Therapeutic Drug Monitoring of 21-Day Oral Etoposide in Patients with Advanced Non-Small Cell Lung Cancer

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ABSTRACT

The purpose of this study was to prospectively test a pharmacodynamic model for therapeutic drug monitoring of 21-day oral etoposide. In our previous studies, etoposide trough concentrations on this schedule were related to the hematological toxicity, expressed as WBC and neutrophil counts at the nadir. The following pharmacodynamic model estimated the absolute neutrophil count at the nadir (ANC) based on the etoposide concentration (Er) and the pretreatment count (ANCp):

\[ \text{ANC} = 0.32(1 + \text{ANCp} \times e^{-2.47 \times Er}) \]

Patients were treated with 40 mg/m²/day etoposide p.o. × 21 days and 100 mg/m² cisplatin i.v. on day 1. All patients had non-small cell lung cancer stage IIIB or IV, had a performance status of 0-2, and had a median age of 66 (range, 42-80). Etoposide was measured in the plasma on day 8 by high-performance liquid chromatography, and dosage adjustments were made for the remainder of the course. We targeted for grade 3 neutropenia (ANC < 500/μl) and attempted to avoid grade 4 neutropenia (ANC < 500/μl). Of 25 patients entered, 22 were evaluable for therapeutic drug monitoring. Three patients developed grade 3 neutropenia, and seven patients developed grade 4 neutropenia. Etoposide concentrations were significantly correlated with ANC in the first course (r = -0.50, P < 0.02). For those patients whose dosages were not changed, the estimated correlation between predicted and actual ANC was 0.77 (P < 0.01). No evidence of significant bias of the pharmacodynamic model was detected. The etoposide dosages were increased in 12 patients and were not changed in the remaining patients. The precision of the model was good in patients whose dosages were not changed but poor in patients whose dosages were increased. The actual observed ANC was compared with the predicted ANC based on the pharmacodynamic model. The prediction was considered accurate if the predicted and actual ANC values were within 500/μl of each other. Using this margin, the ANC was accurately predicted in 10 of 22 patients. Etoposide concentrations >0.3 μg/ml on this schedule were significantly correlated with combined grades 3 and 4 neutropenia (P < 0.0001). In conclusion, the pharmacodynamic model is statistically sound when applied to a population of patients. However, when applied to individual patients for therapeutic drug monitoring, the model lacks precision and accuracy.

INTRODUCTION

Measurements of drugs like aminoglycosides, digoxin, phenytoin, or theophylline for making decisions during treatment are accepted practice in internal medicine. Useful strategies exist for these drugs such that concentrations can be determined at steady-state (i.e., theophylline) or at specified times (i.e., peak and trough for aminoglycosides) and doses adjusted, depending on how far off the measured concentration is from the target (1). In cancer therapy, however, therapeutic drug monitoring has not found a standard role except for methotrexate measurements to guide leucovorin rescue after high-dose therapy (2). Clinical oncologists are well aware of the narrow therapeutic index of antineoplastic drugs and make dose adjustments after toxicity is encountered. The problem of making correct dosing decisions is at least in part attributed to our incomplete clinical assessment of the pharmacokinetic variability between patients, which in turn determines the pharmacodynamic variability (3). Pharmacodynamics is defined as the relationship between drug concentrations and therapeutic or toxic responses. The problem of interpatient variability and the inability to predict the severity of toxicity cannot be overcome unless the relationships between pharmacological measurements and clinical effects are explored. The toxicity of anticancer chemotherapy is mainly due to growth inhibition of rapidly dividing normal tissues exemplified by bone marrow suppression. Troublesome consequences of myelosuppression are neutropenic fever and sepsis. These adverse consequences of chemotherapy are not immediately apparent, and the time interval and degree of toxicity are poorly predictable.

