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ORIGINAL ARTICLE

Gudrun Würthwein · Joachim Boos

Low dose–high dose: what is the right dose? Pharmacokinetic modeling of etoposide

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Abstract *Purpose:* Some clinical studies on etoposide (Eto) have shown marked schedule dependency of the effect (starting at about 1 mg/l) and toxicity (over about 10 mg/l) whereas other studies have not confirmed these results. What are the conclusions we can draw from these inconsistent results when developing new low-dose (LD) and high-dose (HD) Eto schedules? *Methods:* A pharmacokinetic model for Eto based on individual pharmacokinetic data was used to simulate different LD (450 mg/m^2) and HD (1800 mg/m^2) schedules. The duration of exposure and the AUC of relevant concentration ranges (>1 mg/l, 1–10 mg/l, >10 mg/l) as well as peak levels were calculated in relation to the standard low dose (150 mg/m^2 over 2 h daily for 3 days). *Results:* The fourfold dose increase from the LD to the HD schedule was associated with a complementary increase in total AUC. However, variations in infusion time for the HD schedule were associated with large differences in AUC distribution and drug exposure with constant total AUC. Short infusions (0.5 h and 4 h) resulted in extreme peak levels (factors of 17.6 ± 1.5 and 8.7 ± 0.4 compared to the standard LD schedule) and an AUC >10 mg/l (factors of 17.5 ± 4.9 and 17.2 ± 4.8, and $83 \pm 2.4\%$ and $82 \pm 2.4\%$ of the corresponding total AUC), and the 96-h infusion yielded a long duration of exposure to concentrations >10 mg/l (factor 7.9 ± 2.6), whereas continuous i.v. infusion over 55 ± 11 days was associated with a multiple increase in the duration of exposure to "standard" drug concentrations (1 mg/l). *Conclusions:* According to evidence against schedule dependency, only target dose and pharmacokinetic variability would be appropriate rationales for Eto dosing. However, arguing for schedule dependency, simulated pharmacokinetic profiles for new Eto schedules over a wide range support that Eto-containing regimens should be designed on the basis of clear pharmacokinetic hypotheses of target levels, exposure times and AUC distributions, to allow subsequent development of pharmacokinetic/pharmacodynamic modeling.

Keywords Etoposide · Pharmacokinetic modeling · Schedule dependency · Low dose · High dose

G. Würthwein · J. Boos (✉)
University Hospital Münster,
Department of Pediatric Hematology and Oncology,
48129 Münster, Germany
E-mail: BOOSJ@uni-muenster.de
Tel.: +49-251-8347865
Fax: +49-251-8347828

Introduction

High-dose chemotherapy

Preclinical studies of experimental cancer in mice conducted in the 1960s showed that a schedule delivering the maximum tolerated dose yields a higher cure rate [12]. This schedule was then employed for conventional chemotherapy regimens in cancer patients. However, such high (marginally lethal) doses require extended treatment-free periods to permit recovery of normal host cells. During the last 10 to 20 years, high-dose chemotherapy has become a major focus of treatment development. Based on the hypothesis of a dose-effect relationship and "the simple precept that if a little is good, then more is better" [5], many study protocols have included high-dose chemotherapy. Improvements in supportive care and autologous bone marrow and/or peripheral blood stem cell support have made this escalation in dose intensity possible.

The employment of drugs for high-dose chemotherapy is limited by their organ toxicity under standard therapy. Drugs whose dose-limiting toxicity affects the heart (anthracyclines), the nerve system (vincristine), or the kidneys and hearing (cisplatinum) are not suitable for further dose escalations. On the other hand, substances showing more or less solely bone marrow toxicity are suitable for high-dose chemotherapy regimens. Stem cell transplantation circumvents the problems of

toxicity and enables dose intensification with these drugs until other dose-limiting end-organ toxicities occur.

What is "high-dose"?

In vitro assays use an exponential increase in drug concentration to test for cytotoxic activity of compounds. In vivo, however, limits to dose escalations are much lower. For the alkylating agents busulfan and thiotepa, doses about 20- to 30-fold higher compared to standard low-dose regimens are administered, whereas for drugs such as melphalan, cyclophosphamide, carboplatinum and etoposide (Eto) only four- to fivefold dose increases are considered possible before the maximum tolerated dose is reached.

