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Pharmacodynamics of cancer chemotherapy: childhood ALL as a model

William E. Evans*

Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital and Center for Pediatric Pharmacokinetics and Therapeutics, Colleges of Pharmacy and Medicine, University of Tennessee, 332 N. Lauderdale, P.O. Box 318, Memphis, TN 38101-0318, USA

Abstract

Several anticancer drugs have characteristics that make them excellent candidates for dosages individualized based on pharmacological principles, including substantial pharmacokinetic variability and a narrow therapeutic index. Concentration–effect relationships (pharmacodynamics) for many antineoplastic agents have not been well defined, thus limiting the widespread clinical application of pharmacokinetically guided dosing. However, strategic incorporation of pharmacokinetic studies in phase I–III clinical trials has begun to more clearly define these concentration–effect relationships and elucidate clinically important levels of treatment intensity, to either avoid toxicity, enhance efficacy, or both. Clinical, cellular and pharmacogenetic studies have defined pharmacodynamic relationships for several anticancer agents in children with acute lymphoblastic leukemia, including methotrexate, mercaptopurine, teniposide, etoposide, and topotecan. Results of a prospective, randomized clinical trial of conventional vs. individualized dosing of cancer chemotherapy in children with acute lymphoblastic leukemia established the potential clinical benefits of individualized dosing of cancer chemotherapy. These findings were corroborated by the recent observation that concomitant therapy with enzyme-inducting anticonvulsants increases the clearance and decreases the efficacy of acute lymphoblastic leukemia (ALL) chemotherapy.

Keywords: Pharmacodynamics; Antileukemic agents; Childhood ALL

* Tel.: +1-901-495-3663; fax: +1-901-525-6869.
E-mail address: william.evans@stjude.org (W.E. Evans).

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1. Introduction

Anticancer drugs typically have a narrow therapeutic index, such that maximum efficacy often requires dosages that produce plasma concentrations near those that are toxic. This, coupled with highly variable pharmacokinetics of most antineoplastics, makes cancer chemotherapy an ideal class of agents for dosage individualization based on pharmacokinetic and pharmacodynamic principles [1–4]. This review focuses on the clinical pharmacokinetics and pharmacodynamics (PK/PD) of antileukemic agents in children, to illustrate the potential utility of PK/PD-strategies in optimizing chemotherapy for disseminated malignancies.

1.1. Concentration–effect relationships with anticancer drugs

Clinical data began to accumulate in the 1980s, indicating that response rates of several drug sensitive cancers were directly related to the dose or "dose-intensity" of anticancer agents [5]. The concept of "dose-intensity" was subsequently expanded to include the element of time over which a cumulative dose was administered (e.g. mg/m^2 per week), acknowledging that delays in drug therapy may allow tumor re-growth, thereby compromising antineoplastic efficacy [6,7]. It was a logical extension to postulate that for drugs and diseases where dose-intensity is important, using PK/PD principles to control systemic dose-intensity (e.g. AUC) might be a better metric of treatment intensity. Childhood acute lymphoblastic leukemia (ALL) is a disseminated cancer where clinical studies have now shown that chemotherapy fails to cure some patients because they have inadequate systemic exposure to antileukemic agents due to fast drug clearance, and not because their leukemia is de novo resistant.

2. Why anticancer drugs are good candidates for PK/PD dosing

2.1. Highly variable pharmacokinetics

Substantial pharmacokinetic variability is evident for virtually all antineoplastic agents in humans. This variability may occur for numerous reasons, including patient-specific differences attributable to age, gender, changes in organ function, drug interactions, genetic regulation of drug metabolism, disease status, and other clinical or demographic factors. Drug disposition appears to differ broadly between adult and pediatric or geriatric populations, with considerable interpatient and intrapatient variability. Even in the absence of clinically apparent organ dysfunction, drug clearances within a relatively similar population of patients differ as much as 3–10-fold for methotrexate, etoposide, teniposide, doxorubicin, cyclophosphamide, carboplatin, mercaptopurine and bleomycin [3,8–11]. Our experience in children is that intrapatient variability (CV%) for drug clearance is consistently less than the interpatient CV%. This is not unexpected, as changes within an individual are not influenced by genetic differences that exist across a population. An obvious consequence of pharmacokinetic variability is that the administration of a uniform dose (mg/kg or mg/m^2 dosage) of drug

to different patients will produce systemic drug exposures which also range according to the variability in drug clearance.

2.2. Anticancer drug effects are often related to systemic exposure to antineoplastics

Extracellular drug concentration–effect relationships have been observed for many antineoplastics, especially as it relates to dose-limiting toxicity. However, efforts to establish concentration–effect relationships for anticancer *efficacy* are more limited, and this has been impeded by study designs which do not adequately assess the importance of drug concentrations in determining clinical efficacy. Another practical difficulty in defining antineoplastic pharmacodynamics has been the lack of reliable methods by which one can accurately detect or quantitate in vivo tumor response. Fortunately, technologic advances in tumor imaging, tumor marker assays, and detection of minimal residual disease have improved the ability to objectively assess the effects of anticancer drugs. Within the past decade, pharmacokinetic studies have been more widely incorporated into cancer treatment protocols, and pharmacodynamic relationships have been elucidated for a number of antineoplastic agents, including the examples listed in Table 1. It is anticipated that over the next decade, a target concentration range will become more clearly defined for many anticancer drugs. Once accomplished, this should facilitate more widespread clinical implementation of PK/PD strategies in dosing cancer chemotherapy. The ultimate goal for cancer therapy is to develop agents that specifically target cancer cells and not normal tissues, but this will likely remain a goal and not reality for most tumors, in the foreseeable future.

