A Phase I Study of 17-Allylaminogeldanamycin in Relapsed/Refractory Pediatric Patients with Solid Tumors: A Children's Oncology Group Study

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Abstract

Purpose: To determine the recommended phase 2 dose, dose-limiting toxicities (DLT), pharmacokinetic profile, and pharmacodynamics of the heat shock protein (Hsp) 90 inhibitor, 17-allylaminogeldanamycin (17-AAG).

Experimental Design: 17-AAG was administered as a 60-min infusion, on days 1, 4, 8, and 11 of a 21-day cycle at dose levels of 150, 200, 270, and 360 mg/m^2/dose. Pharmacokinetic studies and evaluations for Hsp72 and Akt levels in peripheral blood mononuclear cells were done during the first course of therapy.

Results: Seventeen patients (7 males), median 7 years of age (range, 1-19 years), were enrolled using a standard dose escalation scheme. No DLTs were observed. Although there were no objective responses, three patients remain on therapy at 6+, 7+, and 9+ months with stable disease. One patient with hepatoblastoma had a reduction in α-fetoprotein and stable disease over three cycles. At 270 mg/m^2/dose, the C_{max} and areas under the plasma concentration-time curves of 17-AAG were 5,303 ± 1,591 ng/mL and 13,656 ± 4,757 ng/mL h, respectively, similar to the exposure in adults. The mean terminal half-life for 17-AAG was 3.24 ± 0.80 h. Induction of Hsp72, a surrogate marker for inhibition of Hsp90, was detected at the 270 mg/m^2 dose level.

Conclusions: Drug exposures consistent with those required for anticancer activity in preclinical models were achieved without DLT. Evidence for drug-induced modulation of Hsp90 systemically was also detected. The recommended phase II dose of 17-AAG is 360 mg/m^2/d. Non-DMSO–containing formulations may improve acceptance of this drug by children and their families.

17-Allylaminogeldanamycin (17-AAG) is an ansamycin antibiotic that disrupts the chaperone function of heat shock protein (Hsp) 90, leading to the depletion of many intracellular proteins critical for cell cycle control and signaling by growth factors and hormones. The mechanisms of antitumor activity for Hsp90 inhibitors, such as 17-AAG, include (*a*) blockade of mitogenic signals mediated by Raf-1, (*b*) destabilization and decreased cellular levels of mutant oncoproteins, (*c*) inhibition of survival factors, such as Akt, (*d*) cell cycle arrest, (*e*) inhibition of angiogenesis, and (*f*) inhibition of tissue invasion and metastatic potential through effects on metalloproteinases (1–3). Because inhibition of Raf-1 signaling can down-regulate Bcl-2 expression with subsequent apoptosis of tumor cells, childhood tumors that overexpress Bcl-2, including neuroblastoma, synovial sarcoma, lymphomas, and Ewing sarcoma, are potential candidates for treatment with 17-AAG. In fact, preclinical studies have shown that neuroblastoma cells treated with geldanamycin, the parent drug to 17-AAG, undergo apoptosis that is associated with a decrease in the activity level of Raf-1 and Akt (4). Antitumor activity for Hsp90 inhibitors has been observed in a spectrum of preclinical cancer models, including breast, colon, prostate, non–small cell lung cancer, and glioblastoma multiforme (5–11).

The preclinical pharmacokinetics and metabolism of 17-AAG have been characterized by Egorin et al. (12, 13). 17-AAG rapidly equilibrates in tissues reaching peak concentrations in liver, kidney, spleen, and heart 7- to 20-fold higher than that observed in plasma. Elimination of 17-AAG from tissues is generally slower than from plasma, with measurable drug concentrations remaining in tissue 24 h after dosing. Cytochrome *P*450-3A and epoxide hydrolase are the major enzymes

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Received 9/12/06; revised 11/10/06; accepted 12/1/06.

Grant support: National Cancer Institute grant U01 CA97452.

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Note: A complete listing of grant support for research conducted by Children's Cancer Group and Pediatric Oncology Group before initiation of the Children's Oncology Group grant in 2003 is available online (http://www.childrensoncologygroup.org/admin/grantinfo.htm).

