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A randomized study of epirubicin at four different dose levels in advanced breast cancer. Feasibility of myelotoxicity prediction through single blood-sample measurement*

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Summary. Detailed pharmacokinetic analysis and subsequent evaluation of myelotoxicity were performed in 55 patients who had been randomized to 4 different doses of epirubicin (40, 60, 90 or 135 mg/m^2 given i.v. every 3 weeks). A significantly positive correlation was demonstrated between the AUC and the myelotoxicity of epirubicin. A similar correlation was observed when the metabolite epirubicinol was also considered. The decrease in leucocyte count as expressed by the logarithmic ratio between nadir WBC and initial WBC was linearly correlated with the AUC of either epirubicin alone ($r = -0.55$, $P < 0.001$) or epirubicin and epirubicinol together ($r = -0.63$, $P < 0.001$). As a relationship between the concentration of epirubicin in a single plasma sample taken at 6 h following i.v. administration and the AUC of the drug has been established, a log-linear relationship between the expected decrease in leucocytes and the concentration at 6 h after administration could be calculated. The proposed model is expressed as the equation: $\log WBC_{nadir} = \log WBC_{initial} - 0.0073 \times c_6$ (ng/ml) $- 0.14$.

Introduction

Epirubicin, the 4-epimer of doxorubicin, has been in clinical use for approximately 10 years. Its antitumor activity appears to be almost identical to that of the parent drug [8], but epirubicin is probably less toxic than doxorubicin and can therefore be given at a higher dose. This is the main reason for its wide application in the treatment of a number of different malignancies. The pharmacokinetics of the drug after i.v. bolus administration has been described by an open three-compartment model, showing an initial distribution half-life of 3–20 min, a secondary half-life of 0.5–3 h and a terminal half-life of 10–69 h [2, 6, 9–12]. The pharmacokinetic parameters are subject to considerable interindividual variation, and a given dose may result in highly different AUC values [9]. In agreement with these observations, it is well known from clinical practice that the toxicity of epirubicin differs considerably when the dose is calculated on the basis of the patients' body surface area (milligrams per square meter).

Dose individualization based on pharmacokinetic parameters appears to be an obvious means of optimizing treatment, but simple relationships between pharmacokinetic data such as the peak plasma concentration or the AUC and pharmacodynamic parameters remain to be demonstrated. Complete pharmacokinetic investigations are time-consuming and laborious. The measurement of AUC, for example, demands a rather high number of analyses and is therefore not suitable for daily routine use. Thus, methods are needed that relate pharmacokinetic parameters based on a single or a few analyses to important pharmacodynamic parameters. The objective of the present study was to evaluate the relationship between the AUC and the myelotoxicity of epirubicin and to evaluate the predictability of changes in WBC by single measurements of plasma drug concentration.

Patients and methods

The present pharmacokinetic study was a part of a randomized clinical trial of epirubicin in patients presenting with metastatic breast cancer. The study was accepted by the Danish Health Authorities and by the Ethical Committee. The clinical part of the study is ongoing. After the patients had given their informed consent to participate, they were randomly allocated to receive one of the following four doses of epirubicin: 40, 60, 90 or 135 mg/m^2 given as a 10-min i.v. infusion. The treatment was carried out every 3 weeks either until progression of disease or until a cumulative dose of 1000 mg/m^2 had been given.

Blood counts were performed both before each treatment course and at also 10–14 days (nadir) after the first treatment course in 55 of the 78 patients included in the pharmacokinetic part of the trial. The dose

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Table 1. Patients' characteristics according to treatment

