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Pilot Study of Vincristine, Oral Irinotecan, and Temozolomide (VOIT Regimen) Combined With Bevacizumab in Pediatric Patients With Recurrent Solid Tumors or Brain Tumors

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Background. The combination of vincristine, oral irinotecan, and temozolomide (VOIT regimen) has shown antitumor activity in a pediatric Phase I trial. To further potentiate synergy, we assessed the safety and feasibility of adding bevacizumab to VOIT for children and young adults with recurrent tumors. ***Methods.*** Patients received vincristine (1.5 mg/m^2 on day 1), oral irinotecan (90 mg/m^2 on days 1–5), temozolomide (100–150 mg/m^2 on days 1–5), and bevacizumab (15 mg/kg on day 1) in 3-week cycles, which were repeated for up to six cycles. Cefixime prophylaxis was used to reduce irinotecan-associated diarrhea. ***Results.*** Thirteen patients received 36 total cycles. Six of the first 10 patients required dose reductions due to toxicity during the first cycle (n = 3) or subsequent cycles (n = 3), and these grade 3 side effects included prolonged nausea, dehydration, anorexia, neuropathy, diarrhea, and abdominal pain, as well as prolonged grade 4 neutropenia. After reducing daily temozolomide to 100 mg/m^2, three additional patients tolerated therapy well without the need for dose reductions. Toxicities attributed to bevacizumab were limited to grade 1 epistaxis (1) and grade 2 proteinuria (1). Tumor responses were seen in both patients with Ewing sarcoma. ***Conclusions.*** Reducing temozolomide from 150 to 100 mg/m^2/day improved tolerability, and treatment with this lower temozolomide dose was feasible and convenient as outpatient therapy. Although responses were seen in Ewing sarcoma, the benefit of adding bevacizumab remains unclear. Pediatr Blood Cancer 2013;60:1447–1451.

Key words: bevacizumab; ewing's sarcoma; neuroblastoma; sarcoma; targeted therapy

INTRODUCTION

Treatment for pediatric solid tumors generally employs multiple agents with different mechanisms of action in an attempt to overcome tumor cell resistance. Activity is further improved when synergistic combinations are used, such as the pairing of the methylating agent temozolomide with the camptothecin irinotecan [1]. This combination has been well tolerated and demonstrated activity against a variety of pediatric solid tumors, including Ewing sarcoma [2,3] and neuroblastoma [4]. This activity and tolerability has led investigators to use this drug pair as a therapeutic backbone on which to add other agents, especially those which may result in additional synergy. For example, the addition of vincristine to irinotecan markedly increases the response rate in newly-diagnosed patients with metastatic rhabdomyosarcoma [5]. Because the toxicity profile of vincristine does not overlap with temozolomide or irinotecan, this 3-drug combination has generated recent interest for treatment of pediatric solid tumors [6–8].

Oral administration of 5-day courses of irinotecan can provide greater patient convenience and reduced costs compared to intravenous dosing [9]. A recent Children's Oncology Group Phase I trial established recommended doses of vincristine, oral irinotecan, and temozolomide (VOIT regimen) for patients with relapsed solid tumors [6], and the regimen was attractive because of outpatient administration and the potential for broad spectrum of activity. We hypothesized that this strategy could be taken one step further by adding yet another synergistic agent that had non-overlapping toxicities.

Bevacizumab (Avastin; Genentech, Inc., San Francisco, CA) is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), which is the best-characterized pro-angiogenic factor. Angiogenesis has long been recognized as an attractive therapeutic target for pediatric solid tumors, based on the correlation of expression of angiogenic factors with poor prognosis [reviewed in [10]], and preclinical experiments showing the benefits of VEGF pathway inhibition in tumor types such as Ewing sarcoma [11] and neuroblastoma [12]. There are several reasons why the addition of bevacizumab to the VOIT regimen may be worthy of exploration. First, bevacizumab has already been widely used in tandem with irinotecan for colon cancer and malignant glioma [13,14], and preclinical studies suggest bevacizumab may improve perfusion of camptothecin agents into tumor tissue [15]. In fact, 5-day courses of irinotecan may have anti-angiogeneic effects through inhibition of HIF-1 alpha [16] that could theoretically synergize with bevacizumab. Second, the primary toxicities of bevacizumab (infusion reactions, proteinuria, delayed wound healing, hypertension) do not overlap with those of vincristine (constipation, neuropathy), irinotecan (diarrhea, abdominal pain), or temozolomide (myelosuppression, nausea, fatigue). Third, bevacizumab is already approved for use in colon and lung cancer in combination with other chemotherapy agents, and so is reliably available for study in pediatric trials.

