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ORIGINAL REPORT

Phase II Study of Irinotecan and Temozolomide in Children With Relapsed or Refractory Neuroblastoma: A Children's Oncology Group Study

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ABSTRACT

Purpose
This phase II study was conducted to determine the response rate associated with use of irinotecan and temozolomide for children with relapsed/refractory neuroblastoma.

Patients and Methods
Patients with relapsed/refractory neuroblastoma measurable by cross-sectional imaging (stratum 1) or assessable by bone marrow aspirate/biopsy or metaiodobenzylguanidine (MIBG) scan (stratum 2) received irinotecan (10 mg/m^2/dose 5 days a week for 2 weeks) and temozolomide (100 mg/m^2/dose for 5 days) every 3 weeks. Response was assessed after three and six courses using International Neuroblastoma Response Criteria. Of the first 25 evaluable patients on a given stratum, five or more patients with complete or partial responses were required to conclude that further study would be merited.

Results
Fifty-five eligible patients were enrolled. The objective response rate was 15%. Fourteen patients (50%) on stratum 1 and 15 patients (56%) on stratum 2 had stable disease. Objective responses were observed in three of the first 25 evaluable patients on stratum 1 and five of the first 25 evaluable patients on stratum 2. Less than 6% of patients experienced ≥ grade 3 diarrhea. Although neutropenia was observed, less than 10% of patients developed evidence of infection while neutropenic.

Conclusion
The combination of irinotecan and temozolomide was well tolerated. The objective response rate of 19% in stratum 2 suggests that this combination may be effective for patients with neuroblastoma detectable by MIBG or marrow analysis. Although fewer objective responses were observed in patients with disease measurable by computed tomography/magnetic resonance imaging, patients in both strata seem to have derived clinical benefit from this therapy.

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INTRODUCTION

Approximately 40% of children with neuroblastoma present with high-risk disease, and long-term survival rates for these children are poor.[1] Intensive treatment regimens have resulted in incremental improvements in survival in children older than 1 year of age with advanced-stage disease. However, long-term survival for high-risk patients remains less than 40%.[2,3] There is a pressing need for development of new treatments for patients with relapsed and refractory neuroblastoma that could potentially be incorporated into first-line regimens for patients with high-risk disease.

Irinotecan is a camptothecin prodrug whose active metabolite (SN-38) induces cytotoxicity in the presence of the nuclear enzyme topoisomerase I. The antineuroblastoma activity of single-agent irinotecan has been demonstrated in both the preclinical and clinical settings.[4-10] Temozolomide is an imidazotetrazine prodrug that undergoes hydrolysis to the active metabolite 5-(3-methyltriazen-1-yl)imidazole-4-carbozamide. This metabolite is believed to induce cytotoxicity by methylating DNA, generating O^6-methylguanine adducts. Temozolomide has shown modest activity against neuroblastoma xenografts as a single agent,[11] and complete, partial, and minor responses to this agent have been observed in patients with relapsed or refractory neuroblastoma.[12]

Temozolomide-induced formation of O^6-methylguanine adducts has been shown to facilitate

the creation of topoisomerase I/DNA complexes, suggesting that DNA-methylating agents could potentially augment the activity of camptothecins.[13] Encouraging responses were seen after administration of irinotecan and temozolomide to neuroblastoma xenograft–bearing mice,[14] and objective responses were observed in patients with neuroblastoma treated on a phase I study of this drug combination.[15] This phase II study was carried out by the Children's Oncology Group to determine the response rate of patients with relapsed or refractory neuroblastoma treated with irinotecan and temozolomide.

PATIENTS AND METHODS

Eligibility

Patients were enrolled onto the Children's Oncology Group ANBL0421 study from June 2006 to July 2008. Patients must have been ≤ 21 years of age at the time of initial diagnosis and must have had histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines. All patients had recurrent disease after treatment or had developed refractory disease during treatment with two or more agents, including an alkylating agent and a platinum-containing compound. Patients were eligible only if they had received no prior treatment after initial relapse or development of primary refractory disease. Patients were required to have life expectancies of ≥ 8 weeks and Karnofsky or Lansky scores ≥ 50. Other requirements were as follows: recovery from acute toxic effects of prior therapies; negative pregnancy test for women of child-bearing potential; and adequate organ function as defined by serum creatinine ≤ the upper limit of normal (ULN) for age or glomerular filtration rate ≥ 70 mL/min/1.73 m^2, ALT ≤ 2.5× ULN for age, and bilirubin ≤ 1.5× ULN for age. Patients were required to have an absolute neutrophil count (ANC) ≥ 750/μL, hemoglobin ≥ 8.5 g/dL (transfusion permitted), and an unsupported platelet count ≥ 75,000/μL unless extensive bone marrow involvement was documented. Patients with active diarrhea or uncontrolled illnesses were not eligible. Chemotherapy and localized radiotherapy were not permitted within 2 weeks of study entry. Treatment with biologic agents (including monoclonal antibodies), retinoids, or growth factors was not permitted within 7 days of study entry. Patients who had undergone stem-cell transplantation were eligible if ≥ 3 months had elapsed since autologous transplantation or if ≥ 6 months had elapsed since allogeneic transplantation, provided that there was no evidence of active graft-versus-host disease. Patients taking enzyme-inducing anticonvulsants were not eligible. The protocol was approved by the institutional review boards at participating institutions. Informed consent was obtained from the parent or legal guardian of all participants; assents were approved from minors when appropriate.

