Therapeutic Drug Monitoring in Cancer Management

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Several anticancer drugs display characteristics that make them suitable candidates for therapeutic drug monitoring (TDM), including substantial pharmacokinetic variability and a narrow therapeutic index. However, concentration–effect relationships (pharmacodynamics) of most antineoplastic agents have not been well defined, thus limiting the widespread clinical application of TDM for cancer chemotherapy. Strategic incorporation of pharmacokinetic studies during phase I–III clinical trials should facilitate the identification of concentration–effect relationships and the definition of clinically useful levels of treatment intensity. We review representative clinical studies that have defined pharmacodynamic relationships for methotrexate, teniposide, etoposide, carboplatin, and mercaptopurine. Given that TDM has impacted positively on the clinical use of many drugs belonging to other therapeutic classes, and that pharmacodynamic correlations have been identified in several recent studies of anticancer drugs, we consider implementation of TDM a rational strategy for optimizing the use of selected antineoplastics.

Indexing Terms: pharmacokinetics · chemotherapy · methotrexate · teniposide · etoposide · carboplatin · mercaptopurine

Therapeutic drug monitoring (TDM) entails the measurement and interpretation of drug concentrations in biological fluids, and use of the results in individualizing dosage regimens or assessing drug effects.2 Performed effectively, these efforts should help to maximize the likelihood of achieving a therapeutic response, minimize the probability that a patient experiences drug toxicities, or both. The oncology population typically receives numerous supportive medications, for which dosage individualization is routinely guided by TDM (e.g., aminoglycosides, cyclosporine). Despite the substantial toxicities produced by most anticancer agents, and the potentially life-threatening consequences of ineffective therapy, methotrexate (MTX) remains the only antineoplastic for which TDM is in widespread clinical use. The accrual of pharmacokinetic data during earlier stages of drug development has been recently advocated for many classes of drugs (1), including anticancer agents (2–4). Such information may allow more rapid definition of optimal doses and schedules, thereby enhancing the assessment of new anticancer drugs and providing a foundation for the use of TDM for cancer chemotherapy.

The potential for TDM to enhance antineoplastic use will be greatest for those agents exhibiting the following characteristics: (a) a variable or unpredictable relation between dose and resulting serum drug concentrations; (b) a narrow therapeutic window; i.e., the serum concentrations required for therapeutic effects are close to those producing toxicity; (c) the ability to correlate measured drug concentration with toxicity and (or) efficacy, allowing the delineation of a therapeutic target; and (d) the availability of reliable and clinically feasible assays. The majority of anticancer drugs meet the first two criteria; data to establish the third criterion have only recently emerged from studies of several antineoplastic agents.

Previous reviews have identified numerous areas of potential application for TDM in anticancer management, as well as their current pitfalls (5–8). The purposes of the present review are to (a) summarize the rationale and use for serum drug concentration data during clinical drug development, (b) illustrate that several antineoplastics meet criteria supporting the use of TDM for optimizing therapy, (c) review representative studies that support further investigation of TDM-based strategies for developing antineoplastic regimens, and (d) acknowledge instances in which TDM is unlikely to improve antineoplastic therapy or where obstacles persist against cost-effective utilization of TDM in anticancer therapy.

Basis for Concentration–Effect Relationships with Anticancer Drugs

Pharmacodynamics is the study of drug effect as a function of drug concentration or drug exposure. For drug-responsive tumors, non-phase-specific antineoplastics (agents for which cytotoxic activity is independent of cell growth cycle, e.g., alkylating agents) are generally presumed to behave according to traditional sigmoidal concentration–response curves (6, 9). Such curves classically exhibit a log-linear portion (through which increasing the drug concentration will yield an increasing response), a minimal effective concentration (threshold), and a plateau (above which raising the drug concentration provides no further increase in response). For antineoplastics in which the "steep" portion of the concentration–effect curve lies within the range of clin-
ically achievable drug concentrations, oncolytic (and toxic) responses should be directly related to the intensity of drug exposure (6, 8, 10). Importantly, the pharmacodynamic curves for different drug effects are not necessarily superimposed. It is this dissociation that ultimately allows the clinical separation of toxic from therapeutic responses, thus establishing the therapeutic “window” for a given agent.

