Paclitaxel, Ifosfamide, and Cisplatin Efficacy for First-Line Treatment of Patients With Intermediate- or Poor-Risk Germ Cell Tumors

Darren R. Feldman, James Hu, Tanya B. Dorff, Kristina Lim, Sujata Patil, Kaitlin M. Woo, Maryann Carousso, Amanda Hughes, Joel Sheinfeld, Manjit Bains, Dean F. Bajorin, George J. Bosl, Siamak Daneshmand, Charlene Ketchens, Dean F. Bajorin, George J. Bosl, David I. Quinn, and Robert J. Motzer

ABSTRACT

Purpose

Paclitaxel, ifosfamide, and cisplatin (TIP) achieved complete responses (CRs) in two thirds of patients with advanced germ cell tumors (GCTs) who relapsed after first-line chemotherapy with cisplatin and etoposide with or without bleomycin. We tested the efficacy of first-line TIP in patients with intermediate- or poor-risk disease.

Patients and Methods

In this prospective, multicenter, single-arm phase II trial, previously untreated patients with International Germ Cell Cancer Collaborative Group poor-risk or modified intermediate-risk GCTs received four cycles of TIP (paclitaxel 240 mg/m² over 2 days, ifosfamide 6 g/m² over 5 days with mesna support, and cisplatin 100 mg/m² over 5 days) once every 3 weeks with granulocyte colony-stimulating factor support. The primary end point was the CR rate.

Results

Of the first 41 evaluable patients, 28 (68%) achieved a CR, meeting the primary efficacy end point. After additional accrual on an extension phase, total enrollment was 60 patients, including 40 (67%) with poor risk and 20 (33%) with intermediate risk. Thirty-eight (68%) of 56 evaluable patients achieved a CR and seven (13%) achieved partial responses with negative markers (PR-negative) for a favorable response rate of 80%. Five of seven achieving PR-negative status had seminoma and therefore did not undergo postchemotherapy resection of residual masses. Estimated 3-year progression-free survival and overall survival rates were 72% (poor risk, 63%; intermediate risk, 90%) and 91% (poor risk, 87%; intermediate risk, 100%), respectively. Grade 3 to 4 toxicities consisted primarily of reversible hematologic or electrolyte abnormalities, including neutropenic fever in 18%.

Conclusion

TIP demonstrated efficacy as first-line therapy for intermediate- and poor-risk GCTs with an acceptable safety profile. Given higher rates of favorable response, progression-free survival, and overall survival compared with prior first-line studies, TIP warrants further study in this population.

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INTRODUCTION

Germ cell tumors (GCTs) are considered a model of curable cancer, given their exquisite sensitivity to cisplatin-based chemotherapy, which allows durable complete responses (CRs) to be achieved, even in the face of widely metastatic disease. Standard chemotherapy regimens consist of etoposide plus cisplatin with bleomycin (BEP) or without bleomycin (EP).¹ However, the likelihood of sensitivity to chemotherapy and cure varies significantly

on the basis of clinical and pathologic factors, which have been incorporated into the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic model.² Although good-risk patients in this model have an approximately 90% progression-free survival (PFS) rate after chemotherapy, the corresponding rates for intermediate-risk and poor-risk patients are only 70% to 75% and 45% to 55%, respectively.² Although higher than reported in the IGCCCG article, overall survival (OS) rates also remained suboptimal with BEP in recent randomized phase III studies, with 83% of

Darren R. Feldman, Kristina Lim, Sujata Patil, Kaitlin M. Woo, Maryann Carousso, Amanda Hughes, Joel Sheinfeld, Manjit Bains, Dean F. Bajorin, George J. Bosl, and Robert J. Motzer, Memorial Sloan Kettering Cancer Center; Darren R. Feldman, Dean F. Bajorin, George J. Bosl, and Robert J. Motzer, Weill Medical College of Cornell University, New York, NY; and James Hu, Tanya B. Dorff, Siamak Daneshmand, Charlene Ketchens, and David I. Quinn, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA.