Patients were enrolled onto one of two strata. Patients on stratum 1 were required to have tumor measurable on magnetic resonance imaging (MRI) or computed tomography (CT) scan according to Response Evaluation Criteria in Solid Tumors (RECIST).[16] Patients with disease detectable by metaiodobenzylguanidine (MIBG) scan or by bone marrow aspirate/trephine biopsy could be enrolled onto stratum 1 as long as their disease could be measured by cross-sectional imaging (CT or MRI) techniques. Patients on stratum 2 were required to have disease detectable only by MIBG scan or bone marrow aspirate/trephine biopsy.

Drug Administration

Temozolomide (100 mg/m^2 rounded off to the nearest tablet size) was administered orally at least 1 hour before irinotecan administration on days 1 through 5. Irinotecan (10 mg/m^2) was administered as a 1-hour infusion 5 days per week for 2 consecutive weeks ([daily × 5] × 2). Because preclinical data suggested schedule-dependent effects,[17] on days of coadministration of these two agents, temozolomide was to precede irinotecan by at least 1 hour. Treatment cycles were repeated every 3 weeks up to a maximum of six cycles. For patients who did not experience significant toxicity during the first courses of treatment, subsequent courses could be administered via home-infusion services, if available. Patients were given instructions for use of loperamide to treat diarrhea occurring ≥ 24 hours after irinotecan. Continuous administration of oral cefpodoxime or cefixime (or available equivalent) was recommended to reduce irinotecan-associated diarrhea in patients who experienced clinically significant diarrhea, defined as an increase of ≥ seven stools per day, incontinence of stool, or need for parenteral support for dehydration. Use of antibiotics for prevention of irinotecan-associated diarrhea in patients who had not previously experienced this degree of toxicity was neither specifically required nor prohibited. Filgrastim (granulocyte colony-stimulating factor) was to be administered during subsequent courses of therapy for patients whose ANC was less than 750/μL by day 35 of a given treatment cycle.

Toxicity Monitoring

All patients who received therapy had evaluations of renal, hepatic, and hematologic function weekly. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Response Evaluation

Eligible patients who received at least two courses of irinotecan and temozolomide therapy were considered evaluable for response. Response was assessed after three and six courses of therapy. A summary of the contribution of response in individual sites of disease to overall response designation is provided in Table 1. RECIST criteria were used for response assessment in patients whose disease was measurable by CT or MRI (stratum 1).[16] For patients with MIBG-positive lesions, presence or absence of radioisotope uptake was used to determine response. As per the International Neuroblastoma Response Criteria (INRC), resolution of all MIBG-positive lesions was considered a complete response (CR); resolution of at least one MIBG-positive lesion with persistence of other lesions was considered a partial response (PR).[18]

Table 1. Response Assessment

Response by Individual Site				Overall Response
CT/MRI Lesions	MIBG Lesions	Bone Marrow	Catechols	
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
PR	PR/CR in bone lesions; may have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Any	PR
SD	SD/PR/CR	SD/CR	Any	SD
SD/PR/CR	SD	SD/CR	Any	SD
SD/PR/CR	SD/PR/CR	SD	Any	SD

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; MIBG, metaiodobenzylguanidine; PD, partial disease; CR, complete response; PR, partial response; SD, stable disease.

