0	2	1.2	2	0.6
Response, CR/NED	95	56.2	108	64.3	203	60.2
95% CI, %	48.4 to 63.8		56.5 to 71.5		$P = .1482$	
All eligible patients						
No. of patients	153		152		305	
Response to treatment						
CR to chemotherapy only	80	52.3	99	65.1	179	58.7
NED, CR after chemotherapy and surgery)	11	7.2	8	5.3	19	6.2
Treatment failure	15	9.8	5	3.3	20	6.6
Not evaluable	46	30.1	36	23.7	82	26.9
Early death as a result of disease	1	0.7	1	0.7	2	0.7
Early death as a result of toxicity	0	0.0	2	1.3	2	0.7
Early death as a result of other	0	0.0	1	0.7	1	0.3
Response, CR/NED	91	59.5	107	70.4	198	64.9
95% CI, %	51.2 to 67.3		62.4 to 77.5		$P = .0549$	
Per-protocol analysis						
No. of patients	152		148		300	
Response to treatment						
CR to chemotherapy only	80	52.6	98	66.2	178	59.3
NED, CR after chemotherapy and surgery	11	7.2	8	5.4	19	6.3
Treatment failure	15	9.9	5	3.4	20	6.7
Not evaluable	45	29.6	34	23.0	79	26.3
Early death as a result of disease	1	0.7	1	0.7	2	0.7
Early death as a result of toxicity	0	0.0	2	1.4	2	0.7
Response, CR/NED	91	59.9	106	71.6	197	65.7
95% CI, %	51.6 to 67.7		63.6 to 78.7		$P = .0384$	

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; CR, complete response; NED, no evidence of disease; T-BEP, paclitaxel–bleomycin, etoposide, and cisplatin.

Table 4. PFS and Survival: Primary Table of Results

PFS and Survival	No. of Patients	Observed Events	T-BEP *v* BEP Hazard Ratio	T-BEP *v* BEP Adjusted 95% CI	*P* (log-rank)*	At 3 Years %	At 3 Years 95.45% CI
PFS							
Intent to treat, primary analysis							
BEP	169	48	0.73	0.47 to 1.13	.1531	71.08	63.14 to 77.61
T-BEP	168	37	0.70†	0.44 to 1.10†	.1113†	79.43	72.12 to 85.02
All eligible							
BEP	153	45	0.60	0.37 to 0.97	.0307	70.13	61.82 to 76.98
T-BEP	152	29	0.56†	0.35 to 0.92†	.0181†	82.69	75.28 to 88.06
Per protocol							
BEP	152	44	0.59	0.37 to 0.96	.0289	70.63	62.32 to 77.45
T-BEP	148	28	0.55†	0.34 to 0.91†	.0166†	83.16	75.75 to 88.48
Survival							
Intent to treat, primary analysis							
BEP	169	19	0.89	0.46 to 1.74	.7382	89.83	83.78 to 93.70
T-BEP	168	17	0.88†	0.44 to 1.75†	.7137†	91.23	85.48 to 94.77
All eligible							
BEP	153	17	0.64	0.30 to 1.39	.2501	89.72	83.37 to 93.74
T-BEP	152	11	0.64†	0.29 to 1.41†	.2618†	94.42	88.99 to 97.21
Per protocol							
BEP	152	17	0.58	0.26 to 1.29	.1700	89.65	83.26 to 93.69
T-BEP	148	10	0.57†	0.25 to 1.29†	.1698†	95.04	89.71 to 97.64

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; PFS, progression-free survival; T-BEP, paclitaxel bleomycin, etoposide, and cisplatin.
*To be compared with the adjusted .0455 significance level.
†Cox models with adjustment for baseline α-fetoprotein.

In eligible patients who actually started the allocated treatment (per-protocol population), the response rate (CR/no evidence of disease) was 71.6% in the T-BEP group versus 59.9% in the BEP group ($P = .0384$).