2.3. Most antineoplastics have a narrow therapeutic window

Because most currently available antineoplastics do not exert their pharmacologic effects selectively on malignant cells, the majority of anticancer agents produce potentially significant toxicities in at least a small percentage of patients. Antineoplastic toxicities often involve organ systems with rapid tissue or cell turnover (epithelial, gastrointestinal, hematopoietic), although renal, hepatic, neurologic and pulmonary tissues may also be damaged by anticancer agents or their metabolites. The spectrum of drug toxicity can also be influenced by the administration schedule, in addition to systemic exposure. For example, when 5-fluorouracil is given as an i.v. bolus, bone marrow suppression may become dose-limiting, whereas the same total dose given as a protracted infusion, may produce little hematopoietic toxicity, but significant mucositis and diarrhea [43,44].

Furthermore, maximal antineoplastic exposure is not always synonymous with maximal therapeutic efficacy. When excessive toxicity necessitates a delay of subsequent therapy, the optimization of *delivered* therapeutic intensity may actually entail dosage reductions [45]. For example, Santini [27] has demonstrated in head and neck cancer patients, that the prevention of excessive fluorouracil exposure (AUC or Cp_{ss}) and its associated toxicities during each dosing cycle could reduce the overall number of therapy delays, ultimately preserving adherence to intended protocol dose intensity and improving response rates. Relling et al. showed that when therapy with MP is too intensive, it may

Table 1
Selected clinical studies demonstrating pharmacokinetic–pharmacodynamic relationships for cancer chemotherapy

Drug	Pharmacokinetic parameter	Pharmacodynamic relationship	References
Amsacrine (AMSA)	CL	Granulocytopenia	[12]
Carboplatin	AUC (Plasma)	Thrombocytopenia	[13–15]
	AUC (Plasma	Thrombocytopenia, leukopenia;	[14]
		Ovarian Ca response;	[16]
		Germ cell tumor response	
Cisplatinum	Cp (total) at 12 and 24 h	Nephrotoxicity	[17]
Cytarabine	Intracellular Ara-CTP (ANLL in vitro)	Complete remission (% achieving, duration)	[18–21]
Etoposide	Cp_{ss}	Leukopenia	[22]
	AUC (Unbound)	Leukopenia	[23]
5-Fluorouracil	AUC (Plasma)	Leukopenia, thrombocytopenia	[24]
	AUC (Plasma; total cycle)	Toxicity: mucositis, diarrhea, leukopenia, anemia	[25]
	AUC (Plasma; dose-normalized)	Hepatic metastasis retardation	[26]
	CL and Cp_{ss}	Leukopenia, stomatitis	[27–29]
	CP_{ss}	Response in Head and neck cancer	[30]
Hexamethylene bisacetamide	AUC, Cp_{ss} (and duration), Cp_{max}	Neurotoxicity, acidosis, thrombocytopenia	[31]
Mercaptopurine	RBC metabolite (TGN)	(TGN) Leukopenia	[32]
		ALL Relapse-free survival	[33]
Methotrexate (HD)	CL	ALL Relapse	[34,35]
	Cp_{ss}	ALL Relapse-free survival	[36,37]
	Cp at 48 h	Toxicity: mucositis, nephrotoxicity, myelosuppression	[38,39]
Teniposide	CL, Cp_{ss} (total plasma)	Oncolytic response (leukemia, solid tumor); mucositis	[40]
	AUC (unbound)	Leukopenia	[41]
	AUC (total)	Mucositis	[11,40]
Vincristine	AUC (plasma; cumulative)	Neurotoxicity	[42]

ALL = Acute Lymphoblastic Leukemia; CL = systemic clearance; Cp_{ss} = plasma steady-state concentration; AUC = area under the concentration vs. time curve; HD = High-dose.

compromise efficacy by decreasing the number of weeks during which MP and other chemotherapy can be given to children with ALL [45].

2.4. Additional considerations for anticancer drugs

In clinical practice, most antineoplastics are utilized in conjunction with other drugs, or treatment modalities. It can be difficult to correctly identify the causative agent, if patients are being treated with multiple agents that produce similar toxicities (e.g., bone marrow suppression, mucositis). Empirically, clinicians often resort to "across the board" dosage reductions, potentially compromising the therapeutic intensity of several agents, in order to compensate for excessive activity of a single component of the regimen. Drug-specific measures of cytotoxic and/or toxic effects might help to ascribe toxicity to the correct

drug; unfortunately, the spectrum of toxicities is usually overlapping among anticancer agents. Assuming concentration–effect relationships are well defined, PK/PD strategies could improve the clinical management of toxicity encountered in combination chemotherapy regimens, by providing a more objective basis for decisions to increase or decrease the dose of individual drugs. Also, this could help to identify chemotherapeutic agents being substantially underdosed, or medications that are not being taken due to poor patient compliance.

Cytarabine, methotrexate and mercaptopurine exemplify agents whose hematotoxic effects may be more closely linked to the intracellular accumulation of their active metabolites, Ara-CTP [18,46–49], methotrexate polyglutamates (MTX-PG) [50,51] and thioguanine nucleotides (TGN) [32,52,53], respectively, than to parent drug concentration in plasma. In the case of mercaptopurine, red blood cell TGN concentrations have served as surrogate markers for drug concentrations in normal and malignant cells, which have correlated directly with the occurrence of neutropenia [54], and inversely with ALL relapse [33]. Likewise, MTX-PG concentrations in ALL blasts have been associated with the intensity of antileukemic effects in patients [50], as has Ara-CTP accumulation and retention in AML blasts [47].

