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Treatment of Refractory Germ Cell Tumors in Children with Paclitaxel, Ifosfamide and Carboplatin: A Report from The Children's Oncology Group AGCT0521 Study

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Abstract

Background—TIP (paclitaxel, ifosfamide, cisplatin) is commonly used as salvage for malignant germ cell tumors (MGCT) in adults; however, additional administration of cisplatin at a young age could cause significant short and long-term toxicities in a group of patients with high expected salvage. Because carboplatin has been shown to be effective in pediatric MGCT with less toxicity, the TIP regimen was modified by substituting carboplatin for cisplatin.

Methods—The Children's Oncology Group conducted a phase II trial between November 2007 and June 2011 evaluating "TIC" (paclitaxel 135 mg/m²/day Day 1, ifosfamide 1800 mg/m²/dose Days 1–5 and carboplatin with AUC 6.5 Day 1) in children <21y with relapsed MGCT. The endpoint of the trial was response after 2 cycles, incorporating RECIST response and marker decline.

Results—Twenty patients (12 male, median age 13.5 years) were enrolled. Seventeen patients had tumor markers 10 times above normal. After 2 cycles, by RECIST criteria, eight patients achieved a partial response (response rate 40%), ten had stable disease and two had progressive disease. A 1 log reduction was achieved in 10/17 patients (58.8%) with elevated markers. By

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study defined criteria, combining response by RECIST and marker decline, the response rate was 44%.

Conclusion—TIC is active in relapsed pediatric MGCT and should be considered for salvage therapy in children. In adolescents and older adults with relapse MGCT, TIP or high dose chemotherapy with stem cell remain the standard therapy

Keywords

Chemotherapy; Malignant germ cell tumor; Relapse; Pediatric

INTRODUCTION

Cisplatin-based regimens are considered the standard of care in the first line management of patients with malignant germ cell tumors (MGCT); combined with appropriate local control, survival rates in excess of 70–80% are consistently reported. For patients who relapse, salvage chemotherapy using a cisplatin-containing regimen is appropriate, except for the small subgroup of patients who have platinum refractory disease defined as relapse or progression within four weeks from prior cisplatin regimen. In adults, standard and high-dose chemotherapy regimens have demonstrated efficacy and currently there is no consensus on initial salvage approach. Retrospective series seem to indicate the superiority of tandem or triplet transplant for a subgroup of patients with a higher risk of disease progression^{1–3}. Currently a randomized trial Alliance A031102 (TIGER trial) is underway which is randomizing standard dose chemotherapy versus high dose chemotherapy with stem cell rescue⁴. The most commonly used standard dose salvage regimens include a combination of cisplatin plus ifosfamide with paclitaxel (TIP) or vinblastine (VeIP)^{5,6}. Given the rarity of the disease and the excellent outcomes using first line therapy in children with MGCT, the reports on salvage therapy for pediatric patients with relapsed GCT are very limited⁷.

Although relapsed germ cell tumors may continue to show responsiveness to cisplatin, its continued use is associated with significant short and long-term toxicities, including ototoxicity, neurotoxicity, nephrotoxicity, and, among adult men, a two-fold increase in second malignant neoplasms and risk of cardiovascular disease⁸; these late effects are particularly relevant in children and adolescents. The cisplatin analog carboplatin is effective in pediatric germ cell tumors with a better safety profile and fewer long-term side effects. The UK Children's Cancer and Leukemia Group has used carboplatin-containing regimens as first line for pediatric germ cell tumors since 1989, and have comparable results to cisplatin containing regimens⁹. Based on these factors, in the Children's Oncology Group AGCT0521 trial, the TIP regimen was modified and carboplatin was substituted for cisplatin. The endpoint of the trial was response after 2 cycles. As the role of standard versus high dose chemotherapy for consolidation was unclear, further therapy was at investigator discretion. Herein we report the results of this study using paclitaxel, ifosfamide and carboplatin (TIC).