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Corresponding author: Darren R. Feldman, MD, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; e-mail: feldmand@mskcc.org

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intermediate-risk and 69% of poor-risk patients alive at 2 years.³ Furthermore, although three cycles of BEP or four cycles of EP are considered adequate treatment for good-risk patients, intermediate- and poor-risk patients require four cycles of BEP (BEP $\times$ 4).¹

The combination of paclitaxel, ifosfamide, and cisplatin (TIP) was previously evaluated as second-line treatment in a phase I/II study of patients with testicular primary GCTs who relapsed after a favorable response to first-line chemotherapy. Of 46 patients, 32 (70%) achieved a CR, and 29 (63%) remained continuously disease-free with a median follow-up of nearly 6 years.⁴ This compared favorably to CR and PFS rates of approximately 50% and 25%, respectively, with other conventional-dose chemotherapy regimens such as etoposide, ifosfamide, and cisplatin (VIP) or vinblastine, ifosfamide, and cisplatin as initial salvage treatment in unselected populations.^{5,6} Although patient selection contributed to the superior results achieved with salvage TIP, the regimen's efficacy after prior BEP or EP was nonetheless striking. Therefore, we developed this study to evaluate the efficacy of TIP in the first-line setting for patients with intermediate- and poor-risk GCTs. The prior TIP regimen was slightly adapted to allow outpatient administration and facilitate potential future comparison with BEP $\times$ 4.

PATIENTS AND METHODS

This prospective, multicenter, phase II trial was approved by institutional review boards at both Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Southern California (USC). All patients provided informed consent.

Patients

Eligible patients included men or women with GCT of any primary site and IGCCCG poor-risk or modified intermediate-risk disease. As in prior studies,³ the modification for intermediate risk stipulated that the lactate dehydrogenase (LDH) level had to be 3 or more (rather than 1.5) times the upper limit of normal (ULN) when it was the only feature leading to intermediate-risk classification. The purpose was to exclude patients with nonspecific mild LDH increase unrelated to their GCT diagnosis. Except when urgent treatment was necessary, pathologic confirmation of GCT was required at MSKCC or USC. Patients without pathologic confirmation had to have clinical features compatible with GCT diagnosis (testis mass, high human chorionic gonadotropin or α -fetoprotein, and/or predictable pattern of metastases). Eligibility criteria also included age 18 years or older, no prior chemotherapy, WBC $\geq$ 3,000/ μ L, platelets $\geq$ 100,000/ μ L, serum creatinine less than or equal to the ULN or creatinine clearance $\geq$ 50 mL/min, AST and ALT less than 3 $\times$ ULN, and bilirubin less than 1.5 $\times$ ULN. In cases of liver metastases, AST and ALT levels less than 5 $\times$ ULN were allowed. Patients with active infections, HIV, or concurrent malignancy were ineligible.

Pretreatment Evaluation

Pretreatment evaluation included complete history and physical examination, performance status, CBC, comprehensive metabolic profile, α -fetoprotein, human chorionic gonadotropin, LDH, creatinine clearance, electrocardiogram, and computed tomography (CT) scan of the chest, abdomen, and pelvis.

Treatment Program

Planned treatment consisted of four cycles of paclitaxel 240 mg/m², ifosfamide 6,000 mg/m², mesna 6,000 mg/m², and cisplatin 100 mg/m² once every 3 weeks. Initially, all drugs were distributed equally over 4 days

(paclitaxel 60 mg/m²/d, ifosfamide 1,500 mg/m²/d, mesna 1,500 mg/m²/d [mixed 1:1 with ifosfamide], and cisplatin 25 mg/m²/d). However, after five of the first 25 patients experienced paclitaxel infusion reactions (all during cycle 2), the regimen was changed to administer paclitaxel over 2 days (120 mg/m²/d) with a graduated titration of the infusion rate. Ifosfamide/mesna (1,200 mg/m²/d) and cisplatin (20 mg/m²/d) were also changed to administration over 5 days. In addition, a 30-minute bolus of mesna 120 mg/m² was added 30 minutes before each ifosfamide/mesna infusion to prevent hemorrhagic cystitis.

Dexamethasone 20 mg was given the night before and morning of paclitaxel treatment. Diphenhydramine and an H₂ blocker were administered before each paclitaxel infusion. Patients received a 5-HT₃ antagonist daily, aprepitant on days 4 to 6, and dexamethasone 12 mg/d on days 3 to 7. Pegfilgrastim 6 mg was administered on day 6 or 7 (daily unpegylated filgrastim from day 6 until absolute neutrophil count reached 1.0 or higher was also allowed). After eight of the first 14 patients developed neutropenic fever, the protocol was amended to institute levofloxacin prophylaxis 500 mg/d on days 7 to 13 of each cycle. Either inpatient or outpatient treatment could be given according to patient or physician preference.