3. PK-dosing of anticancer agents

3.1. Methotrexate in acute lymphoblastic leukemia

Systemic clearance of HDMTX is highly variable among children with normal renal and hepatic function (>5-fold range), resulting in a corresponding range of systemic exposure if all patients are treated with the same dose of HDMTX [55]. This raised the question of whether lower systemic exposure to methotrexate may influence event free survival (EFS) in children with ALL. To this end, studies at St. Jude Children's Research Hospital (SJCRH) and subsequently the Pediatric Oncology Group (POG) have found a greater risk of ALL relapse in children with B-lineage ALL who have more rapid systemic clearance of high-dose (1000 mg/m^2) methotrexate (Figs. 1 and 2) [34,36,37]. These findings led to the observation that children with lower exposure to methotrexate (e.g., steady-state plasma concentration <16 μM during a 24-h infusion of 1000 mg/m^2 HDMTX) had a worse outcome (i.e. continuous complete remission, CCR) (Fig. 3) [36,37]. More recently, Seidel also observed that children with ALL who have faster methotrexate clearances have a worse outcome [56].

The SJCRH Total X protocol prospectively randomized 108 children with standard-risk ALL to receive 15 doses of HDMTX (1000 mg/m^2 over 24 h) as part of post-remission therapy [36]. Leucovorin rescue consisted of 30 mg/m^2 intravenously at 36 and 42 h followed by 3 mg/m^2 orally at 54, 66 and 78 h (total=69 mg/m^2) after the start of the HDMTX infusion. Methotrexate clearance was not related to the duration of therapy or total number of doses administered. Interpatient differences in methotrexate clearance resulted in large variability in the steady-state methotrexate serum concentration (range of *median* steady-state methotrexate serum concentration among patients=9.3 to 25.4 μM). Patients whose median steady-state methotrexate serum concentration was <16 μM

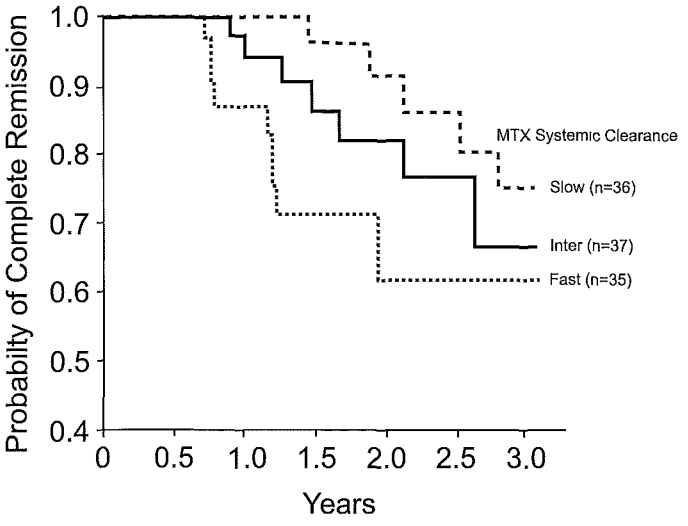

Fig. 1. Kaplan–Meier plots of complete remission durations according to the media rate of methotrexate clearance in three groups of patients (slow, 44.7–71.9 ml/min/m^2, $n=36$; intermediate, 72–83 ml/min/m^2, $n=37$; and fast, 84–132 ml/min/m^2, $n=35$). Statistical comparisons showed a significant difference between the fast-and slow-clearance groups ($P=0.01$), but the differences between the fast-and intermediate-clearance ($P=0.30$) and the slow-and intermediate-clearance ($P+0.07$) groups were not significant. (Reprinted with permission from W.E. Evans, W.R. Crom, D.F. Stewart, et al., Lancet 1 (8373) (1984) 359–362).

($n=59$) were 3.2 times more likely to relapse at any site (hematologic, CNS, or testes) and 6.9 times more likely to have a hematologic relapse at 3.5 years, compared to patients with median steady-state methotrexate serum concentrations ≥ 16 μM ($n=49$).

In the Pediatric Oncology Group study (protocol 8698), newly diagnosed higher-risk B-precursor ALL patients ($n=80$) received HDMTX (1000 mg/m^2) administered over 24 h (biweekly) in a 24-week intensification therapy following remission induction therapy [37]. However, leucovorin rescue was reduced to 5 mg/m^2 (intravenously or orally) every 6 h for five doses (total=25 mg/m^2) starting 48 h after the start of the HDMTX infusion. The median steady-state methotrexate serum concentration during HDMTX infusions was 11 μM in this study, a value lower than the median in the SJCRH protocol [34]. The 4-year EFS was 57.4% in the POG study and was significantly related to the level of systemic exposure to methotrexate. Relapse occurred in 59% of patients (20 of 34) with a median steady-state methotrexate serum concentration less than the population median (11 μM), compared to 33% of patients (three of nine) with a steady-state methotrexate serum concentration equal to the median of 11 μM (Fig. 3), and in only 14% of patients (5 of 37) with median steady-state methotrexate serum concentrations greater than 11 μM [37]. These findings thus corroborate the SJCRH data, indicating a relation between relative systemic methotrexate exposure and efficacy in childhood ALL. It is not surprising that the precise methotrexate concentration with prognostic importance differed in the St. Jude and POG studies (16 μM vs. 11 μM), because other treatment variables were different (e.g. leucovorin dose, hydration, other therapy, etc.). In this regard, the leucovorin rescue dose was 69 mg/m^2 in the SJCRH protocol vs. 25 mg/m^2 in the POG 8698 protocol, thus it is