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doi:10.1158/1078-0432.CCR-06-2270

involved in the metabolism of 17-AAG (12). The major *P*450-3A–generated metabolite of 17-AAG *in vitro* by mouse and human hepatic systems is 17-aminogeldanomycin (17-AG), which retains full bioactivity. The major plasma and urine metabolite of 17-AAG following systemic administration to mice is also 17-AG with plasma concentrations of 1 μg-equiv/mL achieved from 10 to 90 min after injection of 17-AAG.

A variety of 17-AAG dosing schedules have been evaluated in adult phase I trials (14–18). In all of these studies, the primary dose-limiting toxicities (DLT) were nonhematologic with transient elevations in assessments of liver function (grade 3-4 elevations in alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, or alanine aminotransferase), nausea, vomiting, diarrhea, anorexia, and fatigue, the most frequently reported drug-related adverse events. Occasional anemia and thrombocytopenia have also been reported. With doses at or below the maximum tolerated dose, evidence of biological activity, determined by Raf-1 depletion in peripheral blood mononuclear cells (PBMC) and/or induction of Hsp70, has been consistently observed (14, 16).

Patients and Methods

Patient eligibility

Patients >1 and <22 years of age with solid tumors refractory to conventional therapy were eligible for this trial. Other eligibility criteria included a Karnofsky or Lansky performance scale ≥50; adequate bone marrow function [absolute neutrophil count ≥1,000/μL, platelet count ≥100,000/μL (transfusion independent), and hemoglobin ≥8 gm/dL]; adequate renal function (serum creatinine below the upper limits of normal for age or a radioisotope glomerular filtration rate ≥70 mL/min/m^2); adequate liver function (bilirubin ≤1.5 × the upper limit of normal, alanine aminotransferase ≤2.5 × the upper limit of normal for age, and albumin ≥2 g/dL); and full recovery from acute toxic effects of prior chemotherapy, radiotherapy, or immunotherapy with a minimum of at least 2 months for stem cell transplant or rescue without total body irradiation and at least 3 months for prior craniospinal or pelvic radiation. Women who were pregnant were excluded from enrollment because the effects of 17-AAG on the fetus are not known. Women and men of child-bearing potential had to agree to use an effective method of contraception while receiving protocol therapy. Patients were not to have received platelet or WBC growth factors within 7 days of enrollment. Patients could not have uncontrolled infection, severe allergy to eggs, or the use of concomitant steroids, anticonvulsants, anticoagulants, or anticancer drugs.

Informed consent was obtained from the patient or from the patient's parent or guardian, and assent was obtained as appropriate, before protocol enrollment.

Dosage and drug administration

17-AAG was provided by the Cancer Therapy Evaluation Program (National Cancer Institute, Bethesda, MD) as a sterile single-use amber vial containing 50 mg in 2 mL DMSO. The drug diluent (EPL diluent, NSC 704057) was supplied in a 50 mL vial containing 48 mL of 2% egg phospholipids and 5% dextrose in water for injection, USP. The drug was administered at a final concentration of 1 mg/mL i.v. over 60 min.

Trial design

The starting dose for 17-AAG in this phase I trial was 150 mg/m^2/dose, ~50% of recommended phase II dosing for adults treated on the same schedule. The drug was administered on days 1, 4, 8, and 11 every 21 days. Subsequent cohorts of three to six patients received doses of 200, 270, and 360 mg/m^2. Requirements for subsequent courses were that the patient had at least stable disease and again met the laboratory variables defined in the eligibility criteria. Courses could be repeated 17 times, for a maximum total duration of therapy of 12 months.

At least three patients were studied at each dose level. If one of three patients at a given dose level experienced a DLT during the first course of therapy, up to three more patients were accrued at the same dose level. If two or more patients experienced DLT, then the maximum tolerated dose was exceeded and three more patients were treated at the next lower dose level. The maximum tolerated dose was defined as the dose level at which at most one patient experienced DLT with at least two of three to six patients experiencing a DLT at the next higher level.