Clinical data began to accumulate in the 1980s in support of the premise that response rates to antineoplastic regimens were directly related to the doses of drug administered for several drug-sensitive cancers (11). It was also noted that the dose intensity actually delivered to patients was frequently less than that intended in protocol design; this happened for numerous reasons, particularly therapeutic delays required for recovery from excessive toxicity (12–14). Over the next few years, the concept of dose intensity was expanded to include the element of time over which a cumulative dose was administered, an acknowledgment that delays in drug therapy might allow tumor regrowth to compromise antineoplastic efficacy (13, 14).

In contrast to non-phase-specific agents, some antineoplastics require metabolic transformation or actively cycling target cells to exert their cytotoxic effects. The crucial factor determining response to such agents may be the degree of active metabolite formation or the accumulation of intracellular drug complexes (15–21). Although such determinants of response may be influenced by dose intensity per se, they frequently are a more direct function of the duration of exposure above a threshold serum concentration or of the dosing administration schedule (e.g., the same total dose given as a prolonged infusion rather than a bolus) (6, 8, 15, 22–24).

Pharmacodynamic models of antineoplastic activity continue to increase in complexity, as factors relating to tumor cell biology and growth, mechanisms of drug activity or resistance, and physiological variables are being incorporated.

**Do Antineoplastics Meet the Criteria for TDM?**

**Highly Variable Dose–Serum Concentration Relationships for Antineoplastics**

Substantial pharmacokinetic variability has become evident for virtually all antineoplastics studied thus far. This variability may occur randomly at both the interpatient and intrapatient levels, or result from patient-specific differences attributable to body habitus, changes in organ function, drug interactions, genetic regulation of drug metabolism, disease states, age, and other clinical or demographic factors. Drug disposition appears to differ broadly between adult vs pediatric or geriatric populations, and between patients with diseased vs intact organs of elimination. Even in the absence of clinically apparent organ dysfunction, drug clearances within a “homogenous” population have generally been unreliable indices of drug elimination capacity, they are often used in antineoplastic protocols to guide dosage adjustments (5).

Underlying our discussion is the basic pharmacokinetic principle that, for a fixed dose of intravenously administered drug, systemic clearance is the major determinant of systemic exposure, and systemic exposure is most often quantified as the integrated area under the concentration-vs-time curve (AUC), or as the steady-state serum concentration (Cpss). An important consequence of pharmacokinetic variability is that the administration of a fixed dose of drug to different patients will produce systemic drug exposures that also vary according to the differences in drug clearance (Figure 1).

In general, phase I antineoplastic studies are designed to determine the maximum tolerated treatment intensity at which future trials will be conducted to determine which tumors are potentially responsive to the new agent or regimen. To determine dose–response relationships, these trials traditionally include dose escalation protocols involving administration of increasing increments of an absolute quantity of drug (e.g., milligrams) or of doses “normalized” to weight or body surface area, while observing for toxicity to the patient. These study methods are predicated on the unreliable assumption that uniform degrees of systemic drug exposure are experienced by subjects within a dosage cohort, and that dose escalations will be associated with uniform escalations in systemic exposure. In reality, systemic exposures range widely between patients within common protocol dosages, and overlap extensively across dosage increments, even if adjusted for body weight or surface area. When drug response is more closely correlated with systemic exposure than with absolute doses, then studies that fail to account for interpatient pharmacokinetic variability may result in misleading assumptions about the anticipated response at a given (e.g., maximum) intensity of treatment (2, 4, 7, 30).

