A Phase I and Pharmacokinetic Study of Ecteinascidin-743 (Yondelis) in Children with Refractory Solid Tumors. A Children’s Oncology Group Study

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ABSTRACT

Purpose: To determine the dose-limiting toxicity (DLT) and the maximum tolerated dose of ecteinascidin-743 (ET-743, Yondelis) in children with refractory solid tumors, to establish the recommended dose for pediatric phase II trials, and to characterize the pharmacokinetics of ET-743 in children.

Experimental Design: ET-743 was administered as a 3-hour i.v. infusion every 21 days. The starting dose was 1,100 \( \mu \text{g/m}^2 \) with planned dose escalation of 200 \( \mu \text{g/m}^2 \) increments. Pharmacokinetic sampling was done during the first treatment course.

Results: Twelve evaluable patients received a total of 29 courses. One grade 4 DLT (prolonged grade 4 neutropenia) was noted at the first dose level. At the second dose level (1,300 \( \mu \text{g/m}^2 \)), there were two DLTs (reversible grade 4 elevations of hepatic transaminase); hence the maximum tolerated dose was defined as 1,100 \( \mu \text{g/m}^2 \). Overall, reversible hepatic toxicity, manifested as grade 3 or 4 elevations in hepatic transaminase, occurred in more than 50% of the patients. No grade 3 or 4 thrombocytopenia was reported at either dose level and only one episode of isolated creatine phosphokinase grade 4 elevation was observed. One complete response was documented after six courses in a patient with metastatic Ewing sarcoma. The pharmacokinetics of ET-743 in 8 children was characterized by a terminal disposition phase with a mean half-life of 43.8 ± 18.4 hours, a total body clearance of 28.2 ± 10.5 L/h/m\(^2\), and a 959 ± 807 L/m\(^2\) steady-state apparent volume of distribution.

Conclusion: ET-743 is safe. The phase II recommended dose of ET-743 administered as a 3-hour i.v. infusion following premedication with dexamethasone is 1,100 \( \mu \text{g/m}^2 \).

INTRODUCTION

Ecteinascidin-743 (ET-743 or trabectedin, Yondelis) is a tetrahydropyridosquaraine compound isolated from the marine Caribbean ascidian Ecteinascidia turbinata. It is the first of a new class of antitumor agents with a complex transcription-targeted mechanism of action. Its cytotoxic effect seems to be related to its unique three-subunit structure. Two of the subunits are involved in binding to the minor groove of duplex DNA, bending the DNA toward the major groove and causing structural perturbation of the DNA molecule (1). An in vitro cell cycle study revealed that ET-743 delayed cell progression through S phase towards G\(_2\), accumulating cells in S or G\(_2\)-M phases at biologically relevant concentrations and resulting in p53-independent apoptosis (2). ET-743 inhibits transcriptional activation of genes via a promoter-specific mechanism (3, 4) and has been shown to induce apoptosis via a transcription-independent route involving c-jun NH\(_2\)-terminal kinase and caspase-3 (5). The relative resistance to ET-743 of cells deficient in nucleotide excision repair suggests that the cytotoxic effects of ET-743 are partially mediated by nucleotide excision repair proteins (6), but their precise mechanism has not been fully elucidated.

Preclinical studies clearly showed that ET-743 was very active at remarkably low concentrations, achievable under clinical conditions, against a broad spectrum of solid tumor types and with unusually potent selectivity for certain sarcomas. For soft tissue sarcomas, in vitro cytotoxicity occurred in the picomolar range (7) and for non–soft tissue sarcoma cell lines, in the nanomolar range (8, 9). Furthermore, ET-743 was found to have antitumor activity in several other common pediatric malignancies including, neuroblastoma, rhabdomyosarcoma, and medulloblastoma (10–12). ET-743 was also highly active against melanoma, non–small-cell lung, ovarian, renal, prostate, and breast cancer cell lines and solid tumor xenografts (13–15).