	Treatment (mg/m²)			
	40	60	90	135
Number of patients[a]	15	12	14	14
Age (years):				
Median	59	66	60	63
Range	41–72	49–74	31–75	39–74
Performance status (WHO):				
Median	1	0	0	1
Range	0–2	0–1	0–2	0–3
Pretreatment WBC ($\times 10^9$/l):				
Mean	5.6	7.8	7	7
±SD	1.5	2.4	2.5	2.5
Range	3.8–9.2	5–11.8	4.1–13.9	3–12.4
Pretreatment platelets ($\times 10^9$/l):				
Mean	303	305	306	300
±SD	76	155	100	50
Range	203–426	173–739	150–563	235–385
Pretreatment creatinine (μmol/l):				
Mean	84	84	79	77
±SD	31	15	18	15
Range	53–177	49–101	61–130	61–116
Pretreatment ALAT (units/l):				
Mean	29	35	32	30
±SD	16	30	33	25
Range	9–57	7–87	9–132	9–95
Pretreatment bilirubin (μmol/l):				
Mean	6	7	7	7
±SD	3	2	2	3
Range	2–12	5–12	4–10	3–10

[a] Evaluable for myelotoxicity
ALAT, Alanine aminotransferase

was reduced by one step, i.e. from 135 to 90 mg/m², when the nadir WBC reached $<0.4 \times 10^9$/l or the thrombocyte count fell to $<20 \times 10^9$/l. When a WBC of $<3 \times 10^9$/l or a thrombocyte count of $<100 \times 10^9$/l was measured on day 1 of a new course, the treatment was postponed for 1 week until the planned dose could be given. Patients requiring a treatment delay of >3 weeks were excluded.

The pharmacokinetic measurements were carried out during the first course. Blood samples were drawn before and at 5 min as well as at 0.5, 1, 2, 4, 6, 7, 9, 11, 24 and 30 h after treatment. Epirubicin and the active metabolite epirubicinol were analyzed by HPLC [3]. A detailed pharmacokinetic analysis has been described elsewhere [9].

Results

Some important characteristics of the 55 patients who were included in the present analysis are given in Table 1. The patients were uniformly distributed among the four treatment groups according to different clinical parameters.

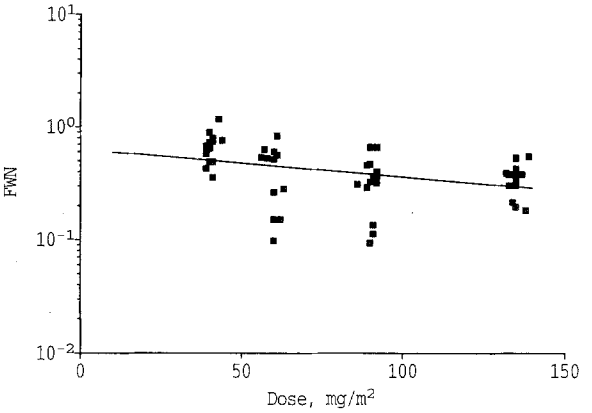

Fig. 1. Relationship between the fractional WBC nadir (FWN) and the delivered dose (mg/m²). The *solid line* represents the log-linear regression line: $y = -0.00246x - 0.198$; $r = -0.36$

Table 2 summarizes some of the pharmacokinetic data obtained. A considerable interindividual variation in both terminal half-life and AUC expressed as clearance (dose divided by the AUC) was evident.

Correlations between a variety of characteristics (patients' age, liver parameters and creatinine clearance) or pharmacokinetic parameters (peak plasma concentration, area under the first-moment curve, mean residence time and AUC of epirubicin and epirubicinol) and decreases in WBC or changes in thrombocyte counts were attempted. Except for the AUCs of epirubicin and epirubicinol, no correlations were found.

The decrease in leucocytes, expressed as the logarithm of the fractional WBC nadir (FWN) and defined as the ratio between the WBC_{nadir} and the $WBC_{initial}$, was compared with the delivered dose (mg/m²) during the first course as shown in Fig. 1. Log-linear regression analysis gave a correlation coefficient of $r = -0.36$ ($P = 0.01$). Considerable variations in myelotoxicity were observed, indicating that the dose in milligrams per square meter is probably inadequate for predictions of myelosuppression.