Evaluation of Response and Toxicity

Patients were observed on days 1, 8, and 15 of each cycle. A CBC and complete metabolic panel were obtained at each visit, and tumor markers were determined on days 1 and 15. If the absolute neutrophil count was less than 1,000/ μ L and/or platelets were less than 90,000/ μ L on day 1, chemotherapy was delayed by 1 week. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. All patients who received at least one dose of chemotherapy were eligible for toxicity assessment.

Chest CT and either CT or magnetic resonance imaging scans with contrast of the abdomen and pelvis were performed at baseline and at treatment completion, with imaging of other sites dictated by patient symptoms or other clinical features. Surgery was recommended for patients with nonseminoma who had normal markers and residual masses after chemotherapy. If viable GCT was found at surgery, two cycles of adjuvant TIP was recommended. In follow-up, patients were seen every 4 to 8 weeks with laboratory tests for the first year and then per standard of care; serial imaging (chest x-rays, CT scans) was also performed per standard of care.

A CR to chemotherapy alone was defined as marker normalization and radiographic resolution or marker normalization plus surgery revealing only necrosis or teratoma (no viable GCT). A CR to chemotherapy plus surgery was defined as marker normalization and complete surgical resection revealing viable GCT with negative margins. A partial response with negative tumor markers (PR-negative) was defined as marker normalization with residual radiographic abnormalities but without progression. CR and PR-negative were considered favorable responses and required confirmation at 4 weeks or later by tumor markers and chest x-ray. An incomplete response (IR) was anything other than CR or PR-negative. The date of IR was considered the date of progression in the PFS analysis. Patients were eligible for response unless they were withdrawn from treatment of toxicity before completing three cycles of chemotherapy. Any patient withdrawn for disease progression was considered an IR.

Biostatistics

The primary end point was the CR rate (to chemotherapy alone or chemotherapy plus surgery) among patients evaluable for response. A Simon two-stage optimal design⁷ with type I error rate of 10% and 90% power was used to differentiate between an uninteresting CR rate of $\leq$ 55% and a CR rate of $\geq$ 75%, which would be worthy of further study. The uninteresting CR rate of 55% was selected because it was the CR rate with BEP $\times$ 4 in the most recently reported phase III trial in patients with intermediate- and poor-risk GCTs at the time the study was designed.³ The first stage consisted of 18 patients; if there were $\geq$ 11 CRs, the study would move to stage two, in which another 23 patients would be accrued. If 27 or

more of 41 evaluable patients in stages 1 and 2 achieved a CR, the regimen would be declared promising. This threshold to declare the regimen promising takes into account the variance of the CR rate as well as the type I and II errors. Patients not evaluable for response were planned to be replaced a priori. After the first 44 patients (41 evaluable) were enrolled, the study was expanded and enrolled 16 additional patients (15 evaluable) to further refine estimates of efficacy and increase experience with administering the regimen. Response rates were reported with exact 95% CIs.

Secondary end points included PFS (time from treatment start to death or disease progression), OS (time from treatment start to death as a result of any cause), and toxicity. PFS and OS analyses included all enrolled patients and were estimated by using the Kaplan-Meier method with the log-rank test being used to compare IGCCCG poor-risk and modified intermediate-risk patients. Statistical analysis was performed by using SAS v9.4 (SAS Institute, Cary, NC) and R 3.1.0. The data cutoff was April 2015.

RESULTS

Patient Characteristics

Sixty patients were enrolled between 2007 and 2013. Patient characteristics are provided in Table 1. Median age was 28 years (range, 18 to 56 years), and 59 (98%) were male. Primary site was testis in 41 (68%), mediastinum in 16 (27%), and retroperitoneum in three (5%). Fifty-four patients (90%) had nonseminoma histology and six patients (10%) had seminoma histology. Forty patients (67%) were classified as having IGCCCG poor-risk disease and 20 (33%) as having modified intermediate-risk disease. Fifty-eight patients (97%) had increased markers and 17 (28%) had liver, seven (12%) had bone, and one (2%) had brain metastases.

