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Phase II Trial of Recombinant Tumor Necrosis Factor- α in Combination with Dactinomycin in Children with Recurrent Wilms Tumor

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Abstract

Tumor necrosis factor (TNF), a peptide produced by macrophages with cytostatic and cytolytic effects, demonstrated single agent anti-tumor activity and synergistic effect when administered with dactinomycin in *in vitro* tumor cell lines, *in vivo* xenograft models, adult and pediatric phase I clinical trials. This phase II pediatric trial evaluated the efficacy and further defined the toxicity profile of recombinant TNF (rTNF) and dactinomycin in patients with recurrent or refractory Wilms tumor. On this two stage Children's Cancer Group trial, dactinomycin (15 micrograms/kg/day, IV) immediately followed by rTNF (200 micrograms/m²/day, IV), once daily for 5 consecutive days, was administered to patients with recurrent or refractory Wilms tumor. Cycles repeated every 21 days to a maximum of 12 courses. Nineteen of 21 consecutive patients, ranging 0.9 to 16.5 years of age at the time of initial diagnosis, were evaluable for response and toxicity. Three patients (15.8%) had a complete response (CR), 5 (26.3%) had stable disease and 11 (57.9%) had progressive disease. Following 59 patient treatment cycles, the most commonly observed grade 3/4 toxicities were thrombocytopenia (40.7%), elevated liver transaminases (23.7%), neutropenia (20.3%), leucopenia (13.6%), anemia (11.9 %), and myalgias (10.2%). Prior to completion of Stage 2, the study closed due to unavailability of rTNF. The documented complete responses and disease stabilization suggests anti-tumor activity of rTNF with dactinomycin in patients with recurrent Wilms tumor. The combination was well tolerated. Although Grade 3/4 adverse events were reported, dose adjustments were not required. Toxicities resolved without significant interventions.

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INTRODUCTION

Tumor necrosis factor (TNF), a polypeptide produced by macrophages and lymphocytes,¹ is cytostatic resulting in cellular arrest and accumulation in the G2 phase of the cell cycle and cytolytic during mitosis.² Although the specific mechanism of action is not well understood, TNF has demonstrated anti-tumor activity in *in vitro* human tumor cell lines including malignant melanoma, sarcomas, squamous cell lung carcinoma, breast, endometrial, cervical, ovarian, colorectal, pancreatic and bladder cancer.³ Further *in vitro* evaluation demonstrated a synergistic anti-tumor effect with simultaneous administration of TNF and other chemotherapeutic agents, particularly those agents known to act on DNA topoisomerase II such as doxorubicin, dactinomycin, teniposide and etoposide.⁴⁻⁷ *In vivo*, recombinant TNF (rTNF) has been shown to stimulate necrosis and tumor regression in murine xenograft models of human tumor cell lines. This activity appears to be selective for malignant cells, as normal fibroblasts appeared to be unaffected by rTNF treatment. Additionally, there is evidence TNF affects tumor vasculature resulting in increased permeability and penetration of chemotherapeutic agents as well as an anti-angiogenic effect.⁸

The experience in adult patients includes three phase I single agent studies of rTNF with different dosing schedules. Recombinant TNF was administered intravenously (IV) once daily for 5 days repeated every 2 weeks for 8 weeks in patients with metastatic refractory malignancies. On this study, 200 micrograms/m²/dose was the maximum tolerated dose (MTD). Hypotension was the dose limiting toxicity (DLT).⁹ Of 34 evaluable patients, 12 (35.3%) had stable disease and 22 (64.7%) had progressive disease. Two additional adult dose escalation trials evaluated rTNF as a single agent administered twice weekly. Blick et al. administered rTNF at doses ranging from 1 to 200 micrograms/m²/dose, alternating IV and intramuscular administration, twice weekly for 4 weeks.¹⁰ Fever, chills, headache, fatigue, anorexia, nausea/vomiting, diarrhea, dizziness and myalgias were the most frequently reported adverse events; however, none were dose limiting. Of 16 evaluable patients, 2 (12.5%) had a documented response; one patient with renal clear cell carcinoma had complete resolution of a neck mass, but no change in retroperitoneal disease and another patient with colon cancer had resolution of malignant ascites. Chapman et al. administered rTNF twice weekly and alternated between IV and subcutaneous routes. Doses ranged 1 to 200 micrograms/m²/dose IV and 5 to 250 micrograms/m²/dose subcutaneous, for 4 weeks with inpatient dose escalation.¹¹ The most common adverse events reported were rigors, fever, headache, fatigue and hypotension. Of the 26 patients enrolled, one patient with B cell lymphoma had a minor response while the remaining patients did not have evidence of disease response.