PFS and Survival

PFS and survival are listed in Table 4. In the intent-to-treat population (including all ineligible patients as well as the patients who did not start the allocated chemotherapy), the 3-year PFS rate was 79.4% in the T-BEP group and 71.1% in the BEP group. PFS curves were not statistically significant (HR, 0.73; CI, 0.47 to 1.13; $P = .153$; Table 4; Fig 2). With the exclusion of the 26 (7.7%) ineligible patients, 3-year PFS rates were 82.7% versus 70.1%, respectively (HR, 0.60; CI, 0.37 to 0.97, $P = .0307$). The difference was significant at the adjusted 0.0455 significance level. This may have been due to the fact that ineligible patients were more often ineligible as a result of having poor-risk GCC in the T-BEP arm and, vice versa, having good-risk GCC in the BEP arm. Moreover, most ineligible patients were treated outside of the protocol (good prognosis with BEP). In addition, one patient in each arm received the opposite treatment. With the additional exclusion of the five patients who did not receive the allocated treatment (per-protocol analysis), 3-year PFS rates were 83.2 versus 70.6%, respectively (HR, 0.59; CI, 0.37 to 0.96; $P = .0289$), similar to the results in eligible patients. Both the PFS analysis in all eligible patients and the per-protocol analysis showed a 12% superior 3-year PFS with T-BEP.

With only 36 events in the intent-to-treat population and 27 events in the per-protocol analysis, differences in overall survival were not statistically significant (HR, 0.89; CI, 0.46 to 1.74; $P = .7382$ in the intent-to-treat population; HR, 0.58; CI, 0.26 to 1.29; $P = .1700$ in the per-protocol analysis (Table 4; Fig 3). Adjustment of the comparisons for the baseline AFP values that were imbalanced between groups did not change these results (Table 4).

DISCUSSION

Recent studies of upfront high-dose chemotherapy or dose-intensified etoposide, ifosfamide, and cisplatin chemotherapy in poor-risk GCC have not demonstrated superiority over the standard BEP treatment.[4,5] In view of the activity of paclitaxel in the second-line treatment setting in phase 2 studies[6,7] the EORTC and other collaborative groups in Europe decided to investigate the addition of paclitaxel to standard BEP in patients with intermediate-risk GCC. The T-BEP dose-finding study showed that the regimen was generally well tolerated, and with the use of primary G-CSF prophylaxis, a dose of paclitaxel 175 mg/m^2 was feasible with standard-dose BEP[8]

This study was designed as a randomized open-label phase II/III study. The study originally aimed to recruit 498 patients. The enrollment onto the study was hampered by logistical problems, including delays in trial initiation in some countries that were anticipated to recruit a large proportion of the total patient group. When paclitaxel finally became generic, and multiple brands became available for use in the European countries, the regulatory burden associated with amending the protocol as well as the cessation of a free-drug supply further reduced the accrual and resulted in the decision by the EORTC to stop the trial with 337 patients randomly assigned.