Treatment Administered

Fifty-five patients (92%) received all four planned cycles of TIP, including two who received an additional two adjuvant cycles (six total cycles) after surgery revealed viable GCTs. One patient had treatment interrupted for surgery for symptomatic growing teratoma syndrome after completing three cycles of TIP (pathology revealed teratoma and secondary somatic malignancy but no viable GCTs), and cycle four was not given. Three patients (all on the initial four-day paclitaxel regimen) experienced allergic reactions to paclitaxel that resulted in premature discontinuation after completion of only one (n = 1) or two (n = 2) cycles. One additional patient was taken off study after one cycle for poor compliance. These latter four patients were not evaluable for response and were replaced.

Efficacy

To replace three patients who were not evaluable, 44 patients were accrued to reach the planned sample size of 41 evaluable patients. Twenty-eight (68%) of 41 evaluable patients achieved a CR, thus meeting the prespecified efficacy end point. An additional six achieved PR-negative status resulting in a favorable response rate of 83%. Five of these six had seminoma with postchemotherapy resection deferred because of either small (< 3 cm) residual lesion size or negative postchemotherapy positron emission tomography scan. Seven patients (six poor risk, one intermediate risk) had an IR as their best response.

After meeting the prespecified efficacy end point, the protocol was amended to allow further accrual, resulting in a total of 60 patients with 56 evaluable for response. Best response was CR in

Table 1. Patient Characteristics

Characteristic	No.	%	Median	Range
Age, years			27.5	18-56
Male sex	59	98		
Histology				
Nonseminoma	54	90		
Seminoma	6	10		
Primary site				
Testes	41	68		
Mediastinum	16	27		
Retroperitoneum	3	5		
IGCCCG risk status				
Intermediate	20	33		
Poor	40	67		
Site of metastatic disease				
Abdomen/pelvis	37	62		
Lung	32	53		
Liver	17	28		
Mediastinum	16	27		
Bone	7	12		
Neck lymph nodes	6	10		
Brain	1	2		
Other	5	8		
Elevated markers	58	97		
HCG > 2.2 mIU/mL	43	72	3,956	3.1-1,205,799
AFP > 15 ng/mL	38	63	1,619	18.1-53,012.3
LDH greater than ULN	48	80	2.67*	1.04-10.92*
No. of treatment cycles				
1	2	3		
2	2	3		
3	1	2		
4	53	88		
6	2	3		

*Value represents the number × the upper limit of normal of LDH.

Abbreviations: AFP, α-fetoprotein; HCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

38, PR-negative in seven, and IR in 11, resulting in a favorable response rate of 80% (95% CI, 68% to 90%), 94% (95% CI, 73% to 100%) for intermediate-risk patients, and 74% (95% CI, 57% to 87%) for poor-risk patients (Table 2).

Postchemotherapy surgery was performed in 38 patients. Pathology revealed teratoma in 16, necrosis in 20, and viable GCT in two patients. Of 38 CRs, 36 were to chemotherapy alone and two were to chemotherapy plus surgery. Both patients with viable GCT at postchemotherapy resection received two additional cycles of adjuvant TIP and remained disease-free at their last follow-up.

All sixty patients were evaluable for PFS and OS, with a median follow up of 4.4 years (range, 1 to 7.6 years) for survivors. Six patients (five poor risk, one intermediate risk) relapsed from either CR (n = 3) or PR-negative (n = 3) status at a median of 6.0 months (range, 2.5 to 13.4 months). The 3-year PFS rate for the entire cohort was 72% (95% CI, 61% to 84%) and was significantly different for intermediate- versus poor-risk patients ($P = .035$). The 3-year PFS for intermediate-risk patients was 90% (95% CI, 78% to 100%) versus 63% (95% CI, 49% to 80%) for poor-risk patients (Fig 1).