The pediatric experience with rTNF consists of a single agent study and combination study. Furman et al. conducted a phase I trial of rTNF as single agent therapy and determined the MTD to be 300 micrograms/m²/day, administered for 5 days repeated every 2 weeks.¹² Hepatotoxicity (elevated bilirubin, ALT or AST), which resolved after discontinuation of the drug, was dose limiting at 350 micrograms/m²/day. Tumor response was documented in 3 of 27 evaluable patients; one patient with non Hodgkin's lymphoma had a partial response after 10 cycles of therapy and two patients, one with adenocarcinoma of the colon and the second with recurrent neuroblastoma, had stable disease while on study for 2 and 4 months respectively.

A second phase I pediatric trial evaluated the effect of escalating doses of rTNF administered with dactinomycin for 5 days, repeated every 21 days, in patients with refractory malignancies.¹³ The MTD of rTNF was determined to be between 200–220 micrograms/m²/day administered for five days. Non-hematologic dose limiting toxicities included hypotension, hemorrhagic gastritis, hyperbilirubinemia and elevated creatinine. Three of 21 evaluable patients demonstrated a response to this combination therapy. One patient with Ewing's

sarcoma had a decrease in the percentage of malignant cells on bone marrow aspiration following one treatment cycle. A second patient with Wilms tumor had a measurable chest mass at the time of enrollment on protocol, which was found to be necrotic on surgical resection following one treatment cycle. A final patient with osteblastoma had stable disease through 8 courses of therapy.

Based on this data, in particular the suspected anti-tumor activity observed in the patient with Wilms tumor, this phase II pediatric trial was developed. The primary objectives were to determine the anti-tumor effect of combination rTNF and dactinomycin therapy at the MTD in pediatric patients with relapsed or refractory Wilms tumor, including patients with anaplastic histology and clear cell sarcoma of the kidney, and to further evaluate the toxicity of these agents administered sequentially.

MATERIALS AND METHODS

Children enrolled on this phase II clinical trial were required to have histologically confirmed Wilms tumor or clear cell sarcoma of the kidney, recurrent or refractory to standard treatment, with measurable disease by radiographic, clinical or histologic means. All patients had an ECOG performance status of 0, 1 or 2, adequate bone marrow function [ANC ≥ 1000 /mcL, platelet count $\geq 100,000$ /mcL (50,000 /mcL following stem cell transplant), hemoglobin ≥ 8 g/dL], adequate renal function (serum creatinine $\leq 1.5 \times$ normal), adequate hepatic function (total bilirubin $\leq 1.5 \times$ normal, SGOT or SGPT $< 2.5 \times$ normal) and adequate cardiac function (shortening fraction $\geq 27\%$ or ejection fraction $> 50\%$). Patients were to have completely recovered from previous chemotherapy or radiation treatment. Written informed consent and all regulatory requirements were met.

Each day prior to receiving chemotherapy, patients were empirically treated with acetaminophen and a normal saline or albumin fluid bolus. Dactinomycin, 15 micrograms/kg/day, was administered intravenously followed immediately (within 10 minutes) by rTNF, 200 micrograms/m²/day intravenously, on days 1 through 5 of each 21 day treatment course. Subsequent chemotherapy cycles began on day 22 pending hematologic recovery from the previous course, defined as an ANC ≥ 1000 /mcL and platelet count $\geq 100,000$ /mcL, and resolution of non-hematologic toxicities. Growth factor support was recommended only for those patients with documented Grade 3 or 4 neutropenia during a previous treatment cycle.

Patients continued on study until either documentation of disease progression, occurrence of severe adverse events, or completion of a maximum of 12 treatment courses. Disease status was determined following even numbered cycles according to the WHO criteria and toxicity was reported based on the Children's Cancer Group (CCG) Toxicity and Complication Criteria based on the NCI Common Toxicity Criteria version 1.0.