From these considerations, the question arises as to the basic pharmacological factors responsible for the improved remission rates and rates of disease-free survival associated with high-dose chemotherapy.

The case of Eto

We focused on the above question using Eto as an example. In vitro studies have demonstrated the importance of both concentration and duration of exposure to Eto cytotoxicity. Inconsistent results have been reported concerning schedule-dependency in vitro. Roed et al. [11] have shown that concentrations 100 times higher than those used for 24-h continuous exposure are required to achieve the same degree of cell kill in a 1-h incubation period. However, Lowis et al. [7] have shown that cytotoxicity is a function of the product of concentration and duration of exposure over a wide range of durations and concentrations. In their study, Eto did not show schedule dependency in vitro. The cytotoxic mechanism of Eto in human ovarian cancer cells also cannot be explained by simple schedule dependency [10].

In vivo, some pharmacological findings have suggested an effect of schedule on Eto activity, whereas no relationship between biological and pharmacological parameters has been found in other studies.

The first study investigating the effect of schedule on Eto activity was reported by Cavalli et al. [1]. Small-cell lung cancer (SCLC) patients treated with divided doses of Eto over several days showed an improved response rate as compared to those treated with single or weekly injections of Eto at equivalent doses. A randomized prospective study by Slevin et al. [13] was pivotal in showing schedule dependency. A total dose of 500 mg/m^2 was given either as a single 24-h infusion or as five daily 2-h infusions of 100 mg/m^2, each being repeated every 3 weeks. The overall response rates were 10% in the 24-h arm and 89% in the 5-day arm. Pharmacokinetic data from this study confirmed that the total systemic exposure (AUC) in each arm was identical, but that the duration of exposure to low levels of drug (>1 mg/l) was doubled in the 5-day arm, suggesting that prolonged maintenance of low levels of Eto is an important determinant of antitumor activity.

A number of clinical studies have confirmed that Eto exhibits increased antitumor activity when given over several days rather than on a single day (summarized in references 3, 4 and 6). Pharmacokinetic analyses have suggested that continuous or prolonged inhibition of the substrate, i.e. topoisomerase II, may be the key factor in the cytotoxic effects of the enzyme inhibitor Eto. The critical Eto concentration for "adequate" inhibition of topoisomerase II has not been precisely determined, and may vary with the tumor type (for SCLC it appears to be >1 mg/l). On the other hand, some data suggest that high peak levels (i.e. >5–10 mg/l) are most often associated with more severe myelosuppression.

Some authors, however, failed to demonstrate an effect when Eto was administered in different schedules (summarized by Lowis et al. [6]). For example, Mead et al. [9] found no notable differences in the response rates or survival between two arms of their study: 54 previously untreated SCLC patients received a total dose of 500 mg/m^2 either as a single dose or over 5 days combined with doxorubicin and cyclophosphamide. Chatelut et al. [2] found no difference in cytotoxicity for a 72-h continuous infusion of 360 mg/m^2 compared to daily doses of 120 mg/m^2 on three consecutive days. What might be the possible consequences of these inconsistent in vivo findings regarding the development of different new or high-dose schedules?

As the pharmacokinetics of Eto have been reported to be dose-linear, the administration of a uniform Eto dose will lead to a uniform AUC irrespective of the administration schedule. As mentioned above, a four- to fivefold increase over standard dosage of Eto in high-dose chemotherapy in conditioning regimens for bone marrow transplantation is considered to be possible without risking an increase in specific organ toxicity. This four- to fivefold dose increase results in a corresponding four- to fivefold increase in total drug exposure. According to the evidence against schedule dependency, only total dose and intra- and interpatient pharmacokinetic variability have to be considered and might be the subject of pharmacokinetically guided dosing.

On the other hand, the evidence for schedule dependency in the activity of Eto has an important impact on future clinical research. It is not only dose and pharmacokinetic variability, but also the choice between short and continuous infusion or between single and repeated administrations which might have an impact on the efficacy of Eto. Thus, prospective randomized studies with clearly phrased clinical hypotheses need to be performed to develop different new schedules. They should take into account data from expected concentration-time curves and host pharmacokinetics.

For a detailed study of these questions, we applied a validated simulation tool for Eto to calculate concentration-time curves together with confidence intervals for a variety of low- and high-dose schedules.