PATIENTS AND METHODS

Eligibility

Children less than 21 years of age with recurrent malignant or chemotherapy-resistant extracranial germ cell tumors were eligible if they had received a first line chemotherapy regimen that included cisplatin. Patients were required to have had histologic verification of malignant GCT at original diagnosis and measurable disease according to RECIST criteria at enrollment on AGCT0521. Patients with tumor marker (AFP and/or β HCG) elevation alone or bone scan findings alone were not eligible. Patients with measurable disease by imaging and elevated tumor markers did not require repeat biopsy for confirmation. Patients with imaging findings only, without concomitant elevation of tumor markers required histologic confirmation of recurrence.

Additional eligibility criteria included: 1) adequate bone marrow function defined as peripheral absolute neutrophil count (ANC) $750/\mu\text{L}$, platelet count $75,000/\mu\text{L}$ (transfusion independent); 2) adequate renal function defined as creatinine clearance (using Schwartz formula) or radioisotope GFR of $70\text{mL}/\text{min}/1.73\text{m}^2$ or normal creatinine for age and gender; 3) adequate liver function defined as total bilirubin $1.5 \times$ upper limit of normal (ULN) for age, and SGPT (ALT) $<2.5 \times$ upper limit of normal (ULN) for age; 4) adequate cardiac function defined as shortening fraction $>27\%$ by echocardiogram, or ejection fraction of 50% by gated radionuclide study; 5) adequate pulmonary function defined as no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry $>94\%$ if there was clinical indication for determination; and 6) adequate control of seizure disorder without enzyme-inducing anticonvulsants. Patients with recurrent GCT previously treated by surgery alone, and patients with pure immature teratoma (any grade), germinoma, or sex-cord stromal tumors were not eligible. All patients and/or their parents or legal guardians signed informed consent prior to participation.

Study Design and Treatment

This was a two stage, Phase II multi-institutional study conducted by the Children's Oncology Group. The primary aim was to evaluate the response rate of recurrent or resistant GCT to the combination of paclitaxel, ifosfamide, and carboplatin (TIC). Response evaluation was performed after 2 cycles of chemotherapy, and further treatment (local and systemic therapy) was at the discretion of the treating physicians.

The chemotherapy regimen consisted of paclitaxel $135\text{ mg}/\text{m}^2/\text{day}$ on day 1, ifosfamide $1800\text{ mg}/\text{m}^2/\text{dose}$ Days 1–5 with mesna $1,080\text{ mg}/\text{m}^2/\text{day}$ divided to three equal doses of $360\text{ mg}/\text{m}^2$ and carboplatin AUC 6.5 Day 1, using the modified Calvert Formula by Marina et al¹⁰. The maximum dose of carboplatin to be administered did not exceed $560\text{ mg}/\text{m}^2$. Filgrastim 5 micrograms/kg/dose daily starting on Day 6 until ANC $>1,500/\mu\text{L}$ post nadir was administered. Criteria to start a cycle was if ANC $750/\mu\text{L}$, and platelets $75,000/\mu\text{L}$. Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care were used as necessary

Evaluation of Response and Toxicity

Imaging response was assessed after two cycles using RECIST criteria. In addition, the study incorporated tumor marker response in patients whose markers were elevated at least ten-fold above normal at study entry. Complete response (CR) was defined as no measurable disease, and normal β HCG and normal AFP (if initial AFP was $\geq 40,000$ ng/ml; otherwise appropriate tumor marker decline). Partial response (PR) was defined as at least 30% decrease in tumor burden and for patients with ≥ 10 -fold marker elevation above normal at enrollment, at least a 1 log (90%) reduction. Progressive disease (PD) was defined as increase in tumor measurement by 20% or increase in markers by 1 log. Stable disease (SD) was defined as neither PR or PD. Patients who demonstrated a CR or PR were considered as responders. Assessment of toxicity was done using CTCAE version 4.

Study Design

The study was designed as a two-stage design. Ten response-evaluable patients were to be enrolled in the first stage and enrollment was stopped until the response status for these patients could be determined. If three or fewer patients demonstrated CR or PR, enrollment was to be terminated with the conclusion that protocol therapy was not considered sufficiently efficacious for further study. If four or more responses were noted in the first stage, 10 more response-evaluable patients were enrolled and study accrual was terminated. If the true response rate was 27%, the probability enrollment would terminate at the end of the first stage was approximately 90%. If the true response rate was 65%, the probability full enrollment of 20 patients would be allowed was 90%. The response rate was estimated accounting for the two-stage design by the UMVUE method of Jung and Kim¹¹.