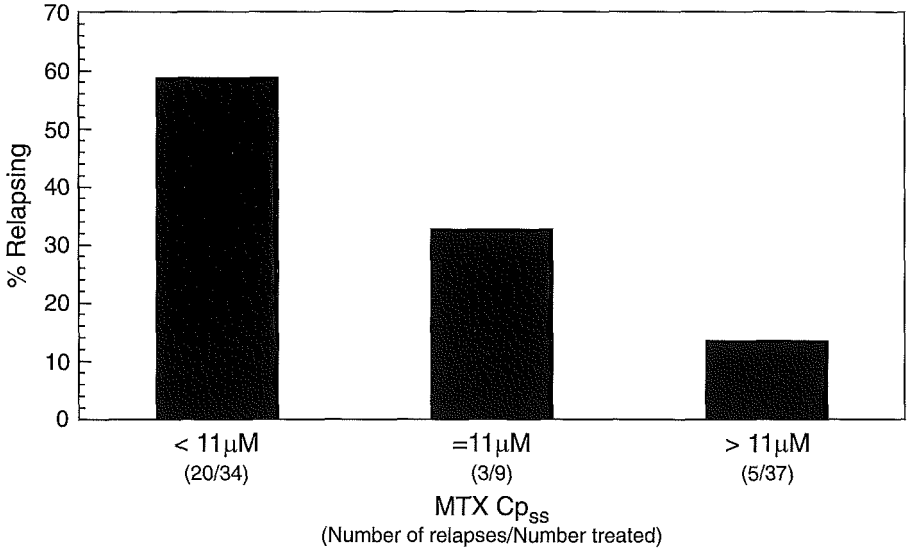

Fig. 2. Relation of systemic methotrexate clearance to leukemic relapse in children with higher-risk non-T, non-B ALL treated on POG 8698 protocol, as described by Camitta et al. [37]. Patients were subdivided by whether their median steady-state methotrexate plasma concentrations were less than the population median (<11 μM, $n=34$), equal to the population median (11 μM, $n=9$), or greater than the population median (>11 μM, $n=37$). The bars represent percentages of patients relapsing in the three subgroups, after comparable durations of follow-up (approximately 4 years). (Reprinted with permission from W.E. Evans, M.V. Relling, J.M. Boyett, et al., Leukocyte Res. 21 (5) (1997) 435–437).

not surprising that the methotrexate exposure level associated with better outcome was higher in the St. Jude protocol (16 vs. 11 μM).

3.2. Optimizing MTX-PG in target tissues (e.g., ALL blasts), in vivo

Whitehead et al. showed that decreased MTXPG formation in ALL blasts may be predictive of a worse clinical outcome [57], reporting that children with B-lineage ALL experienced a better 5-year EFS (65% vs. 12%; $P=0.01$) if their leukemic blasts accumulated higher concentrations of MTXPG (>500 pmol methotrexate polyglutamates/10^9 lymphoblasts) after in vitro incubation with 1 μM methotrexate. To determine whether the extracellular MTX concentration is an important determinant of MTXPG accumulation in ALL blasts in vivo, we measured MTXPG concentrations in leukemia cells from patients randomized to single-agent treatment with HDMTX vs. LDMTX [51]. At 44 h after methotrexate administration, significantly higher concentrations of long-chain MTXPG were achieved in ALL blasts of patients treated with HDMTX (1000 mg/m^2) compared to children treated with LDMTX (986 vs. 355 pmol methotrexate polyglutamates/10^9 lymphoblasts; $P=0.0001$). Eighty-four percent of patients with B-lineage ALL receiving HDMTX exceeded the minimum intracellular MTXPG concentration associated with a favorable outcome by Whitehead et al. [57] (>500 pmol/10^9 blasts), compared to only 64% of B-lineage ALL patients receiving

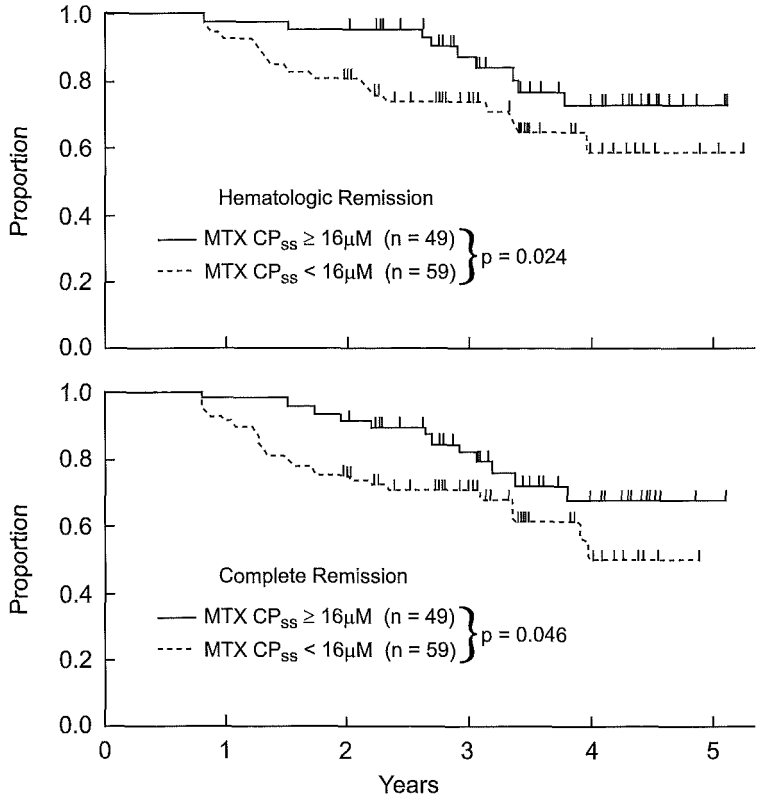

Fig. 3. Kaplan–Meier curves of hematologic remission (upper panel) and complete remission (lower panel) for childhood acute lymphocytic leukemia patients with median steady-state methotrexate plasma concentrations <16 and >16 μmol/l, following 1 g/m^2 i.v. methotrexate. (Reproduced with permission from Evans et al. [36]).

LDMTX. Furthermore, none of the patients with T-lineage leukemia had ALL blast MTXPG>500 pmol/10^9 blasts when treated with LDMTX, whereas 75% (three of four patients) had MTXPG >500 pmol/10^9 blasts when treated with HDMTX. In addition, 82% (28 of 34 patients) of the non-hyperdiploid (<50 chromosomes) B-lineage ALL patients had ALL blast MTXPG >500 pmol/10^9 blasts when treated with HDMTX, compared to only 53% (17 of 32 patients) of non-hyperdiploid B-lineage ALL patients treated with LDMTX.