The National Cancer Institute Common Toxicity Criteria (version 3.0) were used to grade adverse events. Hematologic DLT was defined as drug-related grade 4 neutropenia or thrombocytopenia for >7 days; grade 3 or 4 thrombocytopenia that required transfusion therapy on greater than two occasions during a course; or myelosuppression that caused a delay of more that 13 days between treatment courses. Nonhematologic DLT was defined as any grade 3 or 4 drug-related nonhematologic toxicities with the exclusion of grade 3 nausea and vomiting; grade 3 transaminase (aspartate aminotransferase/alanine aminotransferase) elevation that returned to grade ≤1 or baseline before next treatment course; and grade 3 fever or infection.

Appropriate clinical, laboratory, and disease evaluations were done within 1 week before study entry. Vital signs, creatinine, aspartate aminotransferase, alanine aminotransferase, serum alkaline phosphatase, and bilirubin levels were examined on days 1, 4, 8, and 11 of the first course of therapy and weekly thereafter. Complete blood counts were examined twice weekly and electrolytes were examined weekly throughout the first course of therapy. In subsequent courses, weekly examinations of complete blood counts were done. Disease evaluations were done at the end of first course and then at the end of every other course thereafter.

Criteria for assessment of response

Tumor response was evaluated using the National Cancer Institute Response Evaluation Criteria in Solid Tumors (19). All the patients with measurable disease at the time of enrollment on the study were eligible for response assessment.

Correlative biology studies

In accordance with current ethical considerations for children participating in cancer phase 1 trials (20), participation in the correlative study components of the study without potential for direct benefit to the patient was voluntary. The following pharmacokinetic and pharmacogenetic evaluations, as well as studies to assess surrogate markers of Hsp90 inhibition, were done in patients who consented to participation in the correlative study components of the trial.

Pharmacokinetic and pharmacogenetic evaluations. Blood samples (3-5 mL) for pharmacokinetic studies were collected in heparinized tubes at the following time points after the first dose of 17-AAG: preinfusion, end of infusion, and 5 min, 15 min, 30 min, 90 min, 4 h, 8 h, and 24 h after the end of the infusion. The blood samples were

Table 1. Dose levels completed, number of patients enrolled and evaluable for toxicity, and the number of courses of therapy completed for 17-AAG

Dose level (mg/m^2)	No. patients enrolled	No. patients evaluable	No. courses completed in each evaluable patient
150	3	3	1, 1, 3
200	4	3	1, 1, 2
270	5	3	1, 1, 10
360	5	3	3, 7, 15

Table 2. Patient characteristics for eligible patients (N = 17)

Characteristic	No. patients
Age (y)	
Median	7
Range	1-19
Sex	
Male	7
Female	10
Race	
White	12
Black or African American	2
Other-Asian	1
Other	1
Not reported	1
Ethnicity	
Non-Hispanic	13
Hispanic	3
Not reported	1
Diagnosis	
Atypical teratoid/rhabdoid tumor	1
Ependymoma	4
Ewing sarcoma	1
Juvenile granulosa cell tumor	1
Hepatoblastoma	1
Wilms' tumor	2
Neuroblastoma	1
Peripheral nerve sheath tumor	1
Osteosarcoma	1
Primitive neuroectodermal tumor (CNS)	1
Renal cell carcinoma	1
Synovial sarcoma	2

Abbreviation: CNS, central nervous system.

immediately cooled in an ice water bath. The plasma was then separated by low-speed centrifugation (1,000 × g for 10 min), transferred to a plastic tube, capped, and stored at least −20°C until analysis. Pharmacokinetics of 17-AAG and 17-AG were evaluated using a previously described reverse-phase high-pressure liquid chromatography assay (12).

17-AAG and 17-AG plasma concentration-time data were analyzed by noncompartmental methods using the program WinNonlin version 4.1 (Pharsight Corp., Mountain View, CA). The apparent terminal elimination rate constants (k_z) were determined by linear least squares regression through the 5 to 25 h plasma-concentration time points. The apparent elimination half-life ($t_{1/2}$) was calculated as 0.693 / k_z. Areas under the plasma concentration-time curves (AUC) were determined using the linear trapezoidal rule from time zero to the time of the last detectable sample (C_{last}). AUCs through infinite time ($AUC_{0-\infty}$) were calculated by adding the value C_{last} / k_z to AUC_{last}. The clearance of 17-AAG was calculated as dose / $AUC_{0-\infty}$.