![Fig. 1. Rationale for conducting comprehensive clinical pharmacokinetic and pharmacodynamic studies](image)

When interpatient pharmacokinetic variability is large, as is typical of anticancer drugs, patients treated with the same (fixed) dosage will have substantially different systemic exposure (AUC) to the drug, which will lead to different responses if there is a relationship between drug concentration and response. Pharmacokinetic studies are required to identify the extent and possible causes of variability in drug disposition, whereas pharmacodynamic studies are required to define the relation of drug concentrations to toxic or desired therapeutic effects. With strategic study design, these relationships can be concurrently assessed. Reproduced, with permission, from ref. 28.
Many cancer patients entered in phase I antineoplastic trials have had extensive prior therapy and their organ function is compromised, which reduces their systemic drug clearance relative to that of newly diagnosed patients. If a cohort of such patients with low drug clearances is treated during early phase I trials, serum drug concentrations might be observed that would be produced only by much higher dosages in newly diagnosed recipients with “normal” clearance values. Conceivably, the maximum tolerated dose could be much lower in phase I subjects than in newly diagnosed patients, whereas the maximum tolerated systemic exposure (expressed as an AUC) is likely to be more similar between the two groups. Moreover, prior therapies or poor performance status can reduce patients’ tolerance to antineoplastic toxicity. Hence, a greater propensity to experience drug toxicity and (or) delayed recovery in phase I patients may result not only from intergroup pharmacokinetic differences but also from pharmacodynamic differences in the sensitivity of normal and tumor tissues. Extrapolation of dose–response relationships (e.g., the maximum tolerated dose), particularly when determined in heavily pretreated phase I patients, may thus lead to erroneous conclusions regarding the maximal tolerated treatment intensity in other cohorts of patients. These considerations underscore the need to define or control pharmacokinetic variability when assessing intergroup differences in drug activity.

Improving Assay Availability

A full discussion of the assay technologies under development for marketed and investigational antineoplastics is beyond the scope of this review. Although assay availability is increasing, in some instances the equipment and personnel required to support such work are a barrier to their general clinical use. Many antineoplastics undergo rapid decomposition in plasma or require metabolic activation to chemically unstable intermediates, making the serum concentration of the parent drug a relatively poor measure of exposure to active drug. When selecting an assay method, the importance of detecting metabolites, or discriminating between parent drug and metabolite, will depend on the relative contributions of each moiety to therapeutic or undesired drug effects (1, 9). For some drugs (e.g., mercaptopurine), measuring intracellular concentrations of active metabolites (e.g., erythrocyte 6-thioguanine nucleotides, 6-TGN) may be more informative than the plasma concentration of parent drug (20, 31). Under the typical drug development practices, this information may not be fully known even after a drug is marketed.

A drug that is highly bound (i.e., ≥80%) to plasma proteins may require assays capable of discriminating between free (presumably active) and bound (assumed inactive) drug, before its pharmacokinetic and pharmacodynamic characteristics can be fully understood (e.g., platinum compounds, teniposide, and etoposide) (32, 33).

Serum Concentrations Correlated with Anticancer Drug Effects

Blood (serum) typically serves as the reference compartment for measured drug concentration, although the actual “effect” compartment in which the drug directly exerts its effects may involve other tissues or body fluids. Serum concentrations often serve as an appropriate surrogate to the “effective” concentration, when the sequence of distal pharmacodynamic events producing a measured response is in equilibrium with the serum concentration (6, 8, 34).