The relationship between the AUC_{epi} and the decrease in leucocytes, expressed as the logarithm to the FWN, is shown in Fig. 2. A high correlation ($r = -0.55$, $P < 0.0001$) over the dose range applied suggests a log-linear relationship between the AUC_{epi} and the decrease in WBC. Almost identical results (data not shown) were obtained when the AUC_{epi} was replaced by the total AUC ($AUC_{epi} + AUC_{epiol}$; $r = -0.63$, $P < 0.0001$).

High correlations between the AUC_{epi} and the plasma concentration determined at 6 h after administration (c_6) have previously been reported [9]:
Model I: $AUC_{epi\ I}$ (ng h ml^{-1}) = 39.6 × c_6 (ng/ml) + 302 ($r = 0.93$),

Table 2. Selected pharmacokinetic parameters

	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Clearance (ml min^{-1} m^{-2})	$Auc_{epi}/AUC_{epi+epiol}$
Mean	0.14	1.79	19.5	781	0.71
±SD	0.07	0.66	4.9	183	0.11
Range	0.05–0.36	0.69–3.46	10.5–33	303–1233	0.48–1

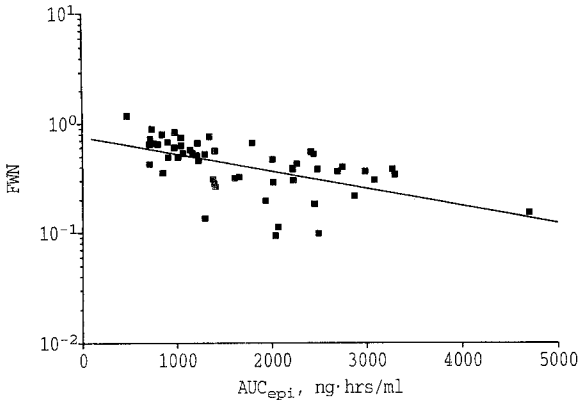

Fig. 2. The log-linear relationship between FWN and AUC_{epi} calculated using complete pharmacokinetic analysis. The *straight line* represents the linear regression line: $y = -0.000115\,x - 0.147$; $r = -0.55$

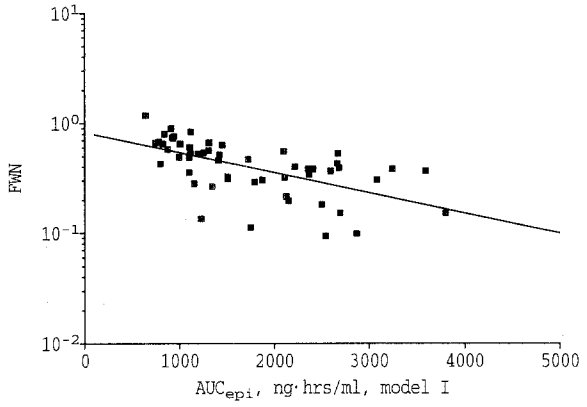

Fig. 3. Correlation between FWN and AUC_{epi} calculated from model I using single-sample determination (6 h after administration). The *solid middle line* represents the regression line: $y = -0.00018\,x - 0.0836$; $r = -0.59$. The *lines surrounding the regression line* show the 95% prediction intervals, and the *dotted lines* indicate the cutoff points used in Table 3

Table 3. Incidence of unexpected high decreases in WBC

	Intervals of AUC estimated from c_6 (ng h m^{-1})		
WBC	0–1000	1000–2000	2000–3000
50% decrease	1/12 (8%)	11/23 (48%)	14/16 (88%)
75% decrease	0/13 (0)	2/23 (9%)	6/16 (38%)

or a combination of two different time points, 2 and 24 h after administration, c_2 and c_{24}:

Model II: $AUC_{epi\ II} = 9.44 \times c_2 + 62.5 \times c_{24} + 158$ ($r = 0.95$).