Methods and materials

Simulation tool for Eto

A simulation tool for Eto [14] was developed combining published individual pharmacokinetic data from 9 children [8] and our own data from 18 children [15]. Both groups received standard i.v. infusions. Eto pharmacokinetics were described by a two-compartment model. Calculated mean pharmacokinetic parameters of this population were: clearance 23.6 ± 4.5 ml/min per m^2, Vc 3.75 ± 0.78 l/m^2, $t_{1/2}\alpha$ 0.7 ± 0.35 h, $t_{1/2}\beta$ 4.1 ± 1.4 h ($n = 27$, means $\pm$ SD). The model was validated by independently reproducing published data for low-dose as well as high-dose regimens, and short-duration as well as continuous i.v. infusions. Clearance was shown to be independent of dose and age. The pharmacokinetic profiles of the drug reported in the literature agreed nicely with the fit of the predictions of the tool regarding duration of exposure above predefined concentrations, peak levels, and concentration at time of bone marrow transplantation after various published schedules.

Based on a population of 27 individual sets of pharmacokinetic parameters, the simulation tool may serve to define concentration-time profiles of high predictive value for different new low-dose and high-dose Eto schedules. The effect of interindividual variation upon exposure times, peak levels and AUC distribution can be studied. Limitations are concerned with the coadministration of other agents that are known to influence Eto clearance significantly, and with renal impairment.

Eto schedules

The commonly used Eto schedule of 150 mg/m^2 over 2 h daily for 3 days, yielding a total dose of 450 mg/m^2, was defined as the standard low-dose regimen. The schedule of 450 mg/m^2 given as a 96-h continuous infusion was selected as a second low-dose schedule. Schedules using 1800 mg/m^2 (four times the standard low dose) administered as 0.5-h, 4-h or 96-h infusions, were defined as high-dose schedules.

Pharmacokinetic parameters of interest were total AUC, peak level, duration of exposure above predefined concentrations (> 1 mg/l, > 10 mg/l) or concentrations in the range of 1–10 mg/l, and AUC related to specific concentration ranges (1–10 mg/l and > 10 mg/l). The calculation of AUC according to specific concentration ranges is shown in Fig. 1.

For all of the parameters, the values calculated for each patient were related to those determined for the standard low dose.

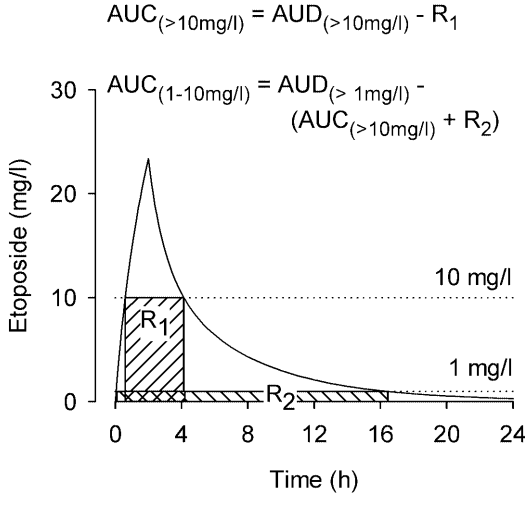

Fig. 1 Calculation of AUC within a given concentration range (*AUD* area under the data, *R* rectangle)

Results

Concentration-time profiles of the different Eto schedules are shown in Fig. 2.

Duration of exposure

The characteristics of drug exposure in predefined concentration ranges are summarized in Table 1 and Fig. 3.

Low-dose schedules

The standard low dose of 150 mg/m^2 over 2 h daily for 3 days led to peak levels of 23.4 ± 3.0 mg/l and a duration of 10.7 ± 2.6 h with exposures > 10 mg/l, 47.9 ± 9.8 h with > 1 mg/l, and 37.2 ± 8.4 h in the range 1–10 mg/l. When the same total dose of 450 mg/m^2 was given as a continuous i.v. infusion (96 h), the steady-state concentration of 3.4 ± 0.7 mg/l was clearly below 10 mg/l, i.e. the possibly critical concentration setting off myelotoxicity. The duration of exposures > 1 mg/l and – as no patient showed concentrations > 10 mg/l – also 1–10 mg/l was about twice as long as after the standard low dose (factor 2.2 ± 0.4 and 2.8 ± 0.6).