Lung cancer is the leading cause of death from cancer in the United States (4). The majority of patients have non-small cell lung cancer. Patients with advanced non-small cell lung cancer commonly receive chemotherapy for palliation of their disease. Our previous Phase II study demonstrated that a 21-day schedule of oral etoposide in combination with i.v. cisplatin was active in patients with advanced non-small cell lung cancer (5, 6). Etoposide was administered at a dosage of 50 mg/m² for 21 days, and 100 mg/m² cisplatin were given on day 1 of a 28-day
cycle. Etoposide plasma concentrations were measured weekly just before the daily dose (trough levels). The etoposide concentrations on this schedule were related to the hematological toxicity, expressed as WBC and neutrophil counts at the nadir (5). The following pharmacodynamic model was developed to estimate the absolute neutrophil count at the nadir \((ANC_n)\) based on the etoposide concentration \((E_r)\) and the pretreatment count \((ANC_p)\):

\[
ANC_n = 0.32(1 + ANC_p \times e^{-2.47 \times Ec})
\]

Subsequently, this model was tested prospectively and performed reliably (7).

A similar regimen consisting of 21-day oral etoposide (50 mg/m²/day) with cisplatin given at a dosage of 33 mg/m² i.v. on days 1, 2, and 3 was used by the CALGB\(^3\) for extensive stage small-cell lung cancer (8). Multiple linear regression analysis of this CALGB trial led to the following pharmacodynamic model (9):

\[
\log_{10}(ANC) = -0.153 - 0.017 \times \text{age} - 0.363
\]

\[
\times E_{C} + 0.530 \times \log_{10} \text{(alkaline phosphatase)}
\]

However, this latter pharmacodynamic equation was not available at the beginning of the trial that is described here. It is important to note that the above equations were derived from groups of patients (population pharmacology), and that their performance when applied to individual patients (therapeutic drug monitoring) remained unknown.

In previous studies of 50 mg/m²/day \(\times 21\) days, we observed grades 3 and 4 neutropenia in 73–83% of all patients (5–9). Therefore, the starting dose was reduced from 50 to 40 mg/m²/day \(\times 21\) days for this trial. Etoposide is marketed in the United States only as a 50-mg capsule. This capsule size was used in the previous studies (5–9). For therapeutic drug monitoring, the 50-mg capsules were not useful because dose adjustments were not feasible. For the sake of prospective therapeutic dose adjustments, 10-mg capsules were obtained from Bristol-Myers Oncology (Princeton, NJ) providing 10-mg capsules of etoposide, which were similar in formulation to the marketed 50-mg capsules (VePesid). The trial was conducted under Investigational New Drug 43,711 from the Food and Drug Administration (Rockville, MD). The commercially available formulation of cisplatin was used.

All patients had laboratory studies performed before study entry and before each treatment cycle: complete blood cell count with differential; electrolytes (including calcium and magnesium); liver and renal function chemistries; lactate dehydrogenase; total protein; and albumin. While on treatment, patients returned weekly to clinic for monitoring of compliance with oral etoposide, complete blood cell counts, and etoposide plasma concentrations. For therapeutic drug monitoring, weekly etoposide samples were obtained just before the daily dose (trough concentrations). The etoposide concentration on day 8 of cycle 1 was used to predict the neutrophil count at the nadir based on the following equation: \(ANC_n = 0.32(1 + ANC_p \times e^{-2.47 \times Ec})\). Based on this prediction, the dose of etoposide was adjusted for the remainder of the cycle. The goal was to avoid grade 4 neutropenia (\(ANC_n < 500/\mu l\); Common Toxicity Criteria by the National Cancer Institute) by means of dose reduction. Grade 3 neutropenia (\(ANC_n 500–999/\mu l\)) was deemed acceptable, and no dose change was made. For grades 0, 1, and 2 projected neutropenia (\(ANC_n \geq 1000/\mu l\)), dose increases were planned. Patients were seen in the clinic on the morning, the blood sample was taken to the laboratory immediately for analysis of the etoposide concentration the same day, and patients were called in the afternoon with dosage instructions. Dose adjustments were made in 20-mg increments. Predicted and actual nadir counts were recorded. Etoposide plasma concentrations were measured by high-performance liquid chromatography according to a method published previously (5). The lower limit of detection was 0.05 \(\mu g/ml\). The day-to-day coefficients of variation for etoposide measurements were less than 10%, as in the previous studies (5–9).