Subsequently, we observed that greater lymphoblast accumulation of MTXPG was associated with evidence of greater acute antileukemic effects in children with newly diagnosed B-lineage ALL [50]. Patients who had complete clearing of circulating blasts within 4 days of single-agent treatment had significantly higher MTXPG concentrations in their blasts at 44 h (2793 vs. 602 pmol/10^9 blasts, $P=0.0039$). Moreover, the estimated $MTXPG_{4-7}$ concentration needed to inhibit de novo purine synthesis by 95% (>483 pmol/10^9 blasts) was more likely to be achieved in vivo by administration of HDMTX compared with LDMTX, 81% vs. 46%, respectively ($P<0.0001$) [50].

3.3. Topoisomerase II inhibitors: teniposide and etoposide

Teniposide and etoposide are topoisomerase II inhibitors with activity against childhood ALL and other malignancies in pediatric and adult populations. Initial pharmacokinetic studies demonstrated that teniposide clearances can range 10-fold within a pediatric population [11,58,59]. Variability in teniposide disposition may result from interpatient differences in liver function, disease status, protein-binding and concomitant therapies [9–11,41,58–62].

In a Phase I/II trial [40], the pharmacodynamics of continuous infusion teniposide were assessed as a determinant of toxicity and oncolytic response in children with ALL, lymphoma, or neuroblastoma. The systemic clearance of teniposide ranged approximately 10-fold, resulting in a 10-fold range of systemic exposures (Cp_{ss} and AUC), among patients within the same dosage level. As a consequence, the ranges of corresponding Cp_{ss} and AUC overlapped extensively across dosage levels, meaning that higher doses did not always produce greater systemic exposure. Importantly, systemic exposure (Cp_{ss}) was found to be significantly higher in responding (15.2 ± 7.4 mg/dl) vs. non-responding patients (6.2 ± 2.8 mg/dl; $P < 0.005$); regardless of the dose administered. The incidence of severe mucositis also increased in association with escalating systemic exposure and extent of pretreatment. An intermediate serum concentration was identified at which the probabilities of both oncolytic response and of toxicity were acceptable (Fig. 4), serving as a target level of teniposide exposure for evaluation in subsequent Phase II–III studies [63].

Both teniposide and etoposide undergo extensive hepatic metabolism and/or biliary excretion. Although the systemic clearance of total (bound and unbound) epidophyllotoxin has shown variable relation to clinical "indices" of hepatic function, such as elevation of alkaline phosphatase and serum transaminases, the intrinsic (i.e., unbound) clearance of

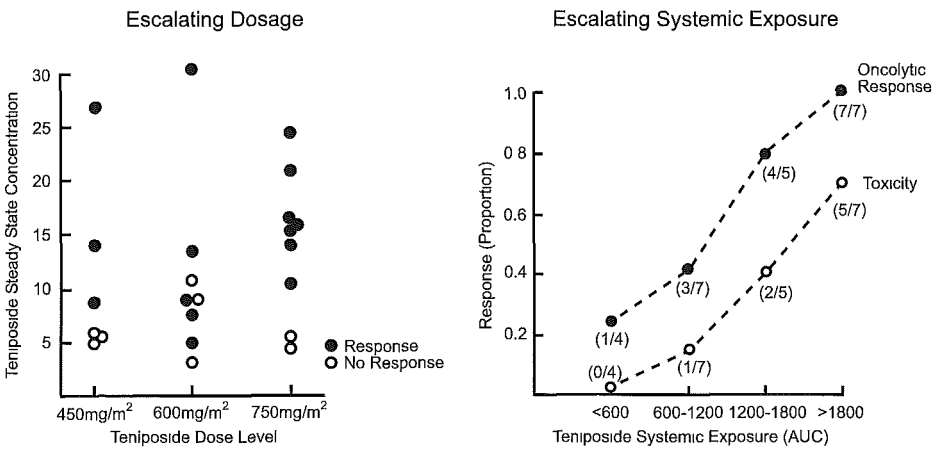

Fig. 4. Left side: steady-state teniposide concentrations at three incremental dose escalations depicting wide variability, and considerable overlap among groups, due to pharmacokinetic variability. Right side: relation of systemic teniposide exposure, irrespective of dose, and the proportion of patients experiencing therapeutic or toxic effects. (Adapted, with data from Ref. [40]). Reproduced with permission from Clinical Chemistry [1].

both drugs is lower in patients with hyperbilirubinemia. The combination of hypoalbuminemia and hyperbilirubinemia in the context of hepatic dysfunction, not uncommon in the oncology population, may produce concomitant changes in protein-binding and metabolism, such that exposure to unbound drug is increased, yet plasma concentrations of *total* drug are unchanged [41,61]. For both etoposide and teniposide, increased exposures to free drug (unbound AUC) have been associated with greater degrees of hematopoietic toxicity [41,61].

In a randomized study of 45 adult patients, Ratain et al. [64] prospectively individualized etoposide doses in a manner designed to target leukocyte nadirs (the previous "dose-limiting" toxicity). Their pharmacodynamic model incorporated etoposide serum concentration and patient specific factors, including pretreatment albumin values, performance status, and transfusion requirements. As a consequence of reducing interpatient variability in the leukopenic nadir, the mean delivered etoposide dose was successfully increased 22% above the fixed dosage regimen, without a concomitant increase in the incidence of grade 4 neutropenia or unacceptable infectious complications. Although assessment of antitumor response was not a primary objective, this study validates a methodology able to decrease the incidence of "underdosing", which might otherwise compromise Phase II efficacy evaluations in patient populations. These authors also evaluated the clinical practicality of this approach, and concluded that optimization of etoposide based on PK data from the first dose was sufficient and not significantly improved by PK assessments of subsequent doses. However, this conclusion cannot always be generalized to agents associated with greater intrapatient pharmacokinetic variability, for which follow-up serum sampling and Bayesian approaches may substantially improve dosage individualization [65].