High-dose schedules

With respect to Eto high-dose regimens, we focused on continuous i.v. infusion and short-duration infusion of a dose four times the standard low dose. Peak levels and the results for duration of exposure were quite different from those with the standard low dose, and were a function of infusion time. Continuous i.v. infusion of 1800 mg/m^2 led to a concentration at steady state of 13.8 ± 2.8 mg/l. The duration of exposures > 10 mg/l was 7.9 ± 2.6 times, and > 1 mg/l still 2.3 ± 0.4 times, longer than after the standard low dose, and exposures in the range 1–10 mg/l was shorter than after the standard low dose (factor 0.7 ± 0.8).

The most prominent change in pharmacokinetic behavior after short-duration infusion of high dose Eto compared to the standard low dose was the resulting high peak level (0.5 h infusion 17.6 ± 1.5 times higher, 4 h infusion still 8.7 ± 0.4 times higher). The duration of exposures > 10 mg/l was longer, and exposures > 1 mg/l and in the range 1–10 mg/l shorter, than after the standard low dose (with the 0.5-h infusion, factors 1.6 ± 0.3, 0.6 ± 0.1 and 0.4 ± 0.1; with the 4-h infusion, factors 1.7 ± 0.4, 0.7 ± 0.1 and 0.4 ± 0.1).

Area under curve

The characteristics of AUC in predefined concentration ranges are shown in Table 1 and Fig. 4.

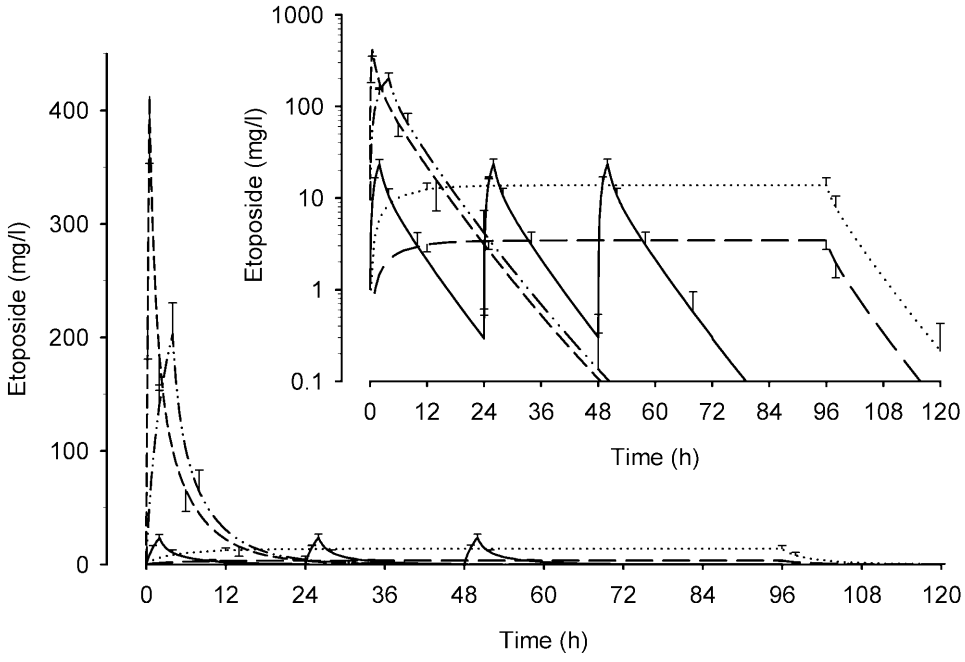

Fig. 2 Concentration-time profiles after different Eto schedules. Simulations based on a simulation tool [14]. Values are means ± SD (*solid line* 150 mg/m^2 over 2 h daily for 3 days, *long dashes* 450 mg/m^2 over 96 h, *short dashes* 1800 mg/m^2 over 0.5 h, *dash dot dot dash* 1800 mg/m^2 over 4 h, *dots* 1800 mg/m^2 over 96 h)

Table 1 Simulation of different low-dose and high-dose Eto schedules showing peak levels, total AUC, duration of exposure and AUC within different concentration ranges. Values are means ± SD