**Statistical Methods.** Pearson correlation coefficients were estimated for evaluating the relationships between etopo-
side concentration and \( \text{ANC}_n \), predicted and actual \( \text{ANC}_n \), age and \( \text{ANC}_n \), and age and etoposide concentration. The \( t \) test was applied to evaluate the relationships between race and etoposide concentration and race and \( \text{ANC}_n \). Differences between actual and predicted values of nadir counts were obtained by subtracting the predicted values from the actual ones. The mean difference between actual nadir counts and predicted nadir counts is a measure of bias. Whether bias equaled zero was evaluated with a paired \( t \) test. The SD of the difference between actual and predicted nadir counts is a measure of precision. Whether this value was \( <500/\mu l \) was tested with a \( x^2 \) test. We classified the prediction as accurate if the actual and predicted nadir counts were within \( 500/\mu l \) of each other. The risk of combined grade 3 and 4 neutropenia for \( E_c >0.3 \mu g/ml \) versus \( E_c <0.3 \mu g/ml \) was estimated by the two-tailed Fisher’s exact test. Whether dose change was related to the development of neutropenia was also evaluated with Fisher’s exact test. The \( t \) test was used to test whether the mean \( \text{ANC}_n \) values of the two groups of patients (those without dose adjustment versus those with dose adjustment) were similar. Unless otherwise stated, the mean \( \pm \) SE is presented.

**RESULTS**

Of 25 patients entered, all were eligible, and 22 were evaluable for therapeutic drug monitoring in the first course. One patient was inevaluable because of a peak that interfered with the etoposide peak on the chromatogram, and two patients were inevaluable because of noncompliance with the prescribed etoposide treatment. All patients were males. Their median age was 66 years (range, 42–80). Twelve patients were white, and 13 were African-American. The performance status was 0 in 4 patients, 1 in 14 patients, and 2 in 7 patients. The tumor stage was IIIIB in 3 patients and IV in 22 patients. Table 1 shows the results for the first treatment cycle. The predicted values for the neutrophil nadir in this table were based on the equation: 

\[
\text{ANC}_n = 0.32 \left(1 + \text{ANC}_p \times e^{-2.47 \times E_c}\right).
\]

No patient had a dosage reduction. The etoposide dosages were increased in 12 patients. Three patients (Table 1, numbers 3, 19, and 20) did not have the planned dose increases due to problems with communications. The observed hematological toxicity was substantial, with three patients developing grade 3 neutropenia and 7 patients developing grade 4 neutropenia in the first treatment cycle (Table 1). The total number of cycles administered on this protocol was 37 (median per patient, 1; range, 1–3).

**Correlations and Associations.** In the whole population of 22 patients, etoposide concentrations were significantly correlated with \( \text{ANC}_n \) in the first treatment course \( (r = -0.50, P < 0.02) \) and in all courses \( (r = -0.48, P < 0.01) \). Predicted and actual \( \text{ANC}_n \) were correlated when tested for all patients in the first course \( (r = 0.52, P < 0.02) \). The patients’ age was correlated with \( \text{ANC}_n \) in the first course \( (r = -0.68, P < 0.0005) \) but not with the etoposide concentration \( (r = 0.37, P < 0.10) \). The patients’ race was neither related to \( \text{ANC}_n \) nor the etoposide concentration (both \( P > 0.3 \)). For those patients whose dosages were not changed, the estimated correlation between predicted and actual \( \text{ANC}_n \) was 0.77 \( (P < 0.01) \).

**Bias and Precision.** For those patients whose dosages were not changed, no evidence of significant bias of the pharmacodynamic model was detected. The estimated bias was 148 \( \pm 199/\mu l \) \( (P < 0.5) \). The precision of the predictor equation was

<table>
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<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Etoposide concentration (( \mu g/ml ) plasma)</th>
<th>Neutrophil nadir*</th>
<th>Neutropenia grade</th>
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<td>Actual</td>
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<td>47</td>
<td>0.09</td>
<td>1.64</td>
<td>2.09</td>
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* Counts times \( 10^3/\mu l \).
The pharmacodynamic model was developed for a 21-day course of unaltered etoposide dosage. Because of study design, the predicted \( \text{ANC}_n \) values of those patients whose dosages were increased were greater than the predicted \( \text{ANC}_n \) of those patients whose doses were kept the same. When the dosages on day 8 of cycle 1 were increased based on the prediction of \( \text{ANC}_n > 1000/\mu l \), this decision rendered the predicted \( \text{ANC}_n \) value potentially invalid. Therefore, as expected, the proportion of patients with incorrectly predicted \( \text{ANC}_n \) was larger in the group who had the dose increase compared with the group without dose change, but this was not statistically significant \( (P < 0.21) \).