Patients with stable disease (SD) had no change in the number of MIBG-positive lesions. The appearance of any new MIBG-positive lesion was considered progressive disease. The Curie scale was used for assessment of MIBG status during central review.[19] Bone marrow involvement was assessed using routine staining; bilateral marrow evaluations were required. Confirmation of a marrow response was required 3 weeks after initial response assessment. Central review of imaging was performed for patients designated as having had objective radiographic responses based on institutional interpretation of imaging studies. Overall response was designated based on INRC.[18] Patients with CR had no evidence of tumor at any site and normal urinary catecholamines. Patients with lesions measurable by cross-sectional techniques were required to have a $\geq$ 30% decrease in the diameter of lesions on repeat imaging when compared with baseline. In addition, a CR in bone marrow together with a PR in the primary tumor was required for designation of a PR in patients on stratum 1 who had marrow involvement at study entry. Patients on stratum 1 who also had MIBG-avid lesions had to have PR or CR in bone lesions and either SD or CR in soft tissue lesions corresponding to sites of disease on cross-sectional imaging. Patients who had SD in any individual site were designated as having an overall response of SD.

Patients with SD or better after three courses of therapy were to receive an additional three courses of irinotecan and temozolomide per protocol. Study therapy was complete after six courses of treatment. Administration of these commercially available drugs could be continued after completion of study therapy at the discretion of the treating physician.

Statistical Analysis

Intent-to-treat analyses of response (by stratum) and survival (overall) were performed. The primary end point, response, was evaluated separately within each stratum using an exact one-stage rule. Of the first 25 evaluable patients on a given stratum, five or more responders (overall best response of CR or PR) were required to conclude that the combination of irinotecan plus temozolomide was worthy of further study. This rule has 91% power (significance level of $\alpha = .098$) to detect a 20% difference in response rate, from 10% under the null hypothesis to 30% under the alternative, within each stratum. Survival curves were constructed using the Kaplan-Meier method.[20] Comparisons of survival curves were performed with a two-sided log-rank test. For event-free survival (EFS), time to event was calculated from enrollment to first occurrence of relapse, progressive disease, secondary malignancy, or death or to time of last patient contact, if no event occurred. For overall survival (OS), time to event was calculated as time from enrollment until death or time to last contact, if the patient was alive. EFS and OS are presented as a point estimates $\pm$ SE. $P < .05$ was considered statistically significant.

RESULTS

Patients

A total of 59 patients were enrolled. Four patients were found to be ineligible (one as a result of incorrect consent, one as a result of low hemoglobin, one as a result of low ANC, and one as a result of administration of therapy before enrollment). The remaining 55 patients form the basis of this report. Patient characteristics are listed in Table 2. Twenty-eight eligible patients were enrolled onto stratum 1, and 27 patients were enrolled onto stratum 2. Patients ranged from less than 3 months to 18.5 years in age; median age at the time of enrollment was 3.6 years. Three fourths of the patients with known stage had International Neuroblastoma Staging

Table 2. Demographics and Clinical Characteristics of Eligible Patients on the Children's Oncology Group ANBL0421 Study

Characteristic	Stratum 1 (n = 28)		Stratum 2 (n = 27)		Overall (N = 55)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	3.2		4.1		3.6	
Range	0.2-14.3		1.5-18.4		0.2-14.3	
INSS stage at diagnosis*						
Stage 4	10	53	21	100	31	77
Other	9	47	0		9	23
Unknown	9		6		15	
MYCN status						
Amplified	9	50	2	13	11	32
Nonamplified	9	50	14	87	23	68
Unknown	10		11		21	
Disease status						
Recurrent	18	69	20	77	38	73
Refractory	8	31	6	23	14	27
Unknown	2		1		3	
Site of disease†						
Bone	13	46	23	85	36	65
Bone marrow	15	54	20	74	35	64
Lymph nodes	10	36	2	7	12	22
Other‡	23	82	8	30	31	56
Prior treatment						
Included Topo/Cy	8	31	13	50	21	40
Did not include Topo/Cy	18	69	13	50	31	60
Unknown	2		1		3	

Abbreviations: INSS, International Neuroblastoma Staging System; Topo, topotecan; Cy, cyclophosphamide.
*INSS stage and *MYCN* status were unknown for patients who had not enrolled onto a Children's Oncology Group study at diagnosis.
†Patients may report more than one site of disease; therefore, percentages do not sum to 100%.
‡Patients on stratum 2 had disease assessable by bone marrow morphology or metaiodobenzylguanidine only. Other sites of disease included lung, liver, abdomen, and the paraspinal region; these could not be accurately measured by cross-sectional imaging.

Table 3. Response to Irinotecan and Temozolomide by Stratum

Best Response	No. of Patients	%
Stratum 1	28	
CR	1	4
PR	2	7
SD	14	50
PD	11	39
Stratum 2	27	
CR	3	12
PR	2	8
SD	15	58
PD	6	23
Not evaluated	1	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, partial disease.