For these reasons, we chose to study this combination in pediatric patients with relapsed solid tumors. Given this regimen is novel and somewhat complex, a pilot study was performed to assess safety and feasibility, starting with full doses of VOIT and bevacizumab that had been established in previous trials [6,17]. Although we thought the most likely application would be for treatment of sarcoma and neuroblastoma, patients with brain tumors were included as well, given reports of activity of irinotecan + bevacizumab in selected recurrent pediatric central nervous system tumors [18,19].

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PATIENTS AND METHODS

Study Population

This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (clinicaltrials.gov NCT00786669). Patients between ages 1 and 30 years with solid tumors or brain tumors which had relapsed or were refractory to standard therapy were eligible. All patients had a Karnofsky (age > 10 years) or Lansky (age ≤ 10) performance score ≥ 50, an absolute neutrophil count of ≥750/μl, hemoglobin ≥ 8/0 gm/dl, a transfusion-independent platelet count of ≥75,000/μl, proteinuria of no greater than trace on dipstick or ≤1 gm/24-hour collection, normal serum creatinine for age or glomerular filtration rate ≥ 70 ml/min/1.73 m^2, bilirubin ≤ 1.5× upper limit of normal, ALT ≤ 5× upper limit of normal, albumin ≥ 2.0 gm/dl, and <grade 2 INR, PTT, and fibrinogen. Exclusion criteria included myelosuppressive chemotherapy within 2 weeks of study entry, anticancer biologic therapy within 1 week, and radiation therapy within 4 weeks (small port) or 6 weeks (larger port). At least 2 months must have elapsed since receiving autologous hematopoietic stem cells. Patients were excluded if they had an allogeneic transplant, had non-healing wounds or major surgical procedures or trauma within 4 weeks, were on enzyme-inducing anticonvulsants or antihypertensive agents, had active infection, or had a history of thrombosis or known thrombophilic condition. Prior therapy with vincristine, temozolomide, or irinotecan was allowed, although patients must not have had disease progression while receiving these agents. Prior therapy with bevacizumab was not allowed. The study was approved by the local institutional review board. Informed consent was obtained from the patient or the parent/guardian, and assent was obtained for patients ≥ 11 years old before enrollment.

Drug Formulation and Administration

The injectable formulation of irinotecan (20 mg/ml) was obtained commercially and dispensed in five individual syringes each course, with instructions to refrigerate until administration. Irinotecan 90 mg/m^2/day on days 1–5 was given orally, either as undiluted compound or mixed with cranberry-grape juice to mask the bitter flavor [9]. Commercially obtained temozolomide capsules were used, and patients unable to swallow capsules were allowed to open them and mix with apple sauce or juice. The starting dose was 150 mg/m^2/day on days 1–5 as previously reported [6], but the final three patients received a dose of 100 mg/m^2/day. Vincristine was administered intravenously over 1 minute on day 1 at the set dose of 1.5 mg/m^2 (maximum 2 mg). Bevacizumab 15 mg/kg (maximum dose 800 mg) was administered over 90 minutes on day 1. On days of concurrent administration, the drug sequence was temozolomide, then bevacizumab, then vincristine, then irinotecan, so that this last agent was always given at least 1 hour after temozolomide. Cefixime 8 mg/kg daily (maximum 400 mg) was administered for 10 days starting 2 days before each chemotherapy cycle to reduce irinotecan-associated diarrhea [20]. There was no planned use of hematopoietic growth factors.