Inspection of the types of incorrectly predicted \( \text{ANC}_n \) revealed that increasing the dose did not significantly increase the proportion of patients with actual \( \text{ANC}_n \) that were lower than predicted \( (P < 0.6) \). Of those patients whose doses were increased, 5 of 12 had actual \( \text{ANC}_n \) values that were more than 500/\( \mu l \) greater than predicted. The actual \( \text{ANC}_n \) values for the two groups of patients were significantly different: 991 ± 254/\( \mu l \) for those whose doses were not changed versus 2609 ± 552/\( \mu l \) for those whose doses were increased \((P < 0.02) \). These results suggest that on average the pharmacodynamic model correctly identified patients with less hematological toxicity from etoposide. However, to be clinically useful the model must not only predict who will not develop neutropenia, but more importantly who will develop severe neutropenia. Of those patients whose dosages were kept the same, 4 of 10 (40%) developed grade 4 neutropenia compared with 3 of 12 (25%) patients in whom the dosages were increased \((P < 0.7) \).

All of the above work was performed prospectively based on the previously validated equation \( \text{ANC}_n = 0.32 (1 + \text{ANC}_p \times e^{-2.47 \times E_c}) \). As stated in the introduction, another pharmacodynamic equation was developed while this trial was in progress: \( \log_{10} (\text{ANC}_n) = -0.153 - 0.017 \times \text{age} - 0.363 \times E_c + 0.530 \times \log_{10} (\text{alkaline phosphatase}) \). This model was developed by multiple linear regression of pharmacodynamic data from 83 patients treated on a CALGB study. Applying this CALGB model retrospectively to the data available from the 22 patients in this trial did not result in any statistical improvement in prediction \((P > 0.02) \). The CALGB model also failed to identify the three patients whose doses were increased and who developed grade 4 neutropenia \((P < 0.7) \).

**DISCUSSION**

Both pharmacodynamic models appear to contain influential predictor variables such as \( E_c, \text{ANC}_p, \text{age}, \) and alkaline phosphatase. The relationship among these predictors is com-
0.530 X log10 (alkaline phosphatase), where are log10(ANC) equation cells X l0/l) from cycle 1 of treatment based on the prediction solid line of identity. However, doses were increased. However, of patients. Applying the phamacodynamic models to imdividual patients for therapeutic drug monitoring lacked accuracy and precision. Specifically, the etoposide trough concentration on day 8 of cycle 1 did not reliably predict the ANC of cycle 1 did not reliably predict the ANC that contributed significantly to the model. In the CALGB study (9), no significant association between ANC and the nadir count was demonstrated, and ANC was left out of the model: log10(ANC) = -0.153 - 0.017 X age - 0.363 X E_c + 0.530 X log10 (alkaline phosphatase).

Two potential confounding problems should be acknowledged: (a) the pharmacodynamic models were developed for 50-mg etoposide capsules given at a dosage of 50 mg/m²/day. This trial used 10-mg etoposide capsules of the same formulation given at a starting dosage of 40 mg/m²/day; and (b) cisplatin was given i.v. on day 1 in combination with the 21-day course of p.o. etoposide, but cisplatin was not measured. Therefore, the contribution of cisplatin to the neutropenia was not assessed. The previous studies of 50 mg/m²/day etoposide × 21 showed an incidence of combined grades 3 and 4 neutropenia between 73 and 83% (5–9). The current study had an incidence of grades 3 and 4 neutropenia of 45% (Table 1). Thus, the dose reduction to 40 mg/m²/day etoposide × 21 had the desired effect.