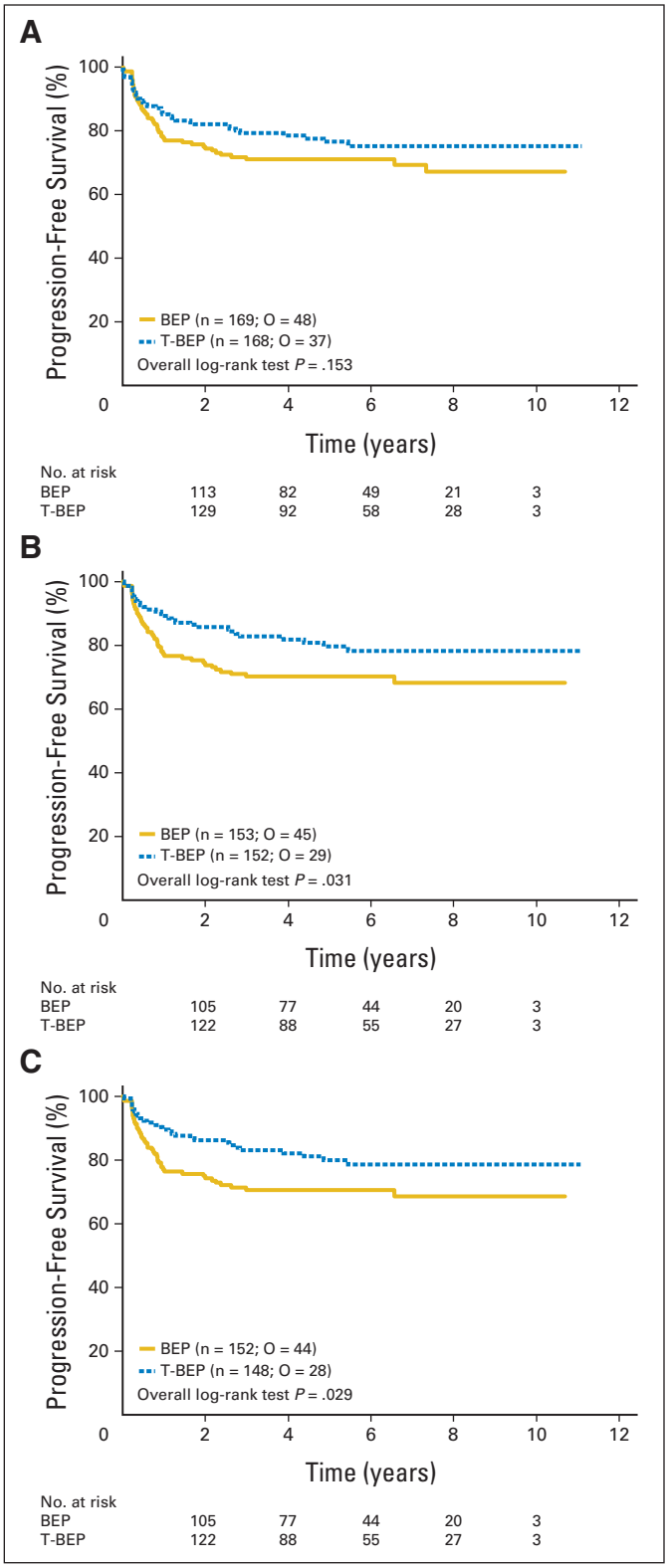

Fig 2. Progression-free survival (A) in intent-to-treat population; (B) for all eligible patients; (C) in the per-protocol population. O, observed events.