All eligible patients who received at least one dose of a protocol-specified agent were to be considered in the analysis of toxicity. The occurrence of each CTC v. 4 adverse experience reported as grade 3 or greater at any time during protocol therapy was ascertained. The proportion of all patients experiencing each of the adverse experiences identified was calculated.

RESULTS

AGCT0521 was open between November 2007 and June 2011, at 77 COG institutions. Data current to December 2016 were used in this analysis. The characteristics of the patient at enrollment on AGCT0521 are displayed in Table 1.

Response Assessment

All twenty patients were assessable for response. After two cycles of TIC, by RECIST criteria alone, eight patients achieved a partial response (40%), ten patients had stable disease and two patients had progressive disease. Seventeen patients had markers ≥ 10 times above normal and were assessable for marker response. After two cycles, markers had at least a 1 log decline in 10 of 17 patients (58.8%) (Table 2).

Using study defined response criteria which combined RECIST response and tumor marker decline (Table 2), 7 of 20 patients were considered responders upon completion of two

cycles. The estimated response rate accounting for the 2-stage design is 44%. All seven patients had partial response by RECIST and their tumor markers had at least a 1 log reduction if elevated greater than 10-fold above normal at enrollment.

Thirteen patients were non-responders by study defined response criteria. Ten patients met study criteria for stable disease, 2 had progressive disease and one patient met the RECIST criteria for partial response but that patient's elevated bHCG did not achieve a 1-log decline. Of the 10 patients with stable disease, tumor markers at enrollment were elevated 10-fold above normal in 8 patients (7 AFP, 1 β HCG). Markers had at least a 1 log reduction in 4/8 patients. Both patients with progressive disease had marker elevation at enrollment (one AFP and one BHCG) and neither patient's tumor markers showed any decrease during therapy.

Treatment post completion of TIC and Outcome

Although the primary endpoint of this study was response to two cycles of TIC, treatment post completion of TIC and outcome were reported in follow-up.

Table 3 gives details of post TIC treatment. As shown, after two cycles of TIC, thirteen patients received standard dose chemotherapy, five patients received high dose chemotherapy with stem cell rescue, one patient received surgery alone and one patient received no further therapy. Seven of the thirteen patients getting standard dose chemotherapy received TIC alone, whereas six received other standard dose chemotherapy regimens. At last follow up six of eight patients with partial response, and seven of ten patients with stable disease were alive. No patient with progressive disease survived.

Toxicity

All 20 patients were evaluable for toxicity. Eighteen patients received both cycles of TIC, whereas two patients were taken off therapy after one cycle due to toxicity. One patient was taken off therapy due to nephrotoxicity. The glomerular filtration rate decreased to less than 70 ml/min/1.73m². Despite a one week delay the GFR did not increase to above 70 ml/min and patient was taken off protocol. The reason why other patient was taken off therapy is unclear. The major grade 3 and 4 toxicities were myelosuppression, with neutropenia, thrombocytopenia and anemia seen in 60%, 45% and 40% of patients. Febrile neutropenia occurred in 25% of patients.

DISCUSSION

This is the first study evaluating a salvage regimen for relapsed germ cell tumors in children. Our study showed that paclitaxel, ifosfamide and carboplatin (TIC) regimen was effective as second line therapy in children with relapsed germ cell tumors. After two cycles of TIC, the estimated overall response rate was 44% using combined RECIST response and tumor marker decline. Forty percent (40%) of patients achieved a RECIST-defined partial response, and using marker decline alone 58.8% of patients with elevated markers had at least a 1 log (90%) reduction of markers. The incorporation of tumor marker decline to enhance response assessment is particularly important in patients with stable disease, as the residual tumor may be a teratoma, and hence response by imaging alone may be inaccurate.