Extracelluar drug concentration–effect relationships have been observed for many antineoplastics; however, their in vivo confirmation has been impeded by study designs that do not adequately account for the drug concentrations achieved clinically. Another practical difficulty in defining antineoplastic pharmacodynamics has been the lack of rapid methods by which one can accurately detect or quantify in vivo tumor response and toxicities (5). Technological advances in tumor imaging, tumor marker assays, and detection of residual disease should improve our capabilities to objectively assess the effects of anticancer drugs. As the assessment of serum drug concentration data and “controls” for pharmacokinetic variability have been incorporated into clinical study designs, pharmacodynamic correlations between systemic drug exposure and oncolytic response (or toxicity) have been identified for numerous antineoplastics, including the examples listed in Table 1. Representative studies defining these relationships are discussed later. Over the next 5–10 years, we expect that the target concentration range (i.e., therapeutic window) will become more clearly defined for many anticancer drugs, which will facilitate more widespread clinical implementation of TDM in managing cancer chemotherapy.

Narrow Therapeutic Window

Because most currently available antineoplastics are only partially selective against malignant cells, it is difficult to cite even a few example agents that do not produce potentially significant toxicities in at least a small percentage of patients. The relatively narrow therapeutic window for anticancer drugs is depicted in Figure 2, with most antineoplastics resembling drug II in this hypothetical example. Antineoplastic toxicities often involve organ systems with rapid tissue or cell turnover (epithelial, gastrointestinal, hematopoietic); however, the renal, hepatic, neurologic, and pulmonary systems may also be damaged by numerous agents or their metabolites. The spectrum of drug toxicity can sometimes be modulated by altering the administration schedule, even at a constant total or cumulative dose. For example, when 5-fluorouracil is given as a bolus, bone marrow suppression may become dose-limiting, whereas the same total dose given as a protracted infusion may produce little hematopoietic toxicity but substantial mucositis and diarrhea (22, 23).

The tendency for adverse effects to emerge amidst the clinical use of most antineoplastics relates in part to the
Table 1. Selected Clinical Studies Demonstrating Pharmacokinetic–Pharmacodynamic Correlations (adapted, ref. 65)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic parameter</th>
<th>Pharmacodynamic relationship</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amscarine (AMSA)</td>
<td>CL</td>
<td>Granulocytopenia</td>
<td>35</td>
</tr>
<tr>
<td>Carboptatin</td>
<td>AUC (plasma)</td>
<td>Thrombocytopenia</td>
<td>36, 37, 38</td>
</tr>
<tr>
<td></td>
<td>AUC (plasma)</td>
<td>Thrombocytopenia, leukopenia; ovarian Ca response</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>AUC (plasma)</td>
<td>Germ cell tumor response</td>
<td>39</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>Cp (total) @ 12 &amp; 24 h</td>
<td>Nephrotoxicity</td>
<td>40</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Intracellular Ara-CTP (ANLL in vitro)</td>
<td>Complete remission (% achieving, duration)</td>
<td>17, 18, 24, 41</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Op_{sys}</td>
<td>Leukopenia</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>AUC (unbound)</td>
<td>Leukopenia</td>
<td>43</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>AUC (plasma)</td>
<td>Leukopenia, thrombocytopenia</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>AUC (plasma; total cycle)</td>
<td>Toxicity: mucositis, diarrhea, leukopenia, anemia</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>AUC (plasma; dose-normalized)</td>
<td>Hemiplegia metastasis retardation</td>
<td>46</td>
</tr>
<tr>
<td>Hexamethylene bisacetamide</td>
<td>AUC, Op_{sys} (duration),</td>
<td>Leukopenia, stomatitis</td>
<td>47, 48, 49</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Erythrocytic intracellular</td>
<td>Leukopenia, ALL relapse-free survival</td>
<td>19, 20, 31, 51</td>
</tr>
<tr>
<td>Methotrexate (high-dose)</td>
<td>CL</td>
<td>ALL relapse</td>
<td>52, 53</td>
</tr>
<tr>
<td></td>
<td>Op_{sys}</td>
<td>ALL relapse-free survival</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Cp @ 48 h</td>
<td>Toxicity: mucositis, nephrotoxicity, myelosupression</td>
<td>55, 56</td>
</tr>
<tr>
<td>Teniposide</td>
<td>CL, Op_{sys} (total plasma)</td>
<td>Oncolytic response (leukemia, solid tumor); mucositis</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>AUC (unbound)</td>
<td>Leukopenia</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>AUC (total)</td>
<td>Mucositis</td>
<td>59</td>
</tr>
<tr>
<td>Vincristine</td>
<td>AUC (plasma; cumulative)</td>
<td>Neurotoxicity</td>
<td>60</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; CL = systemic clearance; Cp = concentration in plasma.