	Standard low dose (150 mg/m^2 3 days)	Low dose (450 mg/m^2)	High dose (1800 mg/m^2)		
Infusion time (h)	2	96	0.5	4	96
Peak level (mg/l)	23.4 ± 3.0	3.4 ± 0.7	412 ± 58.8	203 ± 27.5	13.8 ± 2.8
Exposure duration (h)					
> 1 mg/l	47.9 ± 9.8	100 ± 2.4	29.8 ± 6.5	31.6 ± 6.5	109 ± 3.9
1–10 mg/l	37.2 ± 8.4	100 ± 2.4	13.6 ± 4.1	13.6 ± 4.1	25.2 ± 23.3
> 10 mg/l	10.7 ± 2.6	0	16.2 ± 3.4	18.0 ± 3.4	83.7 ± 24.4
AUC (mg/l·h)					
Total	331 ± 68		1322 ± 270		
1–10 mg/l	201 ± 44	224 ± 65	185 ± 38	202 ± 38	879 ± 26
> 10 mg/l	68 ± 24	0	1101 ± 236	1083 ± 236	328 ± 242

Low-dose schedules

The standard low dose of 150 mg/m^2 over 2 h daily for 3 days led to a total AUC of 331 ± 68 mg/l·h, i.e. an AUC of 201 ± 44 mg/l·h for exposures in the range 1–10 mg/l and an AUC of 68 ± 24 mg/l·h for exposures > 10 mg/l. After low-dose continuous i.v. infusion (96 h), the AUC for exposures in the range 1–10 mg/l was almost equal to that with the standard low dose (factor 1.1 ± 0.1). With the peak exposure for all patients below 10 mg/l there was no drug exposure of > 10 mg/l.

High-dose schedules

As Eto clearance is independent of dose, all high-dose schedules showed a complementary fourfold increase in total AUC with a fourfold dose increase over the standard low dose (1322 ± 270 mg/l·h). However, AUCs in predefined concentration ranges were quite different, and were a function of infusion time. Continuous i.v. infusion of a dose four times the standard low dose led to an almost proportional increase in AUC in the range 1–10 mg/l (factor 4.5 ± 0.8) and > 10 mg/l (factor 4.5 ± 2.6).

With short-duration infusion of high-dose Eto, pronounced alterations in pharmacokinetic behavior were found not only for peak levels but also for AUC > 10 mg/l. With the 0.5-h infusion the AUC > 10 mg/l was 17.5 ± 4.9 times higher and with a 4-h infusion it was still 17.2 ± 4.8 times higher than after the standard low dose. With the 0.5-h infusion, 83 ± 2.4% of the total AUC of the appropriate high-dose schedules was > 10 mg/l, and with the 4-h infusion, the percentage was still 82 ± 2.4%. With both of these short infusion times, the proportion of AUC in the range 1–10 mg/l was about equal to that with the standard low dose (0.5-h infusion, factor 0.9 ± 0.1; 4-h infusion, factor 1.0 ± 0.1).

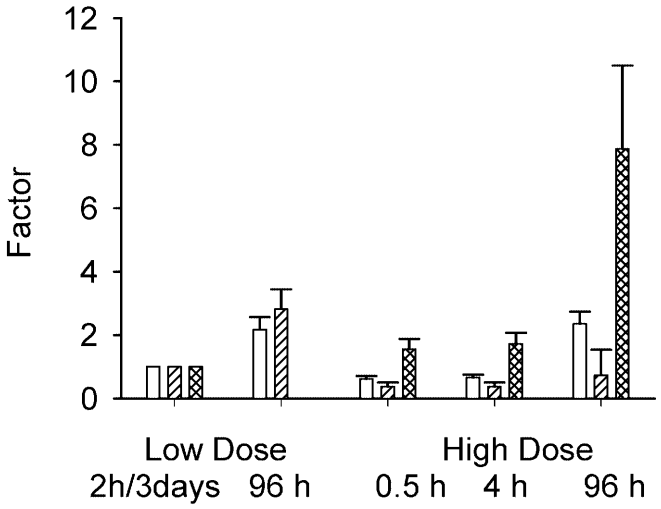

Fig. 3 Simulation of different Eto schedules. Duration of exposure above or within predefined concentration ranges, expressed as a factor in relation to the standard low dose of Eto (150 mg/m^2 over 2 h daily for 3 days). Values are means ± SD. Low dose 450 mg/m^2, high dose 1800 mg/m^2 for different infusion time (*open bars* exposure > 1 mg/l, *hatched bars* exposure 1–10 mg/l, *cross-hatched bars* exposure > 10 mg/l)