Several phase I and II clinical trials of ET-743 using a variety of dosing schedules have been done in adults. The dose-limiting toxicities (DLT) associated with ET-743 were fatigue, neutropenia, and thrombocytopenia. Acute elevations in hepatic transaminases associated with ET-743 administration were common in adults and were dose dependent; however, the elevations were often transient and were not considered to be DLTs. Rhabdomyolysis occurred rarely, particularly in patients with hepatic dysfunction, and was often also complicated by severe myelotoxicity. In phase I trials,
objective antitumor activity was observed against adult tumors including melanoma, breast cancer, ovarian cancer, and mesothelioma and soft tissue sarcoma (16–18). Additional phase II trials to define more precisely the spectrum of antitumor activity and toxicity profile in adult cancers have recently been completed or are ongoing (19–23).

This report presents the results of a Children’s Oncology Group phase I clinical trial of ET-743 given as a 3-hour i.v. infusion every 21 days in children with refractory solid tumors. The study objectives were to identify the recommended dose of ET-743 for phase II pediatric trials, to determine the incidence and severity of toxicities associated with ET-743 administration, and to characterize the pharmacokinetics of ET-743 in children.

PATIENTS AND METHODS

Eligibility

Patients were considered eligible if they were younger than 18 years, had histologically confirmed extracranial solid tumors that were refractory to conventional treatment, life expectancy of at least 8 weeks, and Karnofsky or Lansky performance of at least 50%. Patients must have had adequate bone marrow function (absolute neutrophil count >1,500/mm³, platelet count >100,000/mm³, and hemoglobin >8 g/dL), adequate liver function [total bilirubin <1.5 times normal, alanine aminotransferase (ALT) < 2.5 times normal, γ-glutamyl transpeptidase (GGT) <2.5 times normal, albumin ≥2 g/dL, and normal hepatic fraction alkaline phosphatase (ALP)], adequate renal function (serum creatinine level <1.5 times normal for age), and creatinine phosphokinase (CPK) <2 times normal. In addition, patients had to have recovered from toxicities of all prior therapy: more than 4 weeks since myelosuppressive chemotherapy (6 weeks if prior nitrosourea), at least 2 weeks from local palliative radiotherapy, at least 6 months from substantial bone marrow radiation (craniospinal radiation, total body irradiation, total abdominal/pelvic/cheet irradiation, mantle and hemipelvic irradiation), at least 6 months from stem cell transplantation with no evidence of graft-versus-host disease, and at least 1 week from receiving growth factors. Patients were excluded if they were pregnant or lactating, had severe uncontrolled infection, or were receiving any other anticancer agents. Informed consent was obtained from the patient or his or her legal guardian before study entry in accordance with individual institutional policies and the Declaration of Helsinki.

Drug Administration and Study Design

ET-743 was supplied by PharmaMar, S.A. (Madrid, Spain) in 250 μg vials that were reconstituted with 5 mL sterile water for injection. Further dilutions were made using 250 or 500 mL normal saline and the drug was infused through a central venous catheter.

ET-743 was administered as a 3-hour i.v. infusion every 21 days following premedication with either ondansetron or granisetron. The starting dose was 1,100 μg/m² based on 70% of the adult recommended dose (1,650 μg/m²) with subsequent planned dose escalations in 200 μg/m² increments. No intrapatient dose escalation was permitted. At least three patients were treated at each dose level. If one of the first three patients entered at any dose level had a DLT during the first course of therapy, three additional patients were entered at that dose level. If DLT was noted in two of three to six patients at any given dose level, the MTD was exceeded and three more patients were treated at the next lower dose level provided only three patients had been treated previously at that level. The MTD was defined as that dose level immediately below the dose level at which two of three to six patients experienced DLT. Routine prophylactic use of growth factors was not allowed. Patients were removed from protocol therapy in the presence of progressive disease or DLT, or if the next course had to be delayed for more than 2 weeks due to toxicities.

The first six patients entered on this trial did not receive dexamethasone premedication, but all subsequent patients received p.o. dexamethasone (2.5 mg/m²) every 12 hours for 4 days, starting the day before ET-743 infusion. This modification was the result of drug-related fatalities in three adults enrolled in a phase II randomized cross-over trial comparing the administration of ET-743 in combination with either dexamethasone or placebo. The deaths (one septic shock and two acute renal failure) occurred in patients who were randomized to the placebo arm and who had extremely high plasma levels of ET-743 (unpublished PharmaMar communication).