Fig. 1 illustrates the limitations of using our pharmacodynamic model in this prospective trial. Fig. 2 shows the retrospective application of the CALGB model, which performed worse. Overall, it appears doubtful that applying the models will result in a marked improvement in clinical care. On the other hand, dose adjustments based on the first model did not increase the incidence of severe neutropenia; thus, patients were not harmed by applying the model.

Our current understanding of the pharmacodynamics of etoposide was recently reviewed by McLeod and Evans (13). The influence of etoposide systemic exposure on the hematological toxicity has been clearly demonstrated. The equations that best describe the relationship vary with each study and have included AUC, concentrations at steady-state (Cₛ), and trough concentrations (Eₜ) as in our study. As reviewed by McLeod and Evans (13), two studies have attempted therapeutic drug monitoring of etoposide, one by Ratain et al. (14) and one by Madden et al. (15).

In the prospective study of pharmacologically based dosing by Ratain et al. (14), 45 patients with a variety of solid tumors were randomly assigned to receive a fixed dose of etoposide 125 mg/m²/day by 72 h continuous infusion or to receive individualized dosing to a target WBC nadir of 1700/µl (grade 3 leukopenia corresponding to our grade 3 neutropenia). Dosage modification was determined using an exponential model that included total etoposide dose, starting dose, 24-h etoposide

**Fig. 2** Relationship between the actual and predicted ANC (ANC, cells × 10³/µl) from cycle 1 of treatment based on the prediction equation log₁₀(ANC) = -0.153 - 0.017 X age - 0.363 X E_c + 0.530 X log₁₀ (alkaline phosphatase), where are = ± 500/µl from the solid line of identity. (a) patients whose dosages were not changed; (b) patients whose dosages were increased.
concentration ($C_m$ corresponding to our $E_C$), patient performance status, albumin, and bone marrow function (based on prior transfusion requirements). Our patients were newly diagnosed with non-small cell lung cancer without prior transfusion requirements, and albumin and performance status did not contribute significantly to the model. In the study by Ratain et al. (14), the total dose was increased in patients with individualized dosing, and this was associated with a decrease in the mean WBC at the nadir ($1510 \pm 950 \text{ versus } 2500 \pm 1420/\mu l$). Both the study by Ratain et al. (14) and our study resulted in an increase in the dose intensity without increasing the incidence of life-threatening toxicity. Although the pharmacodynamic model in the study by Ratain et al. (14) did appear to accurately predict the WBC nadir, the degree of variability around the target value indicated that a more specific model was needed before large-scale implementation of this dosing approach (14). This limitation also applies to our study [in fact, Fig. 4A in the publication by Ratain et al. (14) and our Fig. 1 are similar].

In the trial of individualized etoposide therapy by Madden et al. (15), 17 children with acute nonlymphocytic leukemia received a 70 mg/m$^2$ loading dose, followed by 500 mg/m$^2$/day for 96 h. A blood sample was obtained 6 h after the start of infusion, and dosage rates were adjusted to achieve a target plasma concentration within 12 h. Ten of the 17 patients required a dosage increase. This study did not provide further details of the predictive performance of the model used for dosage adjustment (15).

In conclusion, the pharmacodynamic model is statistically sound when applied to a population of patients. However, when applied in individual patients for therapeutic drug monitoring, our present model lacks precision and accuracy. Increasing the sample size of the trial is not expected to be helpful. This will improve the $P_s$ for the population; however, a review of the large CALGB trial indicates that great variability existed and that predictions for individual patients will remain poor (9). Although disappointing, this dilemma is not unique in medical oncology. For instance, we know for a common malignancy and a certain stage what the statistically valid figure of a given median survival time is in the population. However, when faced with an individual patient, the statistically valid figure of a given survival time is clinically meaningless. Because of the variability around the median, which is usually large, even an experienced clinician cannot tell the individual patient what his/her survival time will be. We will need to refine the current predictor variables and search for other variables that improve the pharmacodynamic model. A study of pharmacodynamic modeling of 21-day, single-agent etoposide in patients with relapsed non-Hodgkin’s lymphoma is presently in progress in CALGB.

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REFERENCES


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