A comparison of limited sampling strategies for prediction of Ecteinascidin 743 clearance when administered as a 24-h infusion

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Abstract Purpose: Ecteinascidin 743 (ET-743) is a novel, marine-derived anticancer agent currently under clinical development for the treatment of solid tumors. The aim of this study was to develop and validate limited sampling strategies for the prediction of ET-743 clearance in phase II studies, using two techniques: the stepwise linear regression approach and the Bayesian estimation approach. Methods: Data from a phase I dose-finding study were used with ET-743 administered as a 24-h infusion. Plasma concentration time data from 34 patients treated with 1200, 1500 or 1800 µg/m² ET-743 were randomly divided into an index data set, used for the development of the strategies, and a validation data set. With the linear regression approach, clearance (obtained by non-compartmental analysis) was correlated with the ratios of dose to the observed concentrations. For the Bayesian approach a three-compartment population pharmacokinetic model was developed; optimal time-points were selected using the D-optimality algorithm. The strategies were compared by assessment of their predictive performance of CL in the validation data set.

Results: The linear regression method yielded a single-point sampling schedule with no significant bias and acceptable precision (~0.03% and 21%, respectively). With the Bayesian approach, a three-sample strategy was selected which resulted in less-accurate, but unbiased, predictions (bias 13%, precision 34%). Conclusions: Optimal sampling strategies were developed and validated for estimation of ET-743 clearance. Although the linear regression approach showed slightly better predictive performance, the Bayesian approach is preferred for the current phase II studies as it is more robust and flexible and allows the description of the full pharmacokinetic profile.

Keywords ET-743 · Pharmacokinetics · Population pharmacokinetics · Limited sampling · D-optimality

Introduction

Ecteinascidin 743 (ET-743) is a novel anticancer agent isolated from the Caribbean tunicate Ecteinascidia turbinata. Preclinical studies have revealed potent activity of ET-743 against a panel of solid tumor cell lines and several human tumor xenograft models including melanoma, non-small-cell lung, ovarian, renal, prostate and breast tumors [9, 10, 11, 12, 21]. ET-743 is currently under phase II clinical development for the treatment of solid tumors.

A phase I clinical program has been conducted with ET-743 administered in several schedules and at several dose levels [15, 18, 20, 22, 24]. The pharmacokinetic profile of ET-743 administered as a 24-h infusion every 3 weeks has been described [18, 22]. In this schedule, the recommended dose for further phase II studies was 1500 µg/m² with neutropenia and thrombocytopenia as the dose-limiting toxicities. Hepatic toxicity was observed as well, but was reversible and not dose-limiting. ET-743 exhibits linear pharmacokinetics in the dose range tested (50–1800 µg/m²). Considerable inter-
intrapatient variability (45% and 28%, respectively) for the area under the plasma concentration versus time curve (AUC) was observed. ET-743 displays a long terminal half-life (at 1500 μg/m² the half-life was 89 h). Typical plasma concentration versus time curves of patients treated with 1200, 1500 and 1800 μg/m² as a 24-h infusion are depicted in Fig. 1. Combined pharmacokinetic-pharmacodynamic analyses have revealed increased hepatic and hematologic toxicity with increasing exposure to ET-743, expressed as AUC [3, 22].

ET-743 administered as a 24-h infusion is currently undergoing further clinical development in phase II studies in this schedule to further determine its antitumor activity in different tumor types, including advanced soft tissue sarcoma, melanoma, and breast and renal carcinoma. Promising clinical activity of ET-743 in multiple tumor types has been reported [4, 7, 8, 25]. During the phase II studies the concentration-time profile of ET-743 will be assessed in a large number of patients which will enable further exploration of the population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships.

Standard procedures for the performance of pharmacokinetic studies usually involve extensive sampling, which is very impractical, particularly when studies are performed in multiple centers. By applying optimal sampling strategies however, the number of samples taken can be reduced without a reduction in the accuracy and precision of the estimates of the pharmacokinetic parameters.

Several different techniques are used for the development of optimal sampling schedules. An approach that has been commonly used in oncology is a multivariate linear regression procedure [13, 17, 23]. Plasma concentrations at certain time-points are correlated with the pharmacokinetic parameters of interest, usually AUC or clearance (CL), and one or more time-points that most accurately predict the pharmacokinetic parameter are included in the limited sampling strategy. A second approach uses the D-optimality theory for the selection of optimal time-points, based on previously established population pharmacokinetic parameters [5].

Bayesian estimates of individual pharmacokinetic parameters can be generated based on the prior population pharmacokinetic parameters and the individual plasma concentration-time data available [1, 19].

In this study, these two techniques were applied to the development of limited sampling strategies to assess the pharmacokinetic parameter CL when ET-743 was administered as a 24-h infusion. This parameter was selected as it determines the individual’s exposure to the drug (expressed as AUC) after administration of a dose. Exposure to ET-743 has been shown to be correlated with toxicity during treatment [4, 15, 18]. The validation of the developed sampling schedules was performed on a distinct data set, by comparing the predicted pharmacokinetic parameters with reference values, obtained on the basis of full pharmacokinetic profiles. The different strategies were compared by assessment of their predictive performance.

**Methods**

Patients and pharmacokinetic studies

The development and validation of the optimal sampling strategies was performed using pharmacokinetic data from a phase I dose-finding study with ET-743 administered as a 24-h infusion every 3 weeks. In total 52 patients were treated at nine dose levels ranging from 50 to 1800 μg/m². At the recommended phase II dose of 1500 μg/m², a total of 25 patients was recruited to better characterize the safety profile of ET-743, before commencing an extensive phase II program. During the first course of treatment of all patients, serial blood samples were collected at 15 time-points: preinfusion, at 2, 6 and 23.5 h during the infusion, and at 5, 10, 15 min and 0.5, 1, 2, 4, 6, 9, 12 and 24 h after the end of administration. As ET-743 displays a long terminal half-life, the sampling schedule was extended to the highest dose levels in order to obtain the complete terminal part of the curve. Blood samples were then collected weekly, up to 504 h after the end of administration. The samples were analyzed using a sensitive analytical method which combines miniaturized liquid chromatography with two mass analyzers [14]. This method yields a linear detection range of 10–2500 μg/ml.

In the phase II program with ET-743, patients are treated with 1500 μg/m² ET-743 administered as a 24-h intravenous infusion. For the development of limited sampling strategies for this schedule, only the phase I data from the first course of patients treated at the dose levels 1200, 1500 and 1800 μg/m² were used. Patients were randomly divided into an index data set, which was used for the development of the limited sampling strategies, and a second data set, used for the validation of the created schedules.

Development of limited sampling strategies

With both techniques, limited sampling strategies were developed to assess the pharmacokinetic parameter CL. This parameter was selected as it determines the exposure to ET-743 (expressed as AUC) according to the following equation: \( CL = \text{dose/AUC}. \)

**Linear regression approach**

For all patients of the index and validation data sets, the CL was calculated applying non-compartmental pharmacokinetic analysis.