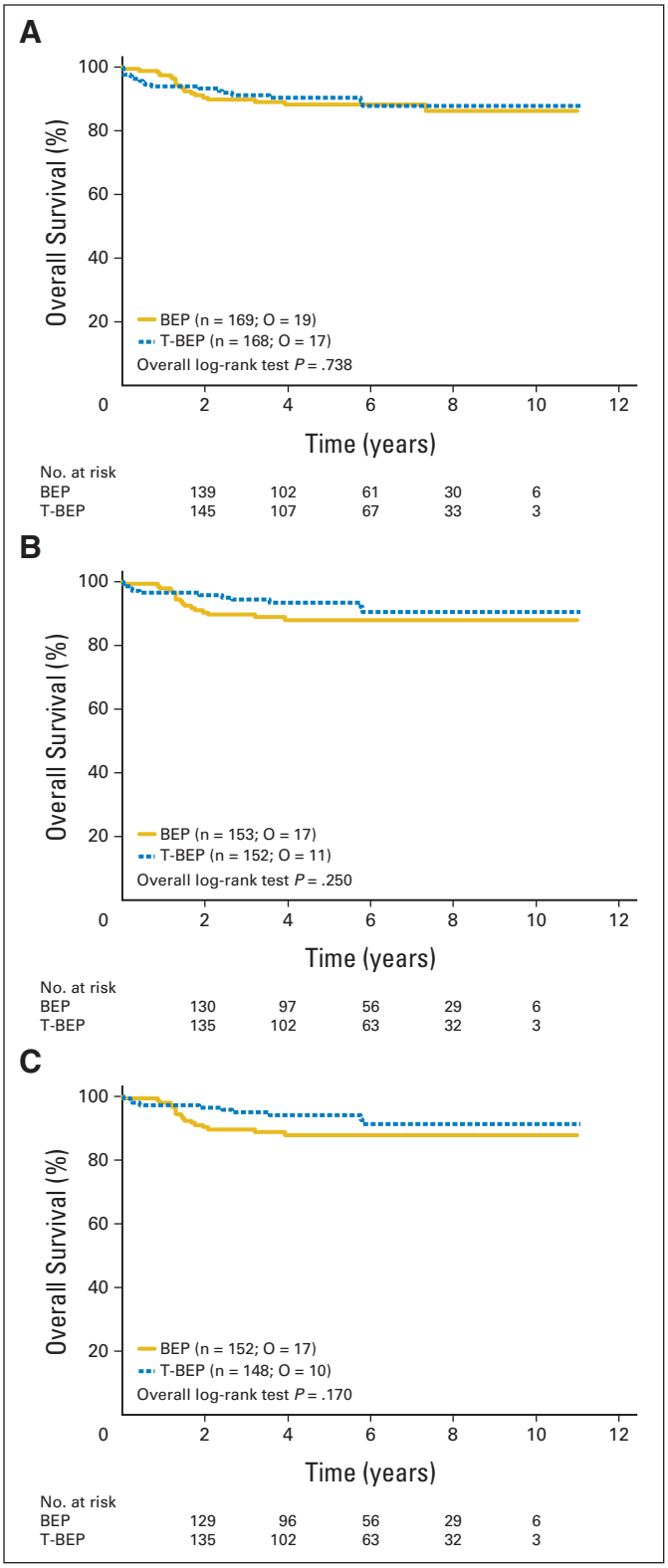

Fig 3. Overall survival (A) in the intent-to-treat population; (B) for all eligible patients; and (C) in the per-protocol population. O, observed events.

The primary efficacy analysis (intent to treat) conducted with 85 of 98 events of PFS planned by design had only a 74% power of demonstrating statistical superiority of T-BEP if the hypothesized treatment effect (HR, 0.56) was present. However, extrapolation of the results obtained in the intent-to-treat population (HR, 0.73) to a hypothetical full-sample size of 98 events would not have reached conventional statistical significance with a theoretical 95% CI for the HR that ranged from 0.49 to 1.01.

The intent-to-treat results were confounded by 13 ineligible patients in each arm (8%) with an unfortunate uneven distribution among the two treatment groups with more good-prognosis patients allocated to the BEP group, most of whom were eventually treated outside of the protocol, and more (four of five) poor-prognosis patients allocated to the T-BEP group. This uneven distribution of ineligibles with the associated different prognostic outcome (good prognosis with BEP and poor prognosis with T-BEP) may have biased the results toward the null hypothesis of no difference. Also, for various reasons, several eligible patients (one patient who received BEP and three patients who received T-BEP) did not start the allocated treatment or received the opposite treatment.

The PFS at 3 years (intent to treat) was 79.4% in the T-BEP group versus 71.1% in the BEP group (HR, 0.73; $P = .153$). However, the PFS for the eligible patient population was 82.7% versus 70.1%, respectively (HR, 0.60; $P = .03$). This difference reached the adjusted level of statistical significance, as did the analysis in the per-protocol population. Both analyses showed a 12% superior PFS at 3 years. Numerically, these observed differences at 3 years were in the order of magnitude of what was anticipated (10%). As could be expected in the setting of GCC, with salvage regimens available and a low number of events, the overall survival was not statistically different.

This trial failed to demonstrate the superior efficacy of T-BEP in the management of the intended intermediate-prognosis GCC risk population on the basis of its primary analysis. However, the eligible-patient analysis as well as the per-protocol analysis that were thought to alleviate the conservative bias induced by the uneven distribution of ineligible or untreated patients that dragged the results toward the null hypothesis of no difference both reached statistical significance. With a small number of events, survival was not statistically significantly different between the two groups. The T-BEP regimen with the use of primary G-CSF prophylaxis was generally well tolerated with only two toxic deaths (1%) in the framework of this large multicenter study. The study showed a favorable toxicity profile of T-BEP in patients with intermediate-prognosis GCC. Whether or not T-BEP has a potential benefit in the poor-risk GCC patient category remains to be determined because this patient group was not planned to be recruited in the study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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