Study Design

This was a single-institution pilot study to demonstrate the safety and feasibility of combining bevacizumab with the previously established VOIT regimen through six treatment cycles lasting 3 weeks each. Common Terminology for Chemotherapy Adverse Events version 3.0 was used to assess toxicity, and VOIT drugs were adjusted if dose-modifying toxicity (DMT) occurred, which was defined as: grade 4 neutropenia > 7 days; grade 4 thrombocytopenia, or grade 3 thrombocytopenia requiring more than two platelet transfusions per treatment course; grade 4 diarrhea or grade 3 diarrhea > 72 hours; grade 4 hepatic toxicity, or grade 3 not resolving to eligibility criteria within 7 days of planned start of next cycle; ≥grade 3 anorexia for >7 days not responding to appetite stimulation within 10 days; ≥grade 3 abdominal pain; grade 4 vomiting or grade 3 lasting >72 hours; ≥ grade 3 electrolyte deficiencies unresponsive to supplementation; or grade 3–4 neuropathy. Bevacizumab-related targeted toxicities included: grade 4 hypertension, or grade 3 not controlled with oral medications; any pulmonary or CNS hemorrhage; any venous thrombosis requiring anticoagulation; ≥ grade 2 arterial thromboembolic event; ≥ grade 2 wound dehiscence; grade 4 proteinuria, or any proteinuria that does not resolve to eligibility criteria within 14 days of planned start of next cycle; any gastrointestinal perforation; and ≥ grade 3 infusion reaction.

Chemotherapy cycles were repeated as soon as every 3 weeks if there was no evidence of disease progression, the patient met eligibility criteria for organ function, and there were no bevacizumab-related targeted toxicities. Patients who experienced the above dose-modifying toxicities had reduction of the most likely responsible drug when this could be determined. For examples, patients with dose-modifying diarrhea or abdominal pain had irinotecan reduced from 90 to 70 mg/m^2/day, while patients with dose-modifying myelosuppression had temozolomide reduced from 150 to 100 mg/m^2/day. For patients with dose-modifying neuropathy, vincristine was omitted. No dose reductions of bevacizumab were planned; instead, for patients experiencing bevacizumab-related targeted toxicities, this drug was omitted.

Patient Evaluation

A history and physical examination were performed weekly during the first course, and then prior to starting each subsequent course. Complete blood counts were obtained twice weekly during the first cycle, and at least weekly thereafter. Complete metabolic profiles were obtained weekly during the first cycle, and prior to each subsequent cycle. Tumor response assessments with relevant imaging studies were performed after cycles 3 and 6, using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [21].

RESULTS

All 13 patients enrolled on the study were evaluable for toxicity and response. The patient characteristics are described in Table I. Apart from two patients with disease refractory to front-line therapy, all had received multiple prior treatment regimens, including 5 (38%) who had received high-dose chemotherapy with autologous stem cell transplantation. One patient had prior temozolomide therapy. All patients had either measurable disease (n = 12) or evaluable disease (n = 1). A total of 36 cycles (median 2, range 1–6) were administered. Three patients completed all six cycles, while four patients withdrew after 1–3 cycles with progressive disease. The remaining six patients withdrew with stable disease after 1–2 cycles for various reasons, including to

TABLE I. Patient Characteristics

	Number
Age, years	
Median in years (range)	12 (1–22)
Sex (male/female)	8/5
Diagnosis	
Ewing sarcoma	2
Rhabdomyosarcoma	1
Clear cell sarcoma	1
Neuroblastoma	2
Hepatoblastoma	1
Hepatocellular carcinoma	1
Adrenocortical carcinoma	1
Wilms tumor	1
Ependymoma	1
Atypical teratoid/rhabdoid tumor	1
Glioblastoma multiforme	1
Prior chemotherapy regimens	
Median (range)	2 (1–7)
Prior radiotherapy	11
Prior high-dose therapy with stem cell transplant	5

undergo surgical resection of a lung metastasis (n = 1), travel difficulties (n = 1), grade 2 rash attributable to temozolomide (n = 1), or for other patient/family reasons (n = 3).

No unexpected adverse events occurred. Toxicities requiring dose modification are detailed in Table II. After 3 of the first 10 patients experienced first-course DMT and three additional patients had DMT during later cycles, the starting temozolomide dose was reduced to 100 mg/m^2/day for the last three patients, with no further DMT seen. The decision to reduce temozolomide was based on the fact that the majority of the DMTs seen were potentially related to temozolomide, such as prolonged nausea, anorexia, dehydration, and neutropenia. In addition, other pediatric solid tumor studies using this lower dose of temozolomide in conjunction with irinotecan demonstrated tolerability and activity [2–4].

Two patients were hospitalized for therapy-related complications (febrile neutropenia and abdominal pain), but no deaths occurred during or within 30 days after stopping protocol therapy. We did not observe hypertension, and only one patient had grade 1 proteinuria, which resolved with a 1-week delay of therapy and did not meet the protocol-specified criteria for omitting bevacizumab.