This leads to correlations between FWN and AUC_{epi} being calculated from the two models. Figure 3 shows the relationship between the log FWN and the AUC_{epi} calculated from model I along with the 95% prediction interval, and the equations for the log-linear relations are given below for models I and II:

$\log FWN = -1.84 \times 10^{-4} \times AUC_{epi\ I} - 0.084$ ($r = -0.59$, $P < 0.0001$) and

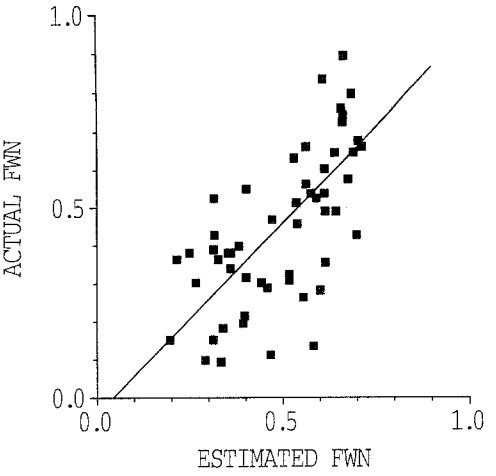

Fig. 4. Correlation between the actual FWN and the FWN estimated from model I (single-sample determination). *Regression line*: $y = 1.039\,x + 0.01$; $r = 0.67$

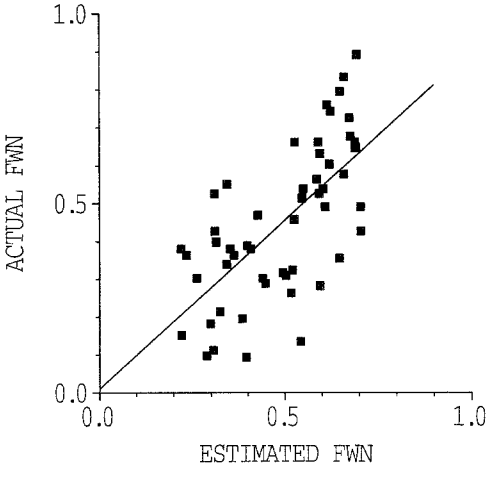

Fig. 5. Correlation between the actual FWN and the FWN estimated from model II (two-sample determination). *Regression line*: $y = 1.004\,x - 0.043$; $r = 0.68$

$\log FWN = -1.9 \times 10^{-4} \times AUC_{epi\ II} - 0.075$ ($r = -0.61$, $P < 0.0001$).

From the above equations, the relationship between the leucocyte decrease and either the c_6 or the c_2 or c_{24} value expressed in nanograms per milliliter can be predicted:

$\log FWN = -0.0073 \times c_6 - 0.14$ and

$\log FWN = -0.0018 \times c_2 - 0.012 \times c_{24} - 0.11$.

Table 3 shows the ability of epirubicin at three different estimated AUC values to decrease the WBC by 50% and 75%, respectively. Figures 4 and 5 illustrate the relationship between the actual FWN and the FWN estimated from models I and II. Linear regression analysis gave slopes that were not significantly different from unity and intersects that were not significantly different from zero. Regression coefficients were 0.67 and 0.68, respectively. Multiple regression analysis using log WBC_{nadir} as the dependent variable and log $WBC_{initial}$ and AUC_{epi} as the independent variables did not improve the models, making the decrease in leucocytes independent of the pretreatment WBC.