Five patients (all poor-risk, all primary mediastinal non-seminomatous GCT [PM-NSGCT]) have died, all attributable to GCT, although two had secondary somatic malignancy in the form of spindle cell sarcoma in one and acute myeloid leukemia in the

Table 2. Efficacy by Risk Group

Outcome Status	Overall (n = 56)		Intermediate Risk (n = 18)		Poor Risk (n = 38)	
	No.	%	No.	%	No.	%
CR	38	68	12	67	26	68
CR to chemotherapy	36	64	11	61	25	66
CR to chemotherapy plus surgery	2	4	1	6	1	3
PR-negative markers	7	13	5	28	2	5
IR	11	20	1	6	10	26
Favorable response	45	80	17	94	28	74
Relapse	6	11	1	6	5	13
From CR	3	5	0	0	3	8
From PR-negative	3	5	1	6	2	5

Abbreviations: CR, complete response; IR, incomplete response; PR, partial response.

other. In the patient with acute myeloid leukemia, molecular analysis identified isochromosome 12p, consistent with derivation from his GCT rather than from treatment-induced leukemia. The secondary somatic malignancy was the cause of progression and

death in both patients, and neither had any evidence of viable GCT following TIP.

The 3-year OS rate for the 60 patients was 91% (95% CI, 84% to 99%; Fig 2). All 20 intermediate-risk patients were alive at last follow-up compared with 3-year OS of 87% (95% CI, 77% to 98%) for poor-risk patients, but this difference was not significant ($P = .12$).

Fig 1. Progression-free survival (PFS) for (A) the entire cohort and (B) stratified by International Germ Cell Cancer Collaborative Group risk group.

Toxicity

Tables 3 and 4 summarize the most frequent grade 3 and 4 hematologic and nonhematologic toxicities experienced, regardless of relationship to TIP. As expected, grade 3 and 4 cytopenias were frequently observed. Neutropenic fever occurred in 11 patients (18%), including eight (57%) of 14 patients before the addition of prophylactic levofloxacin versus only three (6.5%) of 46 after this adjustment. Paclitaxel hypersensitivity reactions occurred in six patients (10%), including five (20%) of 25 on the 4-day paclitaxel dosing schedule (three were prematurely withdrawn from the study) versus one (3%) of 35 on the 2-day dosing schedule. Grade 3 orthostatic hypotension or syncope related to orthostasis occurred in three patients (5%); an additional nine (15%) experienced grade 2 orthostatic hypotension. Although mild (grade 1) sensory neuropathy was frequent, only one patient each experienced grade 2 and grade 3 neuropathy. There were no treatment-related deaths.

DISCUSSION

This prospective multicenter phase II study demonstrates TIP to be an effective and tolerable first-line treatment program for patients with intermediate- and poor-risk GCTs. The trial met its pre-specified primary end point for promising efficacy with 28 of 41 evaluable patients achieving a CR to TIP in the preplanned analysis. This compares favorably to the 55% CR rate with BEP $\times$ 4 in the MSKCC-led Intergroup randomized trial of BEP $\times$ 4 versus BEP $\times$ 2 plus two cycles of high-dose chemotherapy.³ Importantly, the CR rate may underestimate the benefit in this population because CR is difficult to achieve in patients with seminoma who typically do not undergo resection of residual masses after chemotherapy. Favorable response rate (FRR), which includes PR-negative markers and CR, may be a more appropriate end point; the FRR in the first 41 evaluable patients treated with TIP was 83% versus 60% with BEP $\times$ 4 in the

Fig 2. Overall survival (OS) for (A) the entire cohort and (B) stratified by International Germ Cell Cancer Collaborative Group risk group.

forementioned randomized trial.³ Among all 56 evaluable patients, the FRR was 80%, including 74% for poor-risk patients.

Furthermore, 3-year PFS and OS were encouraging, given the large number of patients with PM-NSGCT treated on this study. No patient with a testicular or retroperitoneal primary tumor has died, and with a median follow-up of 4.4 years, the 3-year OS rate was 91%, including 100% for intermediate-risk and 87% for poor-risk patients. These rates are higher than the corresponding 2-year OS rates of 83% for intermediate-risk and 69% for poor-risk patients achieved with BEP $\times$ 4 in the Intergroup trial.³ Treatment with BEP $\times$ 4 in other randomized phase III studies yielded PFS and OS rates ranging from 71% to 73% and 84% to 90%, respectively, for intermediate-risk patients^{8,9} and 45% to 56% and 57% to 73%, respectively, for poor-risk patients.⁹⁻¹¹