Antitumor Activity

Both patients with Ewing sarcoma had responses using RECIST criteria. The first patient had evaluable disease consisting of biopsy-proven multifocal bone metastases on positron emission tomography (PET) scan, which improved after three cycles and disappeared after cycle 6. This patient went on to receive three additional cycles of temozolomide + irinotecan off study and then electively stopped treatment in complete remission.

The second patient with Ewing sarcoma patient experienced partial response by RECIST criteria, which consisted of reduction of an extraosseous mass which arose from a pubic bone metastasis. This reduction occurred after three cycles, and persisted through the six planned cycles of study therapy. He went on to receive two additional cycles of temozolomide + irinotecan, but this was ultimately stopped due to worsening myelosuppression. He underwent radiation to the lesion, and had further recurrent disease 6 months later. One patient with relapsed, progressive neuroblastoma had stable disease through six cycles of treatment, with improvement in bone disease on MIBG scan, resolution of bone marrow disease, and persistence of a soft tissue lesion. He continues with temozolomide and irinotecan off-study. Patients with Wilms tumor, rhabdomyosarcoma, clear cell sarcoma, and adrenocortical carcinoma withdrew after 1–3 cycles with progressive disease. The remaining patients had stable disease noted for 1–2 cycles before withdrawing for a variety of reasons without identified progression.

DISCUSSION

This study builds on the activity and tolerability of the temozolomide + irinotecan backbone by combining two additional

TABLE II. Summary of Dosing, Toxicity, and Response for All Patients

Age (years)	Diagnosis	Prior regimens	Cycles received	TEM dose (mg/m^2/day)	DMT Cycle 1	DMT later cycles	Response
11	Wilms tumor	7	3	150			PD
4	Neuroblastoma	2[a]	1	150			Withdrew with SD
1	Hepatoblastoma	2	2	150	Grade 3 nausea, anorexia, dehydration		Withdrew with SD
12	Rhabdomyosarcoma	1	3	150		Grade 4 neutropenia	PD
10	Ependymoma	5	2	150	Grade 3 neuropathy		Withdrew with SD
18	Glioblastoma	1	1	150			Withdrew with SD
22	Ewing sarcoma	3[a]	6	150	Grade 3 nausea		CR
20	Ewing sarcoma	3[a]	6	150			PR
16	Clear cell sarcoma	2	2	150		Grade 3 diarrhea	PD
18	Hepatocellular carcinoma	4	2	150		Grade 3 abdominal pain	Withdrew with SD
1	Atypical teratoid/rhabdoid tumor	2[a]	1	100			Withdrew with SD
14	Adrenocortical carcinoma	4	1	100			PD
10	Neuroblastoma	2[a]	6	100			SD

TEM, temozolomide; DMT, dose-modifying toxicity. [a]Underwent high-dose chemotherapy with stem cell rescue.

agents with potential synergy. Use of this backbone is becoming increasingly popular, as demonstrated by ongoing trials combining this drug pair with the mTOR inhibitor temsirolimus (clinicaltrials.gov identifier NCT01141244), the Aurora kinase A inhibitor MLN8237 (NCT01601535), and the anti-diabetes drug metformin (NCT01528046). We now show that the VOIT combination can be safely combined with bevacizumab in pediatric patients with recurrent tumors, although the temozolomide dose of 150 mg/m^2/day recommended from the original VOIT Phase I study was associated with frequent toxicity and necessitated dose modification in the current study. It seems unlikely that bevacizumab necessarily contributed to the increased myelosuppression and nausea encountered with this higher temozolomide dose, given that bevacizumab is not commonly associated with these side effects, and has been safely coupled with other conventional chemotherapy regimens given at their full dose [13,14,22]. Instead, it may be that the recommended Phase II dose of VOIT from the initial study [6] was simply too high for this small group of very heavily pretreated patients. For example, a limited number of subsequent patients treated on our study with a lower temozolomide dose of 100 mg/m^2/day did not experience as much toxicity, although this trial was not designed as a formal dose-finding Phase I study. This improved tolerance using a temozolomide dose of 100 mg/m^2/day has also been observed in other studies [2–4,7]. Although it is possible that growth factor could have been used to reduce temozolomide-associated neutropenia and perhaps allow for higher doses to be tolerable [23], the benefit of higher temozolomide doses in this clinical context remains unclear.