3.4. Mercaptopurine, intracellular TGN, leukopenia and outcome in ALL

Mercaptopurine is a cytotoxic agent utilized primarily in the maintenance therapy of ALL, and is a prodrug which undergoes extensive intracellular biotransformation to its active metabolites. The cytotoxic effect of mercaptopurine is primarily attributed to its 6-thioguanine nucleotides (TGN) metabolites, the intracellular accumulation of which is determined by the activities of competing pathways of enzymatic metabolism [52,53,66,68]. The activity of thiopurine methyltransferase (TPMT), one of the enzymes largely responsible for inactivation of mercaptopurine (in addition to xanthine oxidase), is inherited as an autosomal codominant trait, with 1 in 300 individuals inheriting a deficiency in TPMT activity [66,68]. Because TPMT is the predominant inactivation pathway in hematopoietic tissues, where xanthine oxidase is negligible, individuals deficient in TPMT activity accumulate higher intracellular concentrations of TGN, because more MP is available for activation through alternate paths of biotransformation [67]. Clinical studies have shown that TPMT deficient patients will develop extensive MP toxicity, unless substantial MP dosage reductions are made [69,70].

Considerable pharmacokinetic variability has been observed, not only in the plasma concentrations of parent MP following oral administration, but also in the intracellular accumulation of active metabolites at a given level of plasma exposure [32,33,58]. Erythrocytes are generally accepted as an adequate surrogate for assessing the chronic

intracellular accumulation of TGN in normal and leukemic cells, largely because leukemic blasts are not available after the first 4–6 weeks of ALL therapy. Correlations between MP dose (or plasma pharmacokinetics) and hematopoietic toxicity have generally been poor or absent [32,33,71,72], while pharmacodynamic studies in childhood ALL have demonstrated strong correlations between erythrocyte TGN levels and both toxic and therapeutic responses (Fig. 5). Patients who accumulate relatively high levels of erythrocyte TGN are at greater risk of experiencing neutropenia [54], whereas children with ALL who have low erythrocyte TGN concentrations may have a higher probability of disease relapse [33].

Several treatment protocols for childhood ALL titrate MP dosage to the point of acceptable neutropenia; however, the majority of regimens utilize combinations of myelosuppressive chemotherapy, making it difficult or impossible to determine which drug is being dosed excessively. In addition, these regimens often limit the maximum MP dose that can be given, which may prevent the accumulation of adequate intracellular TGN, potentially placing patients at an increased risk of relapse. Routine screening for TPMT activity is feasible and can help to identify subsets of patients at increased risk for excessive accumulation of TGN, which is a significant determinant of toxicity for the 10% who are TPMT heterozygotes and the 0.33% who are TPMT-deficient [73,74]. Monitoring erythrocyte TGN concentrations, in conjunction with WBC counts, is also a rational approach to individualizing MP dosage requirements in ALL combination

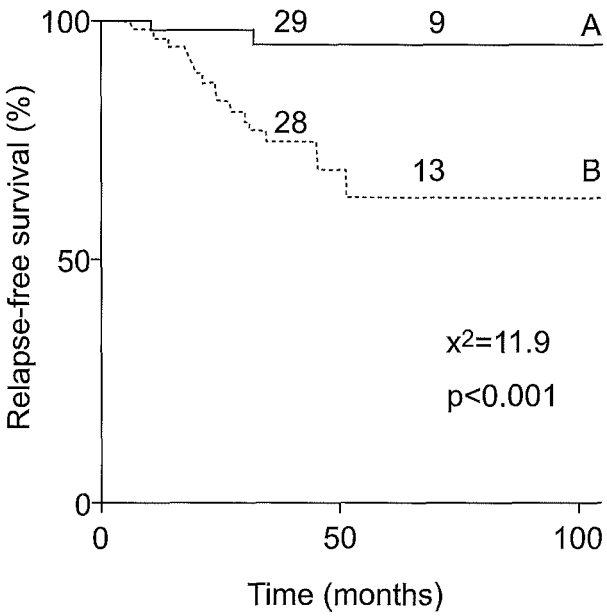

Fig. 5. Actuarial relapse-free survival, from the start of mercaptopurine therapy, for 120 children with ALL; curve A depicts patients with RBC concentrations of mercaptopurine active metabolites (6TGN) above the median (285 pmol/8·10^8 RBCs); curve B depicts patients with RBC below the median. Numbers indicate the proportion remaining at risk, at the time of analysis (reproduced with permission from Lennard and Lilleyman [33]).

regimens; these endpoints may also provide useful information for assessing oral absorption and or compliance.

3.5. A randomized test of PK-dosing in childhood ALL

Subsequent to the above findings, a prospective randomized trial was conducted to assess the clinical benefit of individualizing the dose of HDMTX, teniposide and ARA-C chemotherapy for childhood ALL [75]. The study was designed such that patients randomized to the individualized therapy had systemic clearance of these medications estimated (using a limited sampling strategy and a Bayesian algorithm) with each dose of medication (five doses of each drug over a 1-year period). These clearance estimates were then used to determine the dosage of each medication that was needed to avoid low systemic exposure in patients with fast clearance [75]. For this trial, "low exposure" was defined as any exposure below the population median, such that all patients in the individualized arm were targeted to achieve an AUC between the 50th and 90th percentile of exposure in the conventional treatment arm. Patients randomized to individualized doses of HDMTX, teniposide and ARA-C had significantly fewer courses of treatment with systemic exposures below the target range, compared to patients randomized to conventional dosing (fixed mg/m^2 doses) ($P<0.001$) [75]. More importantly, B-lineage ALL patients treated with individualized therapy had a significantly better continuous complete remission (CCR) rate ($P=0.02$) compared to conventional dosing (76% vs. 66% 5-year CCR) (Fig. 6). In contrast, no statistically significant difference was observed in relapse risk between individualized and conventional HDMTX therapy for patients with T-lineage ALL [75]. We postulate that the lack of benefit from individualized therapy in T-