Fig. 2. Hypothetical relations between drug concentration or exposure and oncolytic response (—) or toxic effects (——) in different patients
Therapeutic windows (shaded areas) correspond to a probability for response of at least 50%, while the likelihood of toxicity is maintained below 20%. Drug I (left panel) does not produce toxicity at concentrations close to those required for efficacy. If dosed adequately, two patients bearing tumors of different drug sensitivities (A > B) can both attain "maximal" likelihood of an oncolytic response, while still avoiding concentrations associated with >20% risk of toxicity (a for patient A, b for patient B). Patient B, having a less sensitive tumor, will require higher concentrations than patient A to produce an equivalent effect; thus, B has a narrower therapeutic window, due to the higher concentration needed to produce 50% efficacy. Drug II (right panel) has a propensity to produce toxicities at concentrations similar to those required for therapeutic effects. Response curves A and B represent patients with differing tumor sensitivities to the drug; dashed curves depict patients differing in predisposition for experiencing toxic effects (e.g., because of prior pretreatments or poor performance status). Patients with a sensitive tumor (A) and high threshold for withstanding toxicity (a) will have a wide therapeutic window (Aa). In contrast, patients with a refractory tumor (B) and poor tolerance to toxicity (b) will require control of serum concentrations within a tighter range (Ba) to maximize efficacy, while avoiding undue risk for toxicity. Unfortunately, most antineoplastic drugs resemble Drug II more closely than Drug I.

concept of "maximizing" therapeutic intensity, i.e., dosing to toxicity. However, maximal antineoplastic exposure is not always synonymous with maximal therapeutic efficacy. When excessive toxicity necessitates a delay of subsequent therapy, optimization of delivered therapeutic intensity may actually entail dosage reductions. For example, Santini et al. (47) demonstrated in head and neck cancer patients that the prevention of exces-
sive fluorouracil exposure (AUC or Cp∞) 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.

It may not be possible to establish a therapeutic window devoid of all risk for toxicity. More relevant issues are (a) how life-threatening or severe are potential toxicities, and (b) in what percentage of patients can one ethically accept the likelihood of reversible toxicity to increase the probability of response? The choice of limits is sometimes arbitrary, and is influenced not only by the nature of the patient population but also by the availability of alternative therapies and the ability of clinicians to manage toxic complications.

Additional Considerations

In clinical practice, most antineoplastics are used in conjunction with other drugs or treatment modalities. Correctly identifying the causative agent can be difficult if similar toxicities are produced by several agents (e.g., bone marrow suppression, mucositis) or if toxicity occurs within overlapping time frames relative to drug administration. Clinicians often resort to across-the-board dosage reductions, unnecessarily compromising the therapeutic intensity of several agents, to compensate for the 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 but, unfortunately, such drug-specific end points have not yet been generally established. Assuming that concentration-effect relationships are well defined, TDM would 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. Clearly, TDM could help to identify a chemotherapeutic agent being substantially underdosed, or not being taken because of poor patient compliance. However, the therapeutic window determined from single-agent phase I/II studies may not directly extrapolate to regimens combining multiple antineoplastics. Moreover, to fully understand antineoplastic interactions and rationally design multiagent regimens, one should characterize the pharmacokinetics and pharmacodynamics of each drug given as a single agent and then in combination regimens (61).