Patient Evaluation and Follow-up

Complete history, physical examination, and routine laboratory studies were done at study entry and weekly thereafter. Routine laboratory studies included twice weekly complete blood counts and hepatic function tests (ALT, total ALP, hepatic fraction ALP, and GGT) during course 1 and weekly thereafter, and weekly serum electrolytes, renal function tests, CPK, prothrombin time, bilirubin, and, if available, 5'-nucleotidase. Complete blood counts and hepatic function tests were obtained twice weekly during course 1. In the event of grade 3 hepatic toxicity, liver function tests were done until values returned to pretreatment levels. All patients had appropriate radiographic evaluations at baseline and then before subsequent cycles of ET-743 for evaluation of tumor response. Subsequent courses of ET-743 were initiated in the absence of disease progression when the following criteria were met: platelets ≥100,000/mm³, absolute neutrophil count ≥1,500/mm³, bilirubin less than the upper limit of normal (ULN), ALT < 2.5 times ULN, GGT < 2.5 times ULN, and hepatic fraction ALP <10% elevated from baseline value. All other nonhematologic toxicities were less than grade 2 within 2 weeks after the anticipated start of the next treatment cycle.

Toxicity

Toxicities were graded according to National Cancer Institute version 2 common toxicity criteria (24). Dose-limiting hematologic and nonhematologic toxicities were defined differently. Nonhematologic DLT was defined as any grade 3 or 4 nonhematologic toxicity attributable to the investigational drug with the specific exclusion of grade 3 nausea and vomiting, grade 3 transaminase (aspartate aminotransferase/ALT) elevation and grade 3 fever or infection. Hematologic DLT was defined as grade 4 neutropenia or grade 4 thrombocytopenia of more than 7 days duration, which required transfusion therapy more than twice in 7 days or which caused a delay of more than 14 days beyond the planned interval between treatment courses.

Response Definition

Response Evaluation Criteria In Solid Tumors (RECIST) criteria were used to classify response for patients with measurable disease at study entry. Complete response was
defined as disappearance of all evidence of disease for a minimum of 4 weeks. Partial response was defined as at least a $30\%$ reduction in the sum of the longest diameter of lesions for a minimum of 4 weeks. An increase of greater than $20\%$ in the sum of the longest diameter of lesions or the appearance of new lesions was defined as progressive disease. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

**Pharmacokinetic Studies**

The plasma pharmacokinetics of ET-743 in children was characterized using a limited sampling schedule, as previously described, with minor modifications to account for the differences in the duration of infusion and to improve the definition of the terminal disposition phase (25). During the first cycle of therapy, heparinized blood specimens (1 to 3 mL) were obtained from patients shortly before treatment, at 2.0 and 2.5 hours after starting the 3-hour i.v. infusion of ET-743, and at 0.5, 1.0, 24, 48, and 72 hours after the end of the infusion. Plasma was obtained by centrifugation ($2,500 \times g$ for 10 minutes at $4^\circ C$) within 15 minutes after collection and stored at $-70^\circ C$ until assayed. A previously described validated analytic method based on reverse-phase high-performance liquid chromatography with electrospray ionization mass spectrometric detection was used to measure the concentration of ET-743 in study specimens (18). During its application to the present study, the mean between-day accuracy of the assay was $100.8 \pm 8.2\%$ with a mean precision of $8.9 \pm 3.3\%$ for standard solutions of ET-743 in plasma at concentrations ranging from $28.5$ to $1138$ pg/mL. ET-743 was measured with an accuracy of $114.9\%$ and precision of $11.6\%$ at the lowest concentration included in the standard curves ($28.5$ pg/mL).

Individual patient plasma concentration-time data were analyzed by noncompartmental methods using routines supplied in the WinNonlin Version 1.1 software package (Scientific Consulting, Apex, NC) as previously described (25). Area under the curve from time 0 to infinity (AUC) for the plasma profiles was estimated by the logarithmic-linear trapezoidal algorithm to the last data point, with extrapolation to time infinity using the estimated value of the slope of the terminal logarithmic-linear phase. Total plasma clearance was calculated as the dose divided by AUC. Mean values of the pharmacokinetic variables were calculated as the geometric mean of the individual patient values (25). SDs of the geometric mean values were estimated by the jackknife method.