In adults, the management of relapsed GCT is either with standard dose chemotherapy or high dose chemotherapy with autologous stem cell rescue^{5,6,12–18}. There are no completed randomized trials comparing these two approaches and currently no consensus exists on whether initial salvage should be standard dose or high dose chemotherapy. Currently a randomized trial, Alliance A031102 (TIGER trial) is underway which is randomizing standard dose chemotherapy with TIP versus high dose chemotherapy with TI-CE⁴. The most commonly used standard dose chemotherapy regimens are ifosfamide and cisplatin with paclitaxel (TIP) or vinblastine (VeIP)^{5,6}. The TIP regimen (paclitaxel 250 mg/m² day 1, with ifosfamide 1200 mg/m²/day for five days and cisplatin 20 mg/m²/d for 5 days) was first reported by Moetzer et al⁵, who treated 30 patients with relapsed non seminomatous testicular GCT and reported a complete response rate of seventy seven percent. Two other studies used a lower dose of paclitaxel and reported a favorable response rate of 60–65%^{19–20}. This was attributed to a lower paclitaxel dose.

Our study modified the TIP regimen used in adults, by substituting carboplatin for cisplatin to decrease toxicity. Cisplatin is associated with both short and long-term toxicities, including ototoxicity, neurotoxicity, nephrotoxicity, 2-fold increase in SMN and cardiovascular disease. Carboplatin has a better toxicity profile with fewer short and long-term side effects, and it has been used as initial therapy for pediatric GCT in the UK since 1989; the outcomes using carboplatin, etoposide, bleomycin, (JEB) are comparable to those with cisplatin-based regimens (PEB)⁹. Recently the US Children's Oncology Group and the UK Children's Cancer and Leukemia Group merged 25 years of clinical trial data on pediatric GCTs to form the Malignant Germ Cell International Collaborative (MaGIC) dataset. In a multivariate analysis of five hundred and nineteen patients, treatment regimen (PEB versus JEB) did not show a significant difference in outcome²¹. In addition, high dose carboplatin is also an integral part of high dose chemotherapy regimens used for relapse GCT in adults^{12–1}. This provided the rationale for substituting carboplatin for cisplatin in the TIC regimen. In addition to this substitution, there were several other differences between the TIP and the TIC regimen used in this trial. The dose of paclitaxel used was lower at 135 mg/m² per cycle in TIC regimen compared to 250 mg/m² per cycle used in TIP, and the ifosfamide dose was higher at 9 grams/m²/cycle versus 6 grams/m²/cycle.

It is difficult to compare the response rates between TIP and our study using TIC. In our study response was evaluated after 2 cycles whereas the response after TIP was evaluated after 4 cycles. The TIC regimen was well tolerated and there was no neurotoxicity or treatment related death. Similar to the TIP regimen, the major toxicity was myelosuppression with fever and neutropenia reported in 25% of patients. There are few other reports of salvage regimen for relapse MGCT in children. In the French TGM 95 trial, nineteen children had refractory or recurrent MGCT. They were treated with surgery and various chemotherapy regimens with 5-year EFS and OS of 26 % and 32% respectively⁷.

Our study has some limitations. Due to the rarity of relapse in pediatric MGCT, the study was designed to accrue a small number of patients. It was designed to evaluate response after only two cycles and hence we cannot comment on role of further consolidation therapy. The dose of paclitaxel in our study was lower than used in TIP, and may account for the lower response rate.

In conclusion, the TIC regimen is active in relapse MGCT and should be considered an option for salvage therapy, particularly in younger children and those with preexisting ototoxicity, suggesting that carboplatin could be used as an alternative to cisplatin in the standard TIP regimen. However, conventional dose chemotherapy with TIP or high dose chemotherapy with TI-CE are currently accepted standard options especially in adolescents and older adults and a current trial is underway randomizing these two approaches.

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Glossary

TIP	Paclitaxel, Ifosfamide, cisplatin
TIC	Paclitaxel, Ifosfamide, Carboplatin
MGCT	Malignant Germ Cell Tumor
RECIST	Response Evaluation Criteria in Solid Tumors
GCT	Germ Cell Tumor
CR	Complete Response
PR	Partial Response
PD	Progressive Disease
SD	Stable Disease
VeIP	Vinblastine, Ifosfamide, Cisplatin
PEB	Cisplatin, Etoposide, Bleomycin
JEB	Carboplatin, Etoposide, Bleomycin
MaGIC	Malignant Germ Cell International Collaborative
TI-CE	Paclitaxel, Ifosfamide, Carboplatin, Etoposide