System stage 4 disease at diagnosis. Although the majority of patients had recurrent neuroblastoma, one fourth had primary refractory disease. Forty percent of the patients had previously been treated with regimens that included the combination of topotecan and cyclophosphamide.

Response and Outcome

Objective responses were observed in three of the first 25 evaluable patients enrolled onto stratum 1 and in five of the first 25 evaluable patients enrolled onto stratum 2. Four of the eight patients who had objective responses had CRs to therapy (one patient in stratum 1; three patients in stratum 2). The overall objective response rate (CR+PR) was 15% (eight of 55 patients) overall, 11% (three of 28 patients) in stratum 1, and 19% (five of 27 patients) in stratum 2 (Table 3). Fourteen of the patients (50%) on stratum 1 and 15 of the patients (56%) on stratum 2 had SD.

Of the three stratum 1 patients with CR or PR, one had a marked decrease in the size of a pleural-based mass accompanied by resolution of bone marrow disease. The patient went on to receive a total of 11 cycles of irinotecan and temozolomide (six cycles delivered as part of this study and five cycles delivered at the treating physician's discretion) before going on to a transplantation-containing experimental regimen. One patient experienced a CR in measurable soft tissue disease and received a total of 13 cycles of irinotecan and temozolomide before undergoing subsequent treatment with a novel agent. One patient had an objective response in nodal and skull disease after three cycles of study therapy but went on to develop progressive disease after three additional cycles of study treatment.

Five patients with disease detectable only by MIBG and bone marrow aspirate/biopsy (stratum 2) had CR or PR. Three of these patients initially had both marrow disease and skeletal involvement, and a CR in the marrow was documented in all of these children after three initial cycles of irinotecan and temozolomide. One of these patients went on to receive stem-cell transplantation after three cycles of study therapy, one patient experienced progression after three additional cycles of study therapy, and one patient continued to receive irinotecan and temozolomide for a total of 12 cycles of this therapy before disease progression.

Among the patients with disease measurable by cross-sectional imaging (stratum 1), 14 patients had a best overall response of SD by INRC criteria. One patient on stratum 1 had SD detectable by CT or MRI only and did not have disease assessable by marrow aspirate/biopsy or MIBG scan. Six patients on stratum 1 had consistent SD on all relevant measures of disease status. Seven patients on stratum 1 had overall SD that was comprised of objective response by some measures but SD by another. Three of these patients had CR or PR in disease detectable by CT or MRI but had SD in MIBG-avid lesions. Conversely, four patients had CR or PR based on MIBG imaging but had SD in lesions measurable on CT or MRI. Fifteen patients with disease detectable only by MIBG scan or bone marrow aspirate/biopsy (stratum 2) had SD as best response to therapy. Of these patients, two had PR based on MIBG scans but had SD in the bone marrow. Four patients with overall SD had no evidence of residual bone marrow disease but had SD detected via MIBG scan.

Fourteen patients had primary refractory neuroblastoma. Two of these 14 patients were among those on stratum 2 who had objective responses to study therapy. One of these patients had previously been treated with the combination of topotecan and cyclophosphamide. Ten patients with refractory neuroblastoma had SD during study therapy, including four patients who had previously received topotecan and cyclophosphamide.

Secondary end points of this study were EFS and OS. Two-year EFS and OS rates in this cohort were 13% ± 9% and 30% ± 10%, respectively (Fig 1).

Toxicity

The combination of irinotecan and temozolomide was generally well tolerated. Toxicities of grade 3 or 4 in severity are listed in Table 4; there were no toxic deaths. Less than 6% of patients experienced grade 3 or 4 diarrhea. Although 18% of patients on stratum 1 and 35% of patients on stratum 2 experienced grade 3 or 4 neutropenia during the first three cycles of therapy, less than 10% of all patients developed evidence of infection while neutropenic. Grade 3 or 4 thrombocytopenia was observed in only two patients (7%) on stratum 1 and five

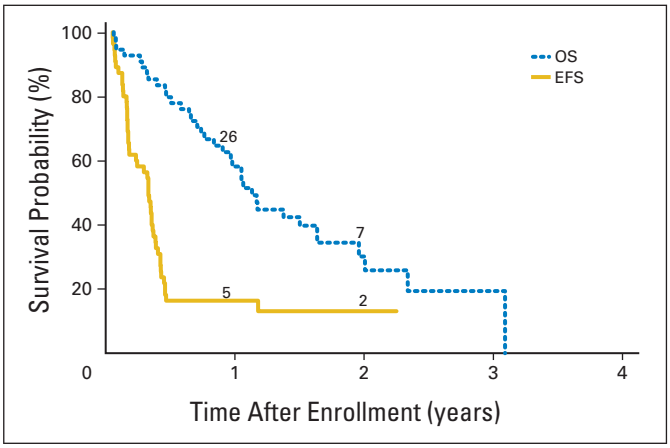

Fig 1. Event-free survival (EFS) and overall survival (OS) curves for all eligible patients on the Children's Oncology Group ANBL0421 study (N = 55). The number of patients at risk for an event (EFS) or death (OS) at year 1 and year 2 are shown along the curves.