The study utilized a two stage design initially enrolling 15 patients. As proposed, a disease response seen in three or more cumulative patients would suggest the regimen was effective and the trial would close to further accrual. If no responses were observed, the trial would also close and the therapy considered ineffective. A response documented in one or two of the initial 15 patients would not provide conclusive evidence of efficacy; therefore, the study would proceed to Stage 2 with enrollment of 20 additional patients. Within this second cohort, a response in three or fewer individuals would indicate treatment failure, whereas, disease response seen in four or more patients would suggest efficacy in this patient population. We consider a response rate of $< 5\%$ to be ineffective and $\geq 20\%$ to be effective. This design has less than 10% type I error rate and greater than 90% power. The expected sample size was 24; however the study was closed prior to completion due to the unavailability of rTNF.

RESULTS

Patient Population

Twenty-one patients, 12 males and 9 females ranging in age 0.9 to 16.5 years at the time of initial diagnosis all with recurrent or refractory Wilms tumor including one patient with documented anaplastic histology, were eligible and enrolled on this trial (Table 1). Of the patients enrolled, 18 children had received dactinomycin with a previous treatment regimen while 3 patients did not have prior exposure to this chemotherapeutic agent. Initial treatment protocols administered in this patient cohort included; National Wilms Tumor Study 5 (NWT5-5)/CCG-4941 (n=2), NWT5-4/CCG 461 [n=12 patients in total; DD4A (4), EE4A (1) and not specified (7)], NWT5-3/CCG 491 (n=2), vincristine-dactinomycin (n=2) and protocols not otherwise specified (n=6). Relapsed disease was subsequently treated according to protocol CCG-4942 in 2 patients and CCG-4921 in 5 patients. A majority of patients (n=14) had received one or two prior treatment regimen while 3 patients had been treated with 3 or more regimen. The number of prior treatment regimen in the remaining 4 patients could not be distinguished. Sites of disease at the time of enrollment included isolated pulmonary lesions (7 patients), abdominal disease (3), renal disease (1), renal and pulmonary (1), abdominal and pulmonary (1), paravertebral and pulmonary (1), paravertebral and liver (1), chest (1), pleural cavity (1), pelvic (1), axillary lymph nodes (1), mesenteric lymph nodes and pulmonary (1) and diffuse disease of the pelvis, paratesticular region, liver and kidney (1). Due to the unavailability of rTNF the study was closed to further accrual prior to completion of Stage 2.

Disease Response

Any patient enrolled who received at least one course of rTNF and dactinomycin was considered evaluable for response provided: (1) the patient demonstrated progressive disease or death while on protocol therapy; (2) the patient was observed on protocol therapy for at least two cycles and the tumor had not been removed surgically prior to the time complete response or partial response was confirmed; or (3) the patient demonstrated a complete or partial response (CR or PR) as confirmed according to protocol criteria. Responses must be sustained for at least four weeks.

Two of the 21 eligible patients enrolled on this trial were not evaluable for disease response. One patient withdrew prior to receiving treatment and the second patient developed grade 4 hypotension following administration of the first doses of dactinomycin and rTNF and was removed from study. Treatment duration for the 19 evaluable patients varied from 1 to 10 cycles with a mean of 2.9 cycles and median of 2.0 cycles (Table 2). Removal from study was due to disease progression in 16 cases and by parental choice in 3 cases following 2, 5 and 7 cycles of therapy. Disease response was evaluated by radiographic methods similar to those used at the time of enrollment when possible.

Of the 19 evaluable patients, 3 were considered to have a complete response following combination therapy with dactinomycin and rTNF (Table 3). One patient, treated with vincristine-dactinomycin then NWT5-4/CCG 461 regimen K, followed by carboplatin, etoposide, ifosfamide and doxorubicin for relapsed disease, had resolution of three chest lesions following two cycles of dactinomycin-rTNF therapy. A second patient with relapsed disease after treatment as per NWT5-3/CCG 491 and CCG-4921 had a documented decrease in the size of a pelvic mass after two treatment cycles. The patient subsequently underwent surgical resection and the residual tumor was found to be necrotic tissue without evidence of viable malignant cells. The final patient, previously treated according to NWT5-4/CCG 461 regimen DD4A followed by carboplatin, etoposide and ifosfamide for relapsed disease, had one enlarged axillary lymph node at enrollment thought to represent active disease. The lesion resolved following four cycles of therapy. No partial responses (PR) were documented. Five

patients had stable disease upon completion of two courses of dactinomycin and rTNF. The remaining 11 patients developed progressive disease following 1 or 2 cycles of treatment. Three patient deaths occurred during the first treatment course, all attributed to their underlying disease. Eight patients completed a minimum of one cycle before disease progression was documented. The response rate was estimated to be 16% (3 of 19 patients).