## RESULTS

Thirteen patients, 12 of whom were evaluable for toxicity and 11 for response, were entered on this trial. Patient demographics for the evaluable patients are listed in Table 1. One patient enrolled at the first dose level was not included in the assessment of DLT because the patient was found to have inadequate platelet count after the infusion was started and the entire dose was not administered. This patient did not experience any DLT. Six patients were entered at the first dose level ($1,100 \mu g/m^2$) and another 6 at the second dose level ($1,300 \mu g/m^2$). One patient, who was entered at the second dose level, had a dose reduction to $1,100 \mu g/m^2$ after experiencing a grade 4 CPK elevation. Twenty-nine evaluable courses for toxicity were administered (13 courses at the $1,100-\mu g/m^2$ dose level and 16 courses at the $1,300-\mu g/m^2$ dose level). Nine patients received 1 course of therapy, 2 received 2 courses, and 1 received 16 courses (10 courses of $1,300 \mu g/m^2$ and 6 courses of $1,100 \mu g/m^2$).

### Toxicity

ET-743 was generally well tolerated. One dose-limiting event, grade 4 neutropenia of 8 days' duration, was encountered at the first dose level ($1,100 \mu g/m^2$). At the second dose level ($1,300 \mu g/m^2$), two of six patients experienced DLT during the first course of therapy; both patients had reversible grade 4 ALT elevation, and one of these two patients also had grade 4 hypokalemia. The patient with hypokalemia had a prior history of potassium and phosphorus wasting and the hypokalemia was not considered to be attributable to ET-743; it therefore was not considered a DLT. There was also one patient with a grade 4 CPK elevation during course 10 ($1,300 \mu g/m^2$) of therapy, which returned to normal after 14 days. It was associated with grade 1 neutropenia and grade 1 ALT elevation. It was felt that this was unlikely related to ET-743 because it occurred in association with vigorous exercise, had not occurred during any of the previous cycles, and did not recur during six subsequent cycles, which were reduced to $1,100 \mu g/m^2$. Thus, $1,100 \mu g/m^2$ was defined as the MTD and the recommended dose for subsequent pediatric phase II trials of ET-743.

Reversible hepatotoxicity was the most common adverse event associated with ET-743 administration, occurring in 58% of patients (Table 2). Peak elevations of hepatic transaminases occurred on the third to fourth day after ET-743 administration, declined to grade 1 ($<2.5$ times normal) at a median of day 14 (range, days 11-22), and returned to normal by a median of day 21 (range, days 18-33). Of the seven episodes of grade 3 or 4 ALT elevation, only one grade 3 episode was associated with a grade 3 neutropenia. There was only one grade 3 GGT

### Table 1  Patient characteristics

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Abbreviation: ABMT, autologous bone marrow transplantation.
elevation, which occurred in a patient with grade 3 ALT elevation. Moreover, for the two patients with dose-limiting grade 4 elevation of ALT, only grade 1 and 2 elevations of GGT were reported. Hepatic fraction ALP was normal in the 22 courses where it was obtained. Other nonhematologic toxicities included grade 1 nausea or vomiting in three patients and grade 1 or 2 fatigue in three patients.

Hematologic toxicity associated with ET-743 administration was minimal. There was one episode of grade 4 neutropenia at the 1,100–A_g/m² dose level and two episodes of grade 3 neutropenia at the 1,300–A_g/m² dose level. Absolute neutrophil counts were maintained at or above 1,500/mm³ in 24 (83%) of the 29 evaluable courses. There was no reported grade 3 or 4 thrombocytopenia. Platelet counts were maintained at or above 150,000/mm³ in 25 (86%) of the 29 evaluable courses. Grade 4 anemia occurred in one course at 1,100 A_g/m² and there was no grade 3 anemia noted. Hemoglobin levels were maintained at or above 10 g/dL in 22 (76%) of the 29 courses.