Surgical expertise at the two high-volume institutions that enrolled patients in this study may have contributed to the excellent outcomes observed with TIP. However, it should be noted that only two patients who achieved a CR had viable disease resected at postchemotherapy surgery. Other limitations of our

Table 3. Grade 3 to 4 Hematologic Toxicities (> 15%)

Toxicity	Grade 3		Grade 4		Total (n = 60)	
	No.	%	No.	%	No.	%
Lymphopenia	42	70	9	15	51	85
Neutropenia	9	15	37	62	46	77
Leukopenia	9	15	36	60	45	75
Anemia	32	53	5	8	37	62
Thrombocytopenia	8	13	7	12	15	25
Febrile neutropenia	10	17	1	2	11	18

study include the single-arm design and relatively small sample size. Comparison with BEP in a randomized trial is necessary before TIP can be established as a standard-of-care option for patients with newly diagnosed intermediate- or poor-risk GCTs. Nevertheless, the favorable results achieved here support conduct of such a study, and a randomized phase II trial of TIP versus BEP has therefore been initiated in this population.

In contrast to the previous salvage TIP regimen, the current regimen was adapted for outpatient administration by eliminating the 24-hour infusion of paclitaxel in favor of shorter daily paclitaxel bolus infusions. Initially, paclitaxel was given at 60 mg/m²/d for 4 days, but after observing an increase in hypersensitivity allergic reactions during cycle 2, the regimen was changed to a bolus infusion of 120 mg/m²/d on days 1 and 2 with graduated titration of the rate. After this change, only one of the remaining 35 patients experienced a paclitaxel hypersensitivity reaction.

A relatively high incidence of neutropenic fever was observed in eight of the first 14 patients despite prophylactic granulocyte colony-stimulating factor. It is possible that altering paclitaxel dosing from a single 24-hour infusion to once per day for 4 days could have contributed to increased myelosuppression, resulting in this high rate of neutropenic fever. Nevertheless, the high incidence

Table 4. Grade 3 to 4 Nonhematologic Toxicities

Toxicity	Grade 3		Grade 4		Total (n = 60)	
	No.	%	No.	%	No.	%
Hypophosphatemia	18	30	0		18	30
Hyperglycemia	13	22	0		13	22
Hyponatremia	8	13	3	5	11	18
Increased ALT	9	15	0		9	15
Hypokalemia	9	15	0		9	15
Fatigue	5	8	0		5	8
Nausea	5	8	0		5	8
Hyperbilirubinemia	4	7	0		4	7
Orthostatic hypotension/syncope	3	5	0		3	5
Increased AST	3	5	0		3	5
Vomiting	3	5	0		3	5
Creatinine or renal failure	2	3	0		2	3
Sensory neuropathy	1	2	0		1	2
GI hemorrhage	0		1	2	1	2
Pulmonary embolism	0		1	2	1	2
Encephalopathy	1	2	0		1	2

NOTE. All grade 3 to 4 nonhematologic toxicities occurring in two or more patients are shown but only selected grade 3 to 4 toxicities occurring in one patient are listed.

of neutropenic fever was ameliorated by adding a prophylactic fluoroquinolone antibiotic.

Because sensory neuropathy was an adverse effect common to both paclitaxel and cisplatin, we were concerned that it might be increased with TIP compared with historic rates with BEP, but this was not observed. Only two patients had grade 2 or higher sensory neuropathy, one with grade 2 and one with grade 3. This is similar to the 4% rate of grade ≥ 2 neuropathy reported with BEP $\times 4$ and much less than the 23% rate with a switch to dose-intensive therapy observed in the recently reported GETUG (Groupe d'Etude des Tumeurs Uro-Génitales) -13 trial.¹¹

Patients with PM-NSGCT are a challenging group to cure. All five deaths in this study occurred in patients with PM-NSGCT. Nevertheless, 62% of these patients remained alive at last follow-up. Although this rate is similar to or slightly better than that historically achieved with BEP $\times 4$ or VIP $\times 4$,¹²⁻¹⁴ the continued poor outcomes of these patients underscore the need for further evaluation of their biologic differences from gonadal/retroperitoneal NSGCTs and for the introduction of novel treatment approaches. For example, one recent study that identified *TP53* mutations and deletions as being associated with cisplatin resistance, found a significantly higher rate of these alterations in tumors from patients with PM-NSGCT compared with those from patients with gonadal primary nonseminomas (69% *v* 5%).¹⁵