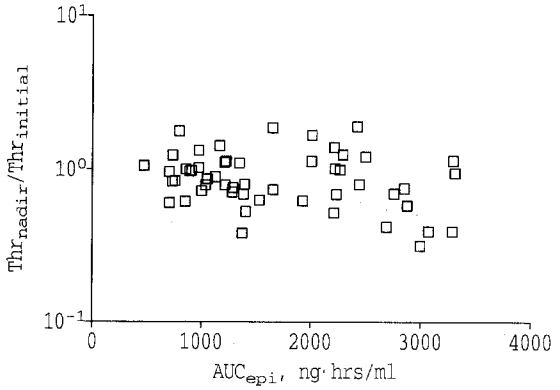

Fig. 6. Semilogarithmic scatter plot of changes in thrombocyte counts vs AUC_{epi}

The relationship between the AUC_{epi} and the change in thrombocytes, presented as a semilogarithmic plot of the ratio between the nadir and the initial platelet counts vs the AUC_{epi} in Fig. 6, showed no correlation. The log-linear regression analysis gave a line exhibiting a slightly negative slope that was not significantly different from zero ($r = -0.26$, $P = 0.06$).

Discussion

The conventional dose calculation for cytostatic drugs is based on the body surface area of the patient (milligrams per square meter). This method clearly has serious drawbacks. As this method does not account for individual pharmacokinetic parameters, it is not surprising that considerable variations in pharmacodynamic parameters occur, often resulting in severe side effects. Previous observations [5] have indicated that the AUC of epirubicin may be predicted from a single-sample determination when 2- or 4-h infusions are given. The present study shows that either single-sample or two-sample analysis can be applied when short-term infusions (10 min), the generally used method of administration, are given. The correlation for the single-sample analysis should be chosen for practical reasons, as the correlation coefficients for both types of analysis are quite similar. This enables the pharmacokinetic parameters to be incorporated in daily clinical practice; thus, patients receiving epirubicin may be subjected to drug monitoring.

Using other anthracyclines, the decrease in WBC has been correlated to the maximal steady-state plasma concentrations of the parent drug alone after long-term infusions (doxorubicin) [1] or to the sum of the AUCs of the parent drug and a metabolite following oral administration (idarubicin) [7]. We attempted to correlate various patient characteristics and pharmacokinetic parameters to the decrease in WBC. No significant correlates were found with the exception of the AUC of epirubicin and the AUC of epirubicin and epirubicinol together. The log-linear relationship between the myelotoxicity and the AUC of epirubicin suggests that the fractional WBC nadir (FWN) can be correlated to the AUC by an exponential equation. This equation resembles the model proposed by Eichholtz-Wirth [4], which was originally based on in vitro experiments concerning the survival fraction. The present results indicate that the concentration at 6 h after administration may replace the AUC when applied in clinical investigations.

The clinical usefulness of myelotoxicity prediction is hampered by the present false-negative results (unexpected high decrease in WBC at "normal" c_6). Linear regression analysis gives an indication of the magnitude of the false-negative and false-positive results. As always occurs in studies based on clinical data, there was great inhomogeneity due to biological variation. Another important factor is that in different disease entities, different fractions of WBC nadirs are accepted. For instance, in strictly palliative treatments, a slight decrease in WBC is accepted; on the other hand, when a cure is intended, a larger decrease can be accepted. In Table 3 we estimated the risk for the occurrence of false-negative results using three different cutoff points for estimated AUC. The percentage of false-negatives are presented for two fractional WBC nadirs (50% and 25%).

Other side effects such as nausea and vomiting are also of interest but are difficult to quantitate by objective methods; thus, further studies are needed to investigate a probable correlation between such parameters and the pharmacokinetics of epirubicin. Ideally, a method should enable dose individualization before treatment. The present results show that the WBC_{nadir} can be predicted from the analysis of a single blood sample. This is too late to enable dose adjustment. At present, however, the role of hematopoietic growth factors has not been clearly established. In selected patients in whom severe leucopenia would be expected based on single-sample measurements, it might be possible to start prophylactic treatment with hematopoietic growth factors. Furthermore, in cases known to exhibit a high AUC value, the physicion is more likely to pay greater attention to possible complications due to expected hematologic toxicity. Thus, although the method presented herein is by no means ideal, the prediction of myelotoxicity from single-sample analysis is of considerable value for subsequent dose adjustment, resulting in safer administration of epirubicin.

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