Table 4. Grade 3 or 4 Toxicities

Toxicity	Stratum 1 (n = 28)		Stratum 2 (n = 27)	
	No. of Patients	%	No. of Patients	%
Hematologic	11	39	14	52
Neutropenia	7	25	12	44
Thrombocytopenia	2	7	5	19
Anemia	4	14	4	15
Fever/infection	3	11	9	33
Pain	3	11	1	4
Anorexia/nausea/emesis	4	14	2	7
Diarrhea	1	4	2	7
Hypokalemia	2	7	3	11

patients (19%) on stratum 2. Hypokalemia was experienced by two patients (7%) on stratum 1 and three patients (11%) on stratum 2. All other grade 3 or 4 toxicities were observed in only one or two patients per stratum.

DISCUSSION

The prognosis for patients with recurrent or refractory neuroblastoma is extremely poor. Garaventa et al[21] reported a 2% 10-year OS rate among 234 children with recurrent stage 4 disease and a 1.5% 10-year OS rate among 317 children with stage 4 disease who experienced progression on therapy. Data from the Children's Oncology Group P9462 study demonstrated that 32% of patients with relapsed or refractory neuroblastoma treated with the combination of cyclophosphamide and topotecan had CRs or PRs to treatment.[22] Because this combination is now being used as initial therapy for high-risk patients, an alternative approach to second-line therapy is needed.

The combination of oral temozolomide and intravenous irinotecan was well tolerated in this cohort of children with relapsed and refractory neuroblastoma. This outpatient regimen was associated with acceptable adverse effects. Cumulative toxicity was not observed. Although treatment on this study was limited to six courses of irinotecan and temozolomide, follow-up data show that patients with SD or better were able to continue this therapy for more than 10 cycles under the direction of their treating physicians. These findings confirm and extend those of smaller studies of this combination in children.[15,23,24] Our findings also confirm those of Kushner et al,[25] who have described a single-institution experience with oral temozolomide (150 mg/m^2/dose for five doses) and intravenous irinotecan (50 mg/m^2/dose for five doses) in patients with neuroblastoma. In that study, the objective response rate among 36 evaluable patients with relapsed or refractory neuroblastoma was low (8%). However, several of the heavily pretreated patients tolerated treatment well and experienced disease control over more than 10 cycles of therapy.[25]

This prospective multi-institutional cooperative group study was designed to assess the objective response rate to irinotecan and temozolomide among patients with disease detectable by CT or MRI and among patients with disease detectable by MIBG or bone marrow analysis only. The CR+PR response rate of 19% observed in patients with disease detectable only by MIBG or bone marrow analysis suggests that this combination of drugs may be effective for patients with disease detectable by MIBG or marrow analysis only. In stratum 1, we failed to reject the null hypothesis of a 10% response rate. This two-agent combination may not merit further study among patients with disease detectable by CT or MRI. However, there does seem to be a clinical benefit associated with this regimen among patients in both strata. In addition to the objective responses described, SD was observed in nearly half of the patients on stratum 1 and in just over half of the patients on stratum 2. Of the 21 patients who received topotecan before enrolling onto this study, 14 had either an objective response (n = 1) or disease stabilization (n = 13). This finding is consistent with data previously generated in preclinical studies and in smaller clinical trials.[7,15,23] Topotecan and irinotecan may be associated with different mechanisms of drug resistance, and prior treatment with topotecan does not seem to preclude the possibility of response to irinotecan-containing regimens.

An all-oral regimen of temozolomide with protracted irinotecan has been studied in patients with relapsed or refractory neuroblastoma and seems to be well tolerated.[26] Recent data indicate that the use of oral irinotecan on a shorter 5-day schedule is also feasible and results in active metabolite (SN-38) exposures that are similar to those achieved with intravenous administration.[27] In future studies, the combination of short-course irinotecan (intravenous or oral) with oral temozolomide could serve as a backbone on which to integrate new agents for the treatment of neuroblastoma.

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