Ultimate sophistication in tailoring antineoplastic regimens could be envisioned by combining TDM with testing tumors for drug sensitivity so that only effective agents are delivered, in adequate but not excessive doses. An initial step toward such practice might be the establishment of a ratio of in vivo drug exposure to in vitro tumor sensitivity that would have a clinically meaningful relationship to therapeutic outcome (Figure 3). Unfortunately, the development of reliable in vitro predictors of in vivo tumor chemosensitivity has been difficult, for reasons enumerated by Bellamy (62). Others (63) have explored the measurement of cytotoxic activity of plasma samples obtained from patients after chemotherapy dosing (e.g., daunorubicin), against tumor cell lines; this approach is somewhat analogous to determining bactericidal titers in antimicrobial therapy. Several ongoing studies will likely lead to advances in this area during the next several years.

Failure to detect a relationship between plasma drug concentration (or systemic exposure) and toxic or therapeutic response can have many causes, including the true lack of such a relation for some antineoplastics. Negative findings may also arise from assessing a drug moiety or metabolite that is inactive, measuring concentrations at inappropriate times or in an inappropriate body fluid, misspecifying the pharmacokinetic or pharmacodynamic model, choosing an uninformative parameter for data analysis, or being unable to accurately assess or quantify drug response. Study samples encompassing too narrow a range of concentrations may not produce adequate diversification of response, whereas use of small patient population samples makes it difficult to appreciate truly heterogeneous responses vs random interpatient variability. Nonetheless, establishing the absence of a correlation between drug exposure and therapeutic or toxic effects is clinically useful, although

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Fig. 3. Assessing the interacting factors of intrinsic tumor sensitivity to a given drug and systemic exposure to the drug, in relation to overall clinical response

Even though in vivo systemic exposure and tumor sensitivity may be independent prognostic features, the interaction of the two ultimately determines patient response. Patient a, with relatively high systemic exposure and good tumor sensitivity (LC50 = concentration required to produce lethality in 50% of cells), should have a better prognosis than patient b, who has lower systemic exposure to chemotherapy (e.g., faster drug clearance) and has a more resistant tumor. Unfortunately, it has proven difficult to develop in vitro methods for determining tumor sensitivity to anticancer drugs that are analogous to culture and sensitivity testing of bacteria to antibiotics. However, once developed, such methods may provide an objective method for selecting anticancer drugs and identifying those patients who would benefit from TDM to maximize systemic exposure to anticancer drugs.
this usually will obviate the need for TDM of the drug in question (3, 5, 54).

Cytarabine and 6-mercaptopurine exemplify agents for which hematotoxic effects are more closely linked to the intracellular accumulation of their active metabolites, Ara-CTP (15–18, 24, 41) and 6-TGN (20, 31, 64), respectively, than to parent drug concentrations in plasma. For 6-mercaptopurine, 6-TGN concentrations in erythrocytes have served as surrogate markers for the drug concentration in normal and malignant cells, and correlate directly with the occurrence of neutropenia (19) and inversely with acute lymphoblastic leukemia (ALL) relapse (51).

TDM in Antineoplastic Trials: Promising Preliminary Results

In the preceding sections, we developed the rationale for using TDM in antineoplastic therapy by emphasizing the correlation of drug effects to systemic exposure rather than to absolute dose intensity (2–4). The following representative examples demonstrate the clinical feasibility of pharmacokinetically based methods for targeting the level of systemic exposure to antineoplastic, and provide impetus for the continued conduct of pharmacodynamic studies to assess drug response in relation to systemic drug exposure.

High-Dose Methotrexate in Acute Lymphoblastic Leukemia

As previously noted, MTX is the only antineoplastic for which serum drug concentration monitoring is in widespread clinical use (5). After high-dose MTX infusions (HD-MTX), TDM is a standard of practice for guiding leucovorin rescue, particularly in patients identified as having delayed MTX clearance or other risk features associated with prolonged cytotoxic concentrations (renal or hepatic dysfunction, "third-space" fluid collections, gastrointestinal obstruction, etc.) (55, 56, 65). In conjunction with measures to facilitate MTX excretion, TDM has helped to reduce the overall incidence of fatal toxicity associated with HD-MTX from about 6% in the 1970s (66), to no toxic deaths in >5000 courses of HD-MTX given at our institution in the past 10 years (65).