In summary, TIP demonstrated efficacy as first-line therapy for intermediate- and poor-risk GCT with an acceptable safety profile. Given that our study showed higher rates of favorable response, PFS, and OS than observed in earlier first-line studies, TIP warrants further study in this population. A multicenter randomized phase II trial of first-line TIP versus BEP is therefore underway to provide more details on how TIP compares with standard chemotherapy in patients with intermediate- or poor-risk

GCT (NCT01873326; Paclitaxel, Ifosfamide and Cisplatin [TIP] Versus Bleomycin, Etoposide and Cisplatin [BEP] for Patients With Previously Untreated Intermediate- and Poor-risk Germ Cell Tumors).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Darren R. Feldman, Sujata Patil, Dean F. Bajorin, George J. Bosl, Robert J. Motzer

Financial support: Darren R. Feldman, George J. Bosl, David I. Quinn, Robert J. Motzer

Administrative support: Darren R. Feldman, Kristina Lim, Charlean Ketchens, George J. Bosl, David I. Quinn, Robert J. Motzer

Provision of study materials or patients: Darren R. Feldman, James Hu, Tanya B. Dorff, Maryann Carouso, Amanda Hughes, Joel Sheinfeld, Siamak Daneshmand, Charlean Ketchens, Dean F. Bajorin, George J. Bosl, David I. Quinn, Robert J. Motzer

Collection and assembly of data: Darren R. Feldman, James Hu, Tanya B. Dorff, Kristina Lim, Maryann Carouso, Amanda Hughes, Siamak Daneshmand, Charlean Ketchens, George J. Bosl, David I. Quinn, Robert J. Motzer

Data analysis and interpretation: Darren R. Feldman, James Hu, Tanya B. Dorff, Sujata Patil, Kaitlin M. Woo, Joel Sheinfeld, Manjit Bains, Siamak Daneshmand, Dean F. Bajorin, George J. Bosl, David I. Quinn, Robert J. Motzer

Manuscript writing: All authors

Final approval of manuscript: All authors

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Darren R. Feldman

Consulting or Advisory Role: Bayer, Gilead Sciences (I), Seattle Genetics

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James Hu

Stock or Other Ownership: Biogen Idec

Consulting or Advisory Role: Amgen, Eisai, Merck Serono

Speakers' Bureau: Eisai

Travel, Accommodations, Expenses: Amgen, Eisai, Merck Serono

Tanya B. Dorff

Honoraria: Sanofi, Pfizer, Astellas Pharma

Consulting or Advisory Role: Dendreon, Genentech, Pfizer, Bayer

Speakers' Bureau: Pfizer, Astellas Pharma

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Kristina Lim

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Sujata Patil

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Kaitlin M. Woo

No relationship to disclose

Maryann Carousso

No relationship to disclose

Amanda Hughes

No relationship to disclose

Joel Sheinfeld

No relationship to disclose

Manjit Bains

No relationship to disclose

Siamak Daneshmand

Consulting or Advisory Role: Photocure, TARIS Biomedical

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Charlean Ketchens

No relationship to disclose

Dean F. Bajorin

Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Astellas Pharma, Genentech, Merck, Fidia Farmaceutici, Eisai, Eli Lilly

Research Funding: Dendreon (Inst), Novartis (Inst), Amgen (Inst), Genentech (Inst), Merck (Inst), Bristol-Myers Squibb (Inst),

Travel, Accommodations, Expenses: Genentech, Merck

George J. Bosl

No relationship to disclose

David I. Quinn

Honoraria: Bayer

Consulting or Advisory Role: Algeta/Bayer, Dendreon, Pfizer, Novartis, Exelixis, Bristol-Myers Squibb, Genentech, Merck, EMD Serono, Janssen Pharmaceuticals

Research Funding: Millennium Pharmaceuticals, Genentech, GlaxoSmithKline, Novartis

Robert J. Motzer

Consulting or Advisory Role: Pfizer, Novartis, Eisai

Research Funding: Pfizer (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (Inst), Eisai (Inst), Novartis (Inst), Genentech (Inst)

Travel, Accommodations, Expenses: Bristol-Myers Squibb