For evaluation of *CYP3A5* polymorphisms, a blood sample (10 mL) was collected in an EDTA tube and then centrifuged at 3,300 × g for 10 min at room temperature. The buffy coat was stored at −20°C until DNA extraction and analysis of CYP3A5 polymorphisms as described previously (14).

DNA was extracted from buffy coats using a QIAamp DNA Mini kit (Qiagen Valencia, CA). *CYP3A5*3* genotyping was done with DNA using a modified method of Hustert et al. (21). In brief, M13 forward or reverse sequences were added to the 5′-terminus of each primer for use in dye primer sequencing chemistry. Amplicons were sequenced with an ABI 377 DNA sequencer (Applied Biosystems, Foster City, CA) using BigDye primer cycle sequencing chemistry. Samples were sequenced on both strands, and those with ambiguous sequencing chromatograms were subjected to a second, independent amplification followed by DNA sequencing. The DNA sequence was visually analyzed using the Sequencher program.

Surrogate biological markers of Hsp90 inhibition. Peripheral blood for correlative biology studies (10 mL) was collected before 17-AAG administration and 24 h after the first dose. Samples were placed into heparinized blood collection tubes and kept at 4°C before batch shipping. Gradient centrifugation using Oncoquick separation tubes (Grenier Bio-One, Longwood, FL) was done to permit collection of PBMCs and any circulating tumor cells. Pellets were washed in PBS and lysed in nonionic detergent buffer supplemented with protease inhibitors. Lysates were clarified by centrifugation, and the protein concentration of lysates was determined by bicinchonic acid assay (Pierce, Rockville, IL) using bovine serum albumin as a standard. Protein samples were heated in reducing loading buffer to 95°C for 5 min. Equal amounts of protein from paired patient samples were loaded onto 10% SDS-PAGE gels. Following electrophoresis, proteins were transferred to nitrocellulose and membranes were probed with primary antibodies, including anti-Hsp72 (C-92F3A-5, Stressgen, Victoria, British Columbia, Canada), anti-Akt (Cell Signaling Technologies, Beverly, MA), and anti–β-actin (Sigma, St. Louis, MO). The anti–β-actin was used as a loading control to ensure equivalent loading of protein in the pretreatment and posttreatment paired samples. Peroxidase-conjugated secondary antibodies, chemiluminescent substrate, and exposure to Kodak XAR-5 film (Rochester, NY) were used for detection. Multiple exposure times were evaluated for each blot to ensure that the band intensities observed were within the dynamic response range of the film.

Results

Seventeen patients with refractory solid tumor were enrolled on this study between March 2004 and September 2005. Three evaluable patients were treated with three to five patients enrolled per dose level (see Table 1). All patients were eligible

Table 3. Course 1 toxicities possibly, probably, or likely related to 17-AAG (n = 12)

Toxicity type	Grade 1	Grade 2	Grade 3
Hemoglobin	1	1	1
Neutrophils		1	
Leucocytes	1		
Fatigue	1		
Fever		1	
Odor	1	1	
Rash/desquamation		1	
Constipation	2		
Heartburn/dyspepsia	1		
Nausea	2		1
Taste alteration		1	
Vomiting	2		1
Hypoalbunimemia	1		
Alkaline phosphatase	1		
ALT	3		
AST	2		
GGT	1		
Hyperuricemia	1		
Abdominal pain	1		
Pain extremity-limb	1		
Pain head/headache	1		
Pain		1	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 4. Pharmacokinetics of 17-AAG and 17-AG

Dose (mg/m^2)	17-AAG				
	$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{0-8} (ng/mL h)	Cl ($L/h/m^2$)	AUC_{0-8} (ng^2/mL h)
150	3.15 ± 0.40	2,189 ± 382	5,022 ± 1,189	30.5 ± 6.3	15,424 ± 7,937
270	3.24 ± 0.80	5,303 ± 1,591	13,656 ± 4,757	21.78 ± 7.59	37,089 ± 13,375

NOTE: All values are expressed as mean + SD.
Abbreviations: Cl, clearance; MRT, mean residence time.

but five were not fully evaluable for toxicity: (*a*) one electively terminated therapy during the first course due to the DMSO odor associated with the drug formulation; (*b*) two had early disease progression and did not complete the first course; (*c*) one experienced disease progression after enrollment but before receiving 17-AAG and withdrew; and (*d*) one developed elevated liver function tests after enrollment and was therefore not eligible to receive protocol therapy. Patient characteristics are shown in Table 2.