In addition to myelosuppression and nausea, we also saw predictable toxicities of irinotecan (diarrhea, abdominal pain) and vincristine (neuropathy). Using the standard bevacizumab dose of 15 mg/kg on a 3-week schedule, no serious toxicities related to this agent were seen, such as hypertension, prolonged proteinuria, or bleeding/thrombosis. Overall, this outpatient therapy was felt to be tolerable, especially using the lower temozolomide dose, and only one patient required admission to the hospital for treatment-related complications. Oral administration of irinotecan allowed for clinic visits as infrequently as once every 3 weeks in patients who were tolerating therapy.

Although the trial was designed only as a safety and feasibility study, the finding of objective imaging responses in both patients with Ewing sarcoma patients treated is encouraging. However, the relative contribution of bevacizumab to the response is impossible to determine, given that temozolomide + irinotecan alone has been reported to have a response rate of 28–63% [2,3]. This situation is similar to a recent report of a partial response and prolonged disease stabilization in two Ewing sarcoma patients treated with bevacizumab combined with gemcitabine + docetaxel [22], which is a drug pair that also has demonstrated activity against Ewing sarcoma [24]. Similarly, a Children's Oncology Group pilot study showed either complete response or stable disease in five of six evaluable patients with relapsed Ewing sarcoma that were treated for 12 cycles with bevacizumab together with vincristine, cyclophosphamide, and + topotecan, another active regimen for this disease [25]. However, the single-agent activity of bevacizumab remains unclear. For example, in a pediatric Phase I trial of single-agent bevacizumab, two of the five patients with Ewing sarcoma patients had stable disease lasting for up to 36 weeks, but no objective responses were seen [26].

In addition to Ewing sarcoma, neuroblastoma is a particular tumor type of interest for this combination. Of the two patients with neuroblastoma patients treated, one withdrew after one cycle, while the other had stable disease throughout the six cycles of planned study therapy, and continues with temozolomide + irinotecan off-study. As with Ewing sarcoma, the contribution of bevacizumab cannot be determined, given previous responses with temozolomide + irinotecan in recurrent neuroblastoma [4]. The single-agent study of bevacizumab did not identify responses in the two patients with neuroblastoma patients who were treated [26].

Although this regimen was ultimately tolerable and feasible for outpatient administration, important questions remain. For example, the precise benefit in terms of antitumor activity can only be assessed in a randomized trial with defined disease strata. Further, even with the substantial savings of using oral instead of intravenous irinotecan, the cost of this 4-drug regimen is considerable. For example, the average wholesale price of drug costs alone for one 3-week cycle to treat a 30 kg patient is well over $5,000 USD, with bevacizumab accounting for over two-thirds of that cost. Unfortunately, there are no consistent, well-established biomarkers to predict which pediatric patients are most likely to respond to bevacizumab-based therapies.

Finally, It remains unclear whether bevacizumab is the best anti-angiogenic agent to treat pediatric solid tumors. Since the initial design of this trial several years ago, newer VEGF-targeting agents have been studied in pediatric trials, such as the decoy receptor aflibercept [27], and tyrosine kinase inhibitors whose targets include the VEGF receptor (pazopanib, cediranib, sorafenib, and sunitinib) [28–31]. Unlike bevacizumab, which has not been associated with single-agent responses in non-CNS pediatric tumors, responses have been reported in Ewing sarcoma using cediranib as a single agent [29]. In addition, pazopanib is now approved as a single agent for treatment of refractory adult soft tissue sarcoma [32], and sorafenib has shown responses in a Phase II trial for recurrent osteosarcoma [33]. These tyrosine kinase inhibitors also have the convenience of oral administration, and all mentioned except cediranib are now commercially available. Further investigation of these agents continues.

In conclusion, the combination of VOIT with bevacizumab was safe and feasible, albeit with a lower starting dose of temozolomide than recommended from an earlier study. It is possible that higher temozolomide doses may be tolerable with subsequent courses in some patients. No unexpected toxicities were encountered, and side effects were more commonly related to the conventional chemotherapy agents. Given that bevacizumab is costly, has the potential for severe side effects, and has uncertain single-agent activity against pediatric solid tumors, the addition of this drug to a therapy backbone may best be suited to a clinical trial. Future studies in this patient population should either formally assess the benefit of combining bevacizumab with chemotherapy in a randomized controlled fashion, or alternatively, investigate combinations with other anti-angiogenic agents which may have single-agent as well as synergistic activity.

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