Although fewer correlations have been made between MTX pharmacokinetics and antineoplastic efficacy (vs toxicity), at least two clinical pharmacodynamic studies (52, 54) have demonstrated that indices of systemic exposure to MTX hold significant prognostic importance in relation to treatment outcome in children with ALL.

Early pharmacokinetic studies identified a 3- to 10-fold interpatient variability in MTX clearance after HD-MTX regimens (53). Coupled with the finding that pediatric ALL patients treated with half-doses of chemotherapy had significantly shorter remissions than those receiving full-dose regimens, we investigated the question of whether variability in MTX systemic exposure, resulting from the administration of fixed doses to a pharmacokinetically diverse population, translated into differences in treatment response. In our Total Therapy XS protocol (54), previously untreated children with standard or intermediate-risk ALL were randomized to receive 15 HD-MTX infusions at a fixed dose (1000 mg/m² over 24 h), in addition to conventional mercaptopurine and low-dose MTX continuation therapy. Confirming earlier findings of pharmacokinetic variability, a 2.7-fold range was observed for MTX clearance and the corresponding steady-state serum concentrations. Multivariate analysis, including other prognostic features known to affect treatment outcome, identified MTX systemic exposure (expressed as the median serum steady-state concentration) as an independent predictor of hematologic relapse, along with blast-cell DNA index and hemoglobin (P = 0.0005). Those patients achieving a median steady-state serum MTX concentration >16 μmol/L were significantly less likely to experience relapse while on therapy, relative to those having lower median MTX concentrations (Figure 4); at follow-up after 3 to 8 years, only the former group demonstrated a significantly improved rate of continued complete remission, relative to historic controls not receiving HD-MTX (67). Interestingly, reanalysis (68) of our MTX pharmacodynamic data after longer follow-up (median 7 years) revealed that MTX systemic exposure was not as important for patients displaying otherwise good prognostic features at diagnosis, but retained its significance in patients having poor prognostic features at diagnosis. Thus, ALL patients who are likely to do well with standard therapy may not require TDM (69), whereas dosage individualization may be of great therapeutic importance for HD-MTX therapy in higher-risk patients.

Borsi and Moe (52), studying higher MTX dosages (8–33 g/m³), have independently corroborated the St. Jude findings, by demonstrating the prognostic significance of MTX clearance in relation to treatment outcome for childhood ALL.

The drug concentration–effect relationships identified in the above pharmacodynamic studies are not sufficient to establish a therapeutic range for MTX in all treatment protocols for ALL. However, they have provided a basis for treatment regimens designed to further examine the importance of systemic MTX exposure in relation to clinical outcome. In the St. Jude Total XII protocol, pediatric ALL patients have been randomized to receive therapy dosed either according to conventional methods (i.e., mg/m²) or through use of pharmacokinetic methods to prospectively target the systemic exposure of selected antineoplastics (MTX, cytarabine, and teniposide), to ensure that serum concentrations will meet or exceed the median drug exposures anticipated in the conventionally dosed group (30). Whether adaptive control dosing will reduce variability in antineoplastic exposure and improve therapeutic outcome with this treatment regimen awaits longer-term follow-up.

Teniposide and Etoposide

Teniposide is an inhibitor of topoisomerase II, with activity against childhood ALL and other malignancies in pediatric and adult populations. Initial pharmacokinetic studies demonstrate that teniposide clearances range as widely as 10-fold within a pediatric population.
Variability in teniposide disposition may result from interpatient differences in liver function, disease status, protein binding, and concomitant therapies (26-29, 58, 