Tumor Response
Eleven patients (28 courses) were evaluable for response. One patient showed a complete response at course 6 according to the RECIST criteria. This patient, who had a recurrence of Ewing sarcoma, had complete resolution of pulmonary metastases and remained on therapy for 16 courses. The patient maintained a complete response for a total duration of 10 months and experienced another recurrence 3 months after stopping treatment. Eight patients developed progressive disease during course 1 and one developed progressive disease before course 3. Another patient with Ewing sarcoma and lung metastases was stable after course 2, but removed from study due to radiation-induced pulmonary toxicity. He progressed 2 months after the cessation of therapy.

Pharmacokinetics
The plasma pharmacokinetics of ET-743 was characterized in groups of four children at each dose level. Mean plasma concentration-time profiles of ET-743 at both doses are shown in Fig. 1. The drug concentration in plasma increased rapidly during the course of the infusion, such that the mean ET-743 concentration in samples acquired at 1 hour and at 30 minutes before the end of the infusion were very similar. As observed in adult patients with cancer (18, 25), plasma levels of the drug decreased in a biphasic manner after the infusion was terminated, characterized by a relatively brief but extremely rapid initial phase of decay that was followed by a considerably slower terminal phase.

Mean pharmacokinetic parameters estimated by non-compartmental analysis of the data from each patient are summarized in Table 3. Mean values ± SD of the observed peak plasma concentration of ET-743 were 6.02 ± 3.28 ng/mL in patients treated with 1,100–μg/m² and 10.52 ± 5.00 g/mL in the cohort that received 1,300–μg/m². There were no significant differences between any of the concentration-independent pharmacokinetic parameters at the two dose levels evaluated. Mean values of the parameters calculated for all eight patients were half-life of the apparent terminal disposition phase (\( t_{1/2,z} \)), 43.8 ± 18.4 hour; total body clearance, 28.2 ± 10.5 L/h/m²; mean residence time, 34.1 ± 19.1 hour; and apparent volume of distribution at steady state (\( V_d \)), 959 ± 807 L/m². There was no relationship
between AUC and the severity of drug-related toxicity in this small group of patients.

DISCUSSION

ET-743 is the first tetrahydroisoquinoline, a new class of antitumor agents isolated from the marine Caribbean ascidian *Ecteinascidia turbinata* with a complex transcription-targeted mechanism of action, evaluated in children with refractory solid tumors. In this Children’s Oncology Group study, we found that ET-743 could be delivered safely as a 3-hour i.v. infusion in an outpatient setting. The recommended starting dose of ET-743 for phase II pediatric studies is 1,100 µg/m² following premedication with dexamethasone.

Hepatotoxicity was the most common nonhematologic and dose-limiting toxicity encountered in this pediatric phase I study. Liver toxicity was also the most common nonhematologic toxicity encountered in adult phase I trials but was not dose limiting due to a different definition of DLT. In adult studies, DLT was defined as grade 3 or 4 transaminase elevation persisting for longer than 7 days or not resolving by 28 days (16, 17, 26, 27). The pattern of ALT elevation in children in our study was also very comparable to that of adults. The onset was between day 2 and 3, with a peak during the first week and resolution by the third week in most patients.

Hematologic toxicity was not predominant in our pediatric population. The definition of hematologic toxicity was similar to that of adult ET-743 phase I trials. Grade 3 or 4 neutropenia was only reported in 25% of patients. No grade 3 or 4 thrombocytopenia was reported at either dose level. In comparison, hematologic toxicity was the DLT in adult phase I trials (16, 17, 26, 27) except for one study in which ET-743 was infused over 72 hours (18). In our small pediatric group, there was no correlation between severity of hepatotoxicity and occurrence of hematologic toxicity. Because none of our patients had biochemical evidence of liver dysfunction before treatment and all patients had normal hepatic fraction ALP both before and during therapy, we were unable to show preexisting liver dysfunction as a factor predictive of severe toxicity, as has been observed in both phase I (16, 28) and phase II adult trials (19).

Rhabdomyolysis, which was a rare toxicity (1.6% of patients) in adult clinical trials (17, 18, 29), was not observed in this small pediatric phase I study. Although there was one child who experienced an isolated and reversible grade 4 CPK elevation during the 10th course of therapy, this adverse event was felt to be unlikely related to ET-743 as it occurred after extensive exercise and did not recur in the six subsequent courses at a reduced dose. The CPK elevation was not associated with renal impairment and was only associated with grade 1 neutropenia and ALT elevation. The CPK level returned to normal levels within 2 weeks.