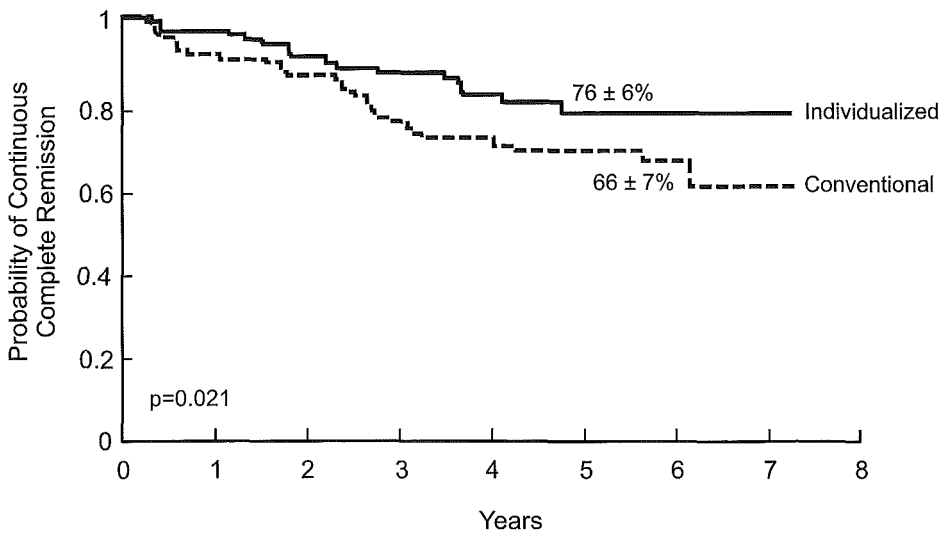

Fig. 6. Kaplan–Meier curves of complete remission for children with B-lineage acute lymphoblastic leukemia treated with pharmacokinetically individualized doses versus conventional (mg/m^2) doses of antileukemic agents. (Reproduced with permission from Evans et al. [75]).

lineage ALL may be related to having used the same target plasma concentration for both B-lineage and T-lineage ALL, given the significant lineage differences in MTXPG accumulation we subsequently observed [51].

3.6. Iatrogenic changes in drug clearance can influence efficacy of antileukemic chemotherapy

Given the above data indicating that faster rates of drug clearance can decrease the efficacy of ALL chemotherapy, it is reasonable to postulate that concomitant therapy with medications that induce drug metabolizing enzymes might reduce the efficacy of ALL chemotherapy. Because seizures occur in 10–20% of children with ALL, it is not uncommon for enzyme-inducing anticonvulsants to be prescribed to ALL patients being treated with cancer chemotherapy. Many of the commonly prescribed antileukemic agents (glucocorticoids, vincristine, anthracyclines, etoposide, and oxazaohosphorines) are metabolized by enzymes that are induced by widely prescribed anticonvulsants (i.e., phenobarbital, phenytoin and carbamazepine). To determine whether concomitant therapy with enzyme-inducing anticonvulsants is associated with compromised efficacy of ALL therapy, we evaluated the outcome of 716 consecutively treated children with ALL, comparing those who received chronic (>30 days) therapy with enzyme-inducing anticonvulsants ($n=40$) to those patients who did not receive chronic anticonvulsant therapy ($n=676$) [76]. This revealed a significant adverse effect of chronic anticonvulsant therapy in children with B-lineage ALL (representing $\sim 85\%$ of cases). After adjusting for known prognostic features (e.g., age and leukemic cell chromosome number), the hazard ratio of a bone marrow relapse was 3.4 for patients with B-lineage ALL taking anticonvulsants, relative to those not taking anticonvulsants ($P<0.001$). Consistent with this finding, faster systemic clearance was documented for teniposide ($P<0.001$) and high-dose MTX ($P=0.051$) in these patients, but not ARA-C (PK studies were not performed on the other drugs). Prior studies by our group [77,78] and others [79–81] have documented that anticonvulsants increase the systemic clearance of vincristine, glucocorticoids, doxorubicin, teniposide and etoposide, and the above study establishes that these iatrogenic changes in drug clearance can adversely affect their treatment efficacy. These findings further corroborate earlier studies establishing that fast systemic clearance of antileukemic agents is associated with decreased efficacy of ALL chemotherapy [34,36,75].

4. Conclusions

Many antineoplastic agents meet criteria supporting PK-individualization to optimize therapy, including extensive pharmacokinetic variability, narrow therapeutic indices, and a relationship between systemic exposure and response.

At present, establishing definitive relationships between drug concentration (or AUC, etc.) and clinical effects remains a work in progress for most cancers. The number of defined pharmacodynamic relationships is steadily increasing, largely as a consequence of including prospective PK/PD studies in cancer clinical trials. Dosing strategies which target levels of systemic exposure are clinically feasible, and childhood ALL is a well-

studied example where PK/PD strategies can improve treatment outcome for a disseminated malignancy. Additional studies are needed in this and other malignancies, to better define these PK/PD relationships and when their use can improve the efficacy of cancer treatment.

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Appendix A. Discussion 17

N. Holford: Referring specifically to the anti-convulsant interaction, did you find that in the individualised treatment group in Total 12, that there was any difference between anti-convulsant users or not? You'd predict, if you believed the concentration hypothesis, that you should not find any concentration difference between them.