Toxicity

Patient enrolled on study who received at least one treatment course with dactinomycin followed by rTNF were evaluable for toxicity. Therefore, 20 of the 21 eligible patients were evaluable during a total of 59 patient treatment courses. Each participating institution performed toxicity reporting and grading according to the CCG Toxicity Criteria version 1.0. The relation of the adverse event to each chemotherapeutic agent was recorded (unrelated, unlikely, possibly, probably, definitely) as was any required action taken, treatment administered or necessary reduction in drug doses. The grade 3 and 4 toxicities observed that were possibly, probably or definitely related to rTNF or dactinomycin are summarized in Table 4. Grade 3 and 4 toxicities most frequently seen were hematologic [thrombocytopenia (24 events, 40.7%), neutropenia (12 events, 20.3%), leucopenia (8 events, 13.6%) and anemia (7 events, 11.9%)], hepatic [elevated liver transaminases (AST 7 events, 11.9%; ALT 7 events, 11.9%)] and myalgias (6 events, 10.2%). Hypotension, an adverse event known to be associated with rTNF therapy, was observed in 4 patients; grade 3 in three and grade 4 in one patient. Grade 3 and 4 toxicities resulted in discontinuation of therapy in 3 patients, due to hypotension (n=2) and malignant effusion (n=1). Dose reduction of dactinomycin (n=1) or both dactinomycin and rTNF (n=1) occurred due to grade 3/4 gastrointestinal (stomatitis) and hematologic toxicity respectively. Of these events, one was disease related, 3 considered probably related to therapy and one definitely related to therapy.

DISCUSSION

Although the majority of patients with favorable histology Wilms tumor are successfully treated with current regimens, novel drugs and treatment approaches are needed for those patients with anaplastic histology, stage IV and V tumors or recurrent or refractory disease. The *in vitro* and *in vivo* single agent anti-tumor activity of rTNF and synergistic effect when administered in combination with other chemotherapeutic agents such as dactinomycin makes it an attractive therapy in pediatric malignancies. Based on this preclinical data and significant tumor necrosis seen in a patient with recurrent Wilms tumor, the combination of rTNF and dactinomycin was evaluated in a larger cohort of patients with relapsed or refractory Wilms tumor in this phase II trial.

The combination of rTNF and dactinomycin provided some degree of benefit to greater than 40% of the patients enrolled on study. Three of 19 patients (15.8%) had a complete response and 5 patients (26.3%) had disease stabilization for at least two courses. All 3 patients with a CR and 4 of the 5 patients with SD were enrolled on study with relapsed as opposed to refractory Wilms tumor demonstrating their disease had prior responsiveness to chemotherapy. Other characteristics of those patients who exhibited either a CR or SD did not vary significantly when compared to the remainder of the study population. Patients in this cohort received 1 or 2 previous treatment regimens, which in all cases included dactinomycin as part of combination chemotherapy. The location of relapsed disease varied and included the abdomen, lung, mediastinum and axilla.

Dactinomycin as single agent, up front chemotherapy resulted in 2 year disease free survival rates of 89% in patients without gross metastatic disease at diagnosis and 53% in patients with metastatic disease when combined with surgical resection and radiation treatment.¹⁴ The response rate of dactinomycin in patients with relapsed or refractory Wilms tumor is difficult

to ascertain. Most salvage regimen include additional chemotherapeutic agents; either vincristine or doxorubicin as used in traditional first line therapy and more recently cyclophosphamide, etoposide and platinum agents.^{15,16} Although the observed responses in this phase II trial could be related to treatment with dactinomycin as opposed to combination therapy, all patients demonstrating a CR or SD had received this agent as part of a prior treatment regimen, suggesting their disease was resistant to dactinomycin. The results of this trial suggest activity of rTNF and dactinomycin in patients with recurrent or refractory Wilms tumor; however, response data from the first stage of the trial were inconclusive and unfortunately the study was closed to further accrual prior to completion of Stage 2 due to the unavailability of rTNF. The results failed to demonstrate a response rate of $\geq 20\%$ required to be considered effective therapy prior to this closure. Due to the supply constraint, assessment and interpretation of the anti-tumor activity as well as toxicity of this combination therapy could not be completed.