Dexamethasone is frequently used to treat delayed chemotherapy-induced emesis and is an inducer of the hepatic cytochrome P450 3A4 subfamily, the predominant isozyme that seems to be responsible for ET-743 metabolism in both humans and rats (30). Due to its potential effect on the elimination of ET-743, antitumor activity was evaluated in xenograft-bearing rats. The efficacy of ET-743 was found to be unimpaired and at the same time, hepatotoxicity was reduced (31), suggesting that pretreatment with dexamethasone protects against ET-743-mediated hepatic damage by decreasing hepatic exposure to ET-743, possibly related to induction of metabolism by cytochrome P450 enzymes (32). In clinical studies, Puchalski et al. (25) examined the pharmacokinetics and drug-related toxicities in a group of 69 sarcoma patients treated in three phase II trials. The clearance of ET-743 was 27% greater in patients receiving dexamethasone. There also seemed to be a reduction in the incidence of severe transaminitis and grade 3 nausea and vomiting, which were not statistically significant, perhaps due to the comparatively small number of patients who did not receive dexamethasone (*n* = 13). In our study, 6 of 12 evaluable patients were premedicated with p.o. dexamethasone following a protocol amendment based on preliminary data in adults suggesting that concomitant p.o. dexamethasone may protect against severe drug toxicity. Because the protocol amendment coincided with the time of dose escalation, none of the patients within the first dose level was premedicated with dexamethasone. The small patient number in this trial and the distribution of dexamethasone administration preclude a meaningful evaluation of the impact of dexamethasone on ET-743 clearance or toxicity in children.

The plasma pharmacokinetics of ET-743 have been studied extensively during the course of phase I and II clinical trials in adult patients with cancer (16–18, 25–27). Drug clearance seems to be independent of the infusion duration when delivered over 1, 3, 24, or 72 hours. The mean total plasma clearance of ET-743 in our group of eight pediatric patients, 28.2 ± 10.5 L/h/m², was within the range of reported values for adults (median, 35.4 L/h/m²; range, 26.3–38.3 L/h/m²). Pharmacokinetic studies in adults revealed that values of *V*<sub>ss</sub> and *t*<sub>1/2,z</sub> tended to be higher when the drug was delivered by continuous i.v. infusion for 24 or 72 hours (*V*<sub>ss</sub>, 1,941–3,866 L/m²; *t*<sub>1/2,z</sub>, 61–89 hours) compared with shorter infusions of 1 or 3 hours (*V*<sub>ss</sub>, 808–910 L/m²; *t*<sub>1/2,z</sub>, 29–39 hours; refs. 17, 26). The *V*<sub>ss</sub> and *t*<sub>1/2,z</sub> of ET-743 in children were very similar to the parameters in adults treated with shorter infusion schedules. The mean AUC provided by 1,100 µg/m² MTD in children (38.9 ± 24.2 ng h/mL) was remarkably similar to the mean AUC for a group of 69 adult patients with sarcoma treated with doses of 1500 µg/m² in phase II studies of the 24-hour infusion schedule (39.9 ± 16.6 ng h/mL; ref. 20) and the AUC of the recommended phase II dose of 1,650 µg/m² for the 3-hour infusion schedule in adults (38 ± 10 ng h/mL; ref. 26). Thus,
despite the slightly lower recommended ET-743 phase II dose for children (1,100 μg/m²) versus adults (1500 μg/m²), there seems to be equivalent ET-743 exposure at these respective MTDs.

Responses to ET-743 have been documented in phase I studies regardless of schedule of administration schedule (16–18). Three of 52 patients achieved objective partial response in one study (16), whereas antitumor activity was observed in 3 of 42 patients (17). Extensive phase II data in adult patients with advanced pretreated soft tissue sarcoma show that ET is able to induce objective responses and tumor control in a clinically relevant proportion of patients (19–21). Therefore, a phase II trial of ET-743 in children with refractory Ewing or soft tissue sarcomas is in development.

REFERENCES

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