W. Evans: Only half the patients of the Total 12 got individualised, and only a small percentage of those ended up getting antiseizure medication. So the numbers were just too small to evaluate. You would hope that we overcame that adverse effect by adjusting the dose up in those kids, we did and clearly those are the patient, on Total 12, who got some of the highest doses of teniposide.

N. Holford: In Total 12, apart from MTX, there wasn't any support for the concentration relationship viewpoint, although you did individualise treatment, you didn't actually find any difference in outcome.

W. Evans: I would not conclude that all the benefit was simply from the methotrexate, and that there was no benefit from the other two drugs. Actually the editors of the New England Journal of Medicine are the ones who changed the conclusion in the abstract, to read "methotrexate," whereas we said "clearance of these three medications," but since the P value was less than 0.05 for only the methotrexate in the AUC versus outcome analysis, they didn't accept our wording.

D. Back: You alluded to the possible importance of cellular factors such as transporters. However, keep in mind that the intention-to-treat analyses of the randomized treatment questions was based on all three medications. Would the difference in the T lineage and the B lineage be partially explained by transporter expression function?

W. Evans: There's no difference in the expression of the reduced folate carrier (RFC) between T lineage and B lineage, and there's no difference in the uptake, either, by that carrier. We don't know very much about the export pumps. There's a bit known now; a couple of the MRPs are involved in pumping methotrexate out of cells, including leukaemia cells. No one has yet looked to see whether those have significant differences between T and B lineage. There is also another component to it and that's the degradation of this drug occurs locally in the leukaemia cells by a lysosomal enzyme, gamma-glutamyl hydrolase. Its has been compared in T and B cells and doesn't look to be much difference.

What we are currently pursuing is a possible facilitated transport process into the lysosome to get the drug in, to get it degraded, as a possible source of difference between T and B lineage. There is still a lot to be done, mainly because that MRPs export of the drug from leukaemia cells was only discovered in the last couple of years. There are significant lineage differences in FPGS activity, which we reported 5 years ago.

A. Breckenridge: You and your colleagues are clearly very aggressive in optimising the dose in childhood ALL; how exportable is this to the adult situation?

W. Evans: The question is how exportable is it to the paediatric situation, as well. It's hard to do in a setting where you only treat less than six leukaemia patients a year, whereas we treat 70 to 100 a year. How do you gear up to do this? I think part of the exportability is trying to learn what causes some of this variability and control for that, in an easy fashion like avoiding the enzyme-including anti-convulsants. The other would be to try and use a first-dose clearance assuming nothing changes like liver function, renal function, drug interaction, using that to go forward for the next two and a half years to dose medications. We are doing dose adjustments for the thiopurines using molecular diagnostics and TGN monitoring. In terms of adults, it's just as doable as individualising doses of antibiotics or any other drug. There are people doing this; I'm referring to the concentration controlled clinical trials for drugs like carboplatin. They are using a surrogate, serum creatinine, and an equation to predict renal clearance of carboplatin, and then the predicted clearance is used to adjust dose. They don't have to measure the drug concentration, but you have another source of variability in the estimation of clearance from a surrogate, as well as the clearance itself.

M. Reidenberg: I'm curious if you have any insight into the attitudal barriers of the oncology community to look at this question long before you did. It has been shown that these drugs are 30 years old, and when they were initially worked up, the variation in pharmacokinetics was known. It was also pretty well understood that they had to get into the tumour to work. And yet oncologist think by using a square metre of body surface instead of kilos of body weight they are being scientific. What's the barrier been to using the phase I studies to at least look and see whether individualisation works in oncology where individualization of those has been used by neurologists since the time these oncology drugs were developed, so the idea was well known in the medical community.

W. Evans: I don't know. First of all the National Cancer Institute has now pretty much required PK studies in all phase I and II trials, in kids and adults, so we are seeing the data being generated on the PK. The strategies have been, let's just throw all the drugs at patients we can, and even if one of them is being underdosed, we'll cover up for that because we are going to give them 6 or 8 drugs. And so no one drug makes any difference. What you do then, is expose the patient to a lot of toxicity, and a lot of risk, that maybe you wouldn't have to do if you knew which drug you were underdosing and you could target that one appropriately. I think that's where mercaptopurine really is a nice example. We are very grateful that Wellcome didn't throw out mercaptopurine in the 1940s–had they known it was a substrate for a polymorphic enzyme, with today's strategies they might have tossed it in the trash. The drug got introduced in 1953, Hitchings and Elion received the Nobel prize for these medications and a few other drugs, and today it's a mainstay of treatment for childhood ALL. Fifty years later, we are a lot smarter how we

use it, and the hope is that we are going to be that much smarter about new drugs much quicker in the future.

P. Joubert: Related to the story of schedule dependence in adults, we tried with a new oncology drug to talk the oncologists into also trying it with regular once a day dosage in addition to a long schedule and a short schedule, but they didn't budge on that. What are your feelings on schedule dependence?

W. Evans: They can be very important for at least two reasons. One is related to the exposure to the tumour, and the cycle time of the tumour cell cycle, to make sure you are exposing the tumour for an appropriate period of time; so the drug can work on as much of the tumour as possible. The second is a PK one, and a good example taxol. In clinical trials it was first given as a long infusion, because of a stability problem. But then, managed care and cost constraints forced people—when it got approved—to use short infusions; they went to 2 or 3 h infusions that they could give in the outpatient-clinic. And at that point, non-linear kinetics of taxol were observed in man for the first time. Now you had a drug with non-linear clearance by simply changing the way you were giving it, from 24 h to 2 or 3 h. I think those are things that are largely ignored when these decisions are made for convenience or for cost. The good thing about 6-mercaptopurine is that giving a little bit every day was probably the right way to give that drug. It has to be incorporated into DNA to have its cytotoxicity, and so you want to have some around all the time as DNA synthesis is going on in leukemia cells.

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