Adverse events were reversible and few patients required more than symptomatic or supportive management during resolution of toxicity. Therapy discontinuation or drug dose adjustments as a result of therapy related toxicity occurred in only 4 patients. The toxicity profile was similar to that observed on the previous phase I pediatric trial of these agents administered in combination and to that expected with administration of a biologic agent. Hypotension, although observed in several patients, was easily managed with minimal intervention, which may reflect protocol required administration of pretreatment IV fluid bolus and premedication. Hematologic toxicity is a known adverse event following dactinomycin therapy with grade 3 and 4 thrombocytopenia reported in 13–17% of patients and grade 4 neutropenia in up to 41% of patients treated with dactinomycin, most commonly as part combination therapy with vincristine.^{17–19} Similar rates of thrombocytopenia (15%) were seen on the pediatric phase trial of single agent rTNF.¹² Although there was no clinical consequence, treatment with both dactinomycin and rTNF resulted in an increased frequency of thrombocytopenia, but not neutropenia. Evaluating the impact of rTNF on the incidence and severity of thrombocytopenia is difficult as all patients received prior treatment with chemotherapy. Hepatic toxicity was also not increased in this patient cohort.

In view of the disease response data suggesting anti-tumor activity and tolerable toxicity profile, combination therapy with dactinomycin and rTNF may benefit patients with relapsed or refractory Wilms tumor and if available warrants further evaluation.

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Table 1

Patient Demographics

Age at Diagnosis:	Years
Range	0.9–16.5
Mean	5.4
Median	4.2
Age at Registration:	
Range	2.0–22.2
Mean	8.6
Median	7.1
Sex:	Patient No. (n)
Male	12
Female	9
Race:	
Caucasian	16
Hispanic	3
African-American	2
Prior Disease Response:	
Relapsed	11
Refractory	5
Not Distinguished	5
Prior Treatment Regimens:	
≥ 3 Prior Regimen	3
< 3 Prior Regimen	14
Not Distinguished	4
Previous Dactinomycin:	
Yes	18
No	3

Table 2

Courses Administered to Patients Evaluable for Response

Number of Courses	Number of Patients	Percentage of Total
1	4	21
2	8	42
4	4	21
5	1	5
7	1	5
10	1	5

Table 3

Patient Response

Disease Response	Patient No. (n)
Complete Response	3
Partial Response	0
Stable Disease	5
Progressive Disease	11
Not Evaluable	2

Table 4

Grade 3 and 4 Toxicity in 59 Patients Courses

Toxicity	Grade 3	Percent	Grade 4	Percent
Blood and Bone Marrow				
Leukopenia	5	8.5	3	5.1
Neutropenia	4	6.8	8	13.6
Thrombocytopenia	11	18.6	13	22
Anemia	5	8.5	2	3.4
Lymphopenia	2	3.4	1	1.7
Hepatic				
Elevated SGOT	7	11.9	-	-
Elevated SGPT	7	11.9	-	-
Elevated Bilirubin	-	-	1	1.7
Blood Pressure				
Hypotension	3	5.1	1	1.7
Renal and Genitourinary				
Systolic BP	-	-	3	5.1
Diastolic BP	1	1.7	2	3.4
Hematuria	3	5.1	-	-
Gastrointestinal				
Stomatitis	1	1.7	4	6.8
Nausea	-	-	1	1.7
Neurologic				
Motor	1	1.7	-	-
Cerebellar	1	1.7	1	1.7
Mood	5	8.5	-	-
Allergy				
Bronchospasm	2	3.4	-	-
Performance Status				
	2	3.4	1	1.7
Peripheral Capillary leak				
	1	1.7	-	-
Myalgias				
	6	10.2	-	-

CCG Toxicity and Complication Criteria based on the NCI Common Toxicity Criteria version 1.0