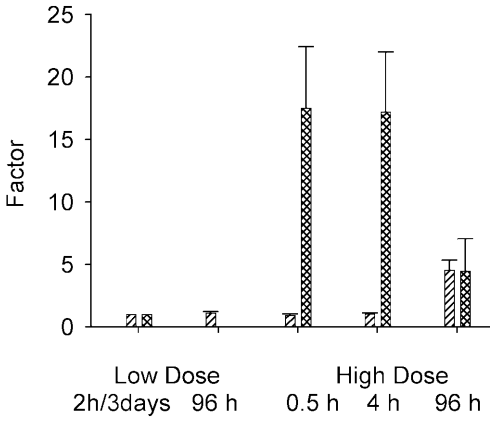

Fig. 4 Simulation of different Eto schedules. AUC above or within predefined concentration ranges, expressed as a factor in relation to the standard low dose of Eto (150 mg/m^2 over 2 h daily for 3 days). Values are means ± SD. Low dose 450 mg/m^2, high dose 1800 mg/m^2 for different infusion time (*hatched bars* AUC 1–10 mg/l, *cross-hatched bars* AUC > 10 mg/l)

Discussion

The pharmacological basis for high-dose chemotherapy is limited. There are a few reports of phase I studies on single-drug dose escalation or drug combination dose-finding trials, or providing reliable definitions of the maximum tolerated dose. Phase II studies optimizing dose schedules in a systematic fashion or evaluating pharmacokinetic-pharmacodynamic relationships (dose response) are few and far between. This observation might be explained by the rapid development of stem cell technology and bone marrow transplantation combined with the fact that only a small number of patients are treated with high-dose chemotherapy rather than "standard treatment".

Pharmacokinetic characteristics of Eto

For Eto, a linear relationship between AUC and dose is observed. Thus, a four- to fivefold dose escalation from low dose to high dose leads to an equivalent increase in total drug exposure. According to the evidence against schedule dependency, the increase in the total dose together with the inter- and intraindividual variability of Eto would be the only acceptable rationales for Eto dosing.

On the other hand, some in vivo studies have indicated the potential impact of the administration schedule in enhancing the efficacy of Eto (summarized in references 3, 4 and 6). The simulations performed in the present study pointed to the fact that high-dose schedules offer the alternatives of focusing on excessive peak concentrations, on extended times of predefined standard drug concentrations, or on AUCs in predefined concentration ranges. Extreme schedules of high-dose Eto might result in maximum peak levels of up to 500 mg/l by rapid infusion. On the other hand, maximum time of exposure > 1 mg/l can be achieved by continuous i.v. infusion of 1800 mg/m^2 over 55 ± 11 days!

Based on the pharmacological hypotheses, one might be able to choose between quite different Eto schedules, depending on whether high peak levels or a long duration of exposure above predefined plasma concentrations are desired. Table 2 summarizes some of these pharmacological "intent to treat" options. "High-dose"

Table 2 High-dose or low-dose chemotherapy? The pharmacological "intent to treat"

What do we intend?	What do we have to do?	Example
High peak level	High-dose infusion as short as possible	High-dose bolus: peak level 500 mg/l
Long duration of exposure > 10 mg/l	High-dose continuous i.v. infusion	High-dose 130-h infusion: steady-state level 10 mg/l
Long duration of exposure in the range 1–10 mg/l	Repeated short-duration infusion or repeated oral administration or continuous i.v. infusion	Standard low dose: 2-h infusion daily for 3 days
Long duration of exposure to 1 mg/l	Continuous i.v. infusion	High-dose 55-day infusion or low-dose 14 day infusion: steady state level 1 mg/l
Large proportion of AUC > 10 mg/l	High-dose short-duration infusion	High-dose 0.5-h infusion: 82% of total AUC > 10 mg/l

chemotherapy following the sole principle of "more is better" cannot be a reasonable strategy. The simulation tool enabled us to predefine pharmacokinetic profiles for new Eto schedules over a wide range. Based on these profiles, Eto-containing regimens should be designed on the basis of target levels and exposure times derived from clear pharmacokinetic hypotheses, to allow the subsequent development of pharmacokinetic-pharmacodynamic modeling and schedules optimized to fit the clinical situation.

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