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Table 1

Patient Characteristics

Patient Characteristics	Value
Age	
Mean	11.5 yrs
Standard Deviation (Range)	6.06 yrs (1–18 yrs)
Sex, M:F	12:8
Histology	
Mixed GCT	7
Yolk sac tumor	6
Choriocarcinoma	2
Embryonal carcinoma	1
Germinoma	1
Malignant teratoma	1
Non seminomatous GCT	2
Sites of Measurable Disease	
Retroperitoneum	7
Lung	5
Mediastinum	3
Liver	3
Ovary	2
Pelvis	6
Brain	1
Vagina	1
Number of measurable metastatic sites	
1	13
2	6
3+	1
Tumor Markers Pre-Treatment	
AFP (ng/ml)	
Mean	2742.4
Standard Deviation (Range)	7353.6 (2–31919)
B HCG (mIU/ml)	
Mean	946.9
Standard Deviation (Range)	2872.9 (0–12086)

Table 2

Tumor Marker and RECIST Response

RECIST Response	AFP and bHCG Not Assessable	Only Tumor Marker AFP and Declined at Least 1 log	Only Tumor Marker AFP and Did Not Decline 1 log	Only Tumor Marker bHCG and Declined at Least 1 log	Only Tumor Marker bHCG and Did not Decline 1 log	Total
Partial Response	1 /	5 /		1 /	1	8
Stable Disease	2	4	3		1	10
Progressive Disease			1		1	2
Total	3	9	4	1	3	20

/ Patients in the noted category are considered responders for the application of the protocol design rule.

Table 3

Therapy Post TIC and Patient Outcomes

Patient No	Sites of Measurable Disease for Response Assessment	Response by RECIST to 2 cycles of TIC	Additional Treatment	Months from Off Protocol Therapy to Last Contact	Status at last Contact
1	Brain	Partial Response	PAC/GEM/OX, XRT A-HSCT, Oral Etoposide	10	Dead
2	Pelvis	Partial Response	Surgery	61	Alive
3	Lungs	Partial Response	TIC	35	Alive
4	Ovary Lungs	Partial Response	TIC × 1, A-HSCT Oral Etoposide	8	Dead
5	Lungs Liver	Partial Response	Surgery, PAC/GEM/OX A-HSCT × 2	53	Alive
6	LNs (abdomen)	Partial Response	TIC × 4, Surgery	34	Alive
7	Vagina	Partial Response	TIC × 2, Surgery	48	Alive
8	Liver Retroperitoneal LN	Partial Response	TIC, VAC	46	Alive
9	Pelvis	Stable Disease	A-HSCT, Surgery, XRT	55	Dead
10	Abdomen Pelvis	Stable Disease	Surgery TIC × 2	38	Alive
11	Abdomen Pelvis	Stable Disease	Surgery, TIC CDDP/DOX/CYC	35	Alive
12	Pelvis (LNs)	Stable Disease	PAC/GEM/OX, Surgery Oral Etoposide	21	Dead
13	Retroperitoneal LN	Stable Disease	TIC × 2, XRT	3	Dead
14	Mediastinum Retroperitoneal LN	Stable Disease	PAC/GEM	81	Alive
15	Mediastinum	Stable Disease	No	25	Alive
16	Liver LN(abdomen)	Stable Disease	TIC × 2 Surgery	75	Alive
17	Lungs Abdomen Pelvis	Stable Disease	PAC/CBP × 4 Surgery	36	Alive
18	Ovary	Stable Disease	TIC × 6	34	Alive
19	Lungs	Progressive Disease	TIC × 2, A-HSCT	6	Dead
20	Mediastinum	Progressive Disease	Surgery, PAC/GEM	0.8	Dead

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A-HSCT: Autologous stem cell transplant; XRT: radiation; PAC/GEM/OX: Paclitaxel, gemcitabine, oxaliplatin; TIC – paclitaxel, ifosfamide, carboplatin; VAC: vincristine/dactinomycin, cyclophosphamide; CDDP/DOX/CYC: cisplatin, doxorubicin, cyclophosphamide; PAC/CBP: paclitaxel, carboplatin; PAC/GEM: paclitaxel, gemcitabine