Toxicity. Except for the challenges associated with DMSO-associated odor, 17-AAG administration was well tolerated (Table 3). No first course DLTs were observed at dose levels ranging from 150 to 360 mg/m^2. The most common non-DLTs included anemia, transient elevations of serum transaminases, and vomiting (well controlled with antiemetics). During the third course of therapy, one patient developed bacterial sepsis, grade 3 elevations of serum transaminases, and a gastrointestinal hemorrhage presenting as melena. The patient made a complete recovery but did not receive additional drug on study.

Response. No complete or partial responses were observed. Five patients have had stable disease for three or more courses of therapy, one patient each with ependymoma (3 courses), hepatoblastoma (3 courses), Ewing sarcoma (7 courses), synovial sarcoma (10 courses), and malignant peripheral nerve sheath tumor (15 courses). The child with hepatoblastoma also had a reduction in serum α-fetoprotein (14,373-2,237 IU) and a 19% decrease in tumor size.

Pharmacokinetics. Pharmacokinetic analyses for both 17-AAG and its active metabolite, 17-AG, are shown in Table 4. Adequate numbers of samples were available for analysis at 150 and 270 mg/m^2. Mean clearance and terminal $t_{1/2}$ values for 17-AAG were 25.5 ± 8.0 $L/h/m^2$ and 3.2 ± 0.6 h, respectively. *CYP3A5*3* (6986 A>G) and *CYP3A5*6* (14690 G>A) genotypes were determined for eight of nine patients who consented to pharmacogenomic studies. One sample did not yield DNA for PCR amplification. One patient was heterozygous for the *CYP3A5*3* allele and the remaining seven patients were homozygous for the *CYP3A5*3* allele. None of the patients carried the *CYP3A5*6* allele. The pharmacokinetic variables measured in this patient were not different from the other patients evaluated nor did this patient experience any unusual toxicity.

Pharmacodynamic data. Studies to evaluate surrogate markers of Hsp90 inhibition, such as Hsp72, and Akt were done in PBMCs collected in eight subjects (three at 150 mg/m^2, three at 270 mg/m^2, and two at 360 mg/m^2) before and 24 h after 17-AAG administration. Sample number and paired samples were limited due to variable sample quality and RBC contamination, precluding quantitation of changes in levels of markers of interest. Elevation of Hsp72 was seen at 24 h post–17-AAG at the 270 mg/m^2 dose level. One patient sample from dose level 3 (270 mg/m^2) also showed reduction of Akt, a client of Hsp90 that is destabilized and depleted by inhibition of Hsp90 chaperone function (Fig. 1). Due to poor sample quality, data from other dose levels could not be reliably generated.

Discussion

This is the first reported phase 1 trial of 17-AAG in children with refractory solid tumors. The children enrolled in this trial tolerated 17-AAG doses as high as 360 mg/m^2, which is moderately higher than the recommended adult dose (220 mg/m^2; ref. 18). Although a maximum tolerated dose was not defined, we showed Hsp72 elevation in PBMCs, a surrogate marker for Hsp90 inhibition, in patients treated at all dose levels. Due to concerns about the tolerability of the increasing volume of DMSO-containing diluent required as dose escalation proceeded (e.g., a patient with a bovine serum albumin of 1.5 m^2 would receive >500 cc of drug), combined with the knowledge of new non-DMSO formulations in development, we elected to terminate dose escalation at the 360 mg/m^2 dose level. Should further pediatric studies be pursued using this DMSO-based formulation, we would recommend using the 360 mg/m^2 dose administered on days 1, 4, 8, and 11 of a 21-day schedule.

Our evaluation of PBMCs from children treated with 17-AAG suggests that at the dose levels examined, inhibition of Hsp90

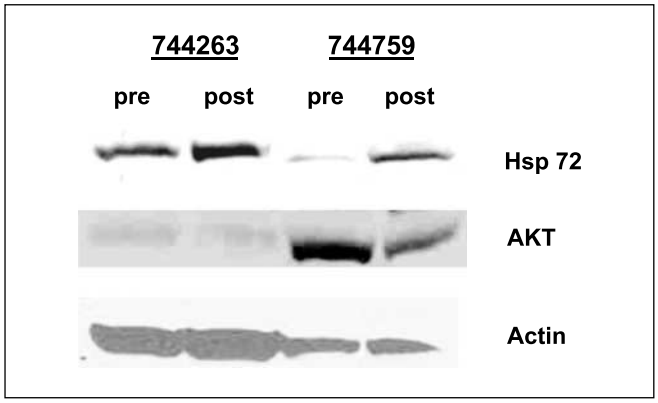

Fig. 1. Inhibition of Hsp90 in PBMCs. Drug-induced elevation of Hsp72 and depletion of Akt were evaluated by immunoblotting at dose level 3 (270 mg/m^2) in two patient samples before 17-AAG treatment and 24 h after the first dose.

Table 4. Pharmacokinetics of 17-AAG and 17-AG (Cont'd)

		17-AG		
MRT (h)	V_{ss} (L/m^2)	$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{0-8} (ng/mL h)
2.46 ± 0.85	72.1 ± 16.0	6.1 ± 0.7	958 ± 225	4,014 ± 1,929
2.21 ± 0.25	43.2 ± 12.1	4.6 ± 1.5	2,139 ± 1,105	10,213 ± 4,983

can be achieved. The value of Hsp72 induction in predicting antitumor response is unclear, and the extent to which modulation of Hsp90 function was achieved in tumor is not known. However, the ability of 17-AAG to modulate its target *in vivo* supports further evaluation of this approach.

The pharmacokinetic studies in this pediatric population suggest that clearance of 17-AAG in children (27.2 + 7.7 L/h/m^2) may be somewhat faster than that observed in adults (18.3 + 5.9 L/h/m^2; ref. 14). This difference in clearance may in part have contributed to the lack of DLT observed in children at dose levels above the adult maximum tolerated dose. The 17-AAG $t_{1/2}$ of 3.0 ± 0.5 h in children is similar to the $t_{1/2}$ of 3.4 ± 1.7 h observed in adults (ref. 14).

Because variability in drug metabolism may result from drug interactions or polymorphisms in the cytochrome *P*450 system, the pathway that is responsible for converting 17-AAG to 17-AG, concomitant administration of potent inhibitors or inducers of *CYP3A4/5* was not allowed on this trial. Nine patient samples were evaluated for polymorphisms *CYP3A5* and one of the eight samples analyzed had a single allele with the *CYP3A5*3* polymorphism. This polymorphism was not associated with greater toxicity in this single patient. However, it is possible that in larger patient populations, polymorphisms in this drug-metabolizing pathway may affect on toxicity of the drug because 28% of Caucasians and 50% of African Americans have at least one *CYP3A5*1* allele, which is associated with significantly higher amounts of hepatic and intestinal *CYP3A5* (21, 22).

In summary, this pediatric phase I study showed that 17-AAG, administered twice weekly (days 1, 4, 8, and 11) every 21 days, is safe and well tolerated in children with refractory solid tumors at doses as high as 360 mg/m^2/dose. At this or higher dose levels, we anticipate that the odor and volume of DMSO required will limit the tolerability of this formulation in the pediatric population. As other non-DMSO formulations of Hsp90 inhibitors are being developed, we did not attempt to further increase the dose of 17-AAG. Based on promising preclinical data in pediatric malignancies (4), the results of ongoing phase 1 and 2 trials in adults, and the disease stabilization observed in a subset of children treated on this trial, further study of Hsp-90 inhibitors in childhood tumors is warranted.

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Clinical Cancer Research

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Clin Cancer Res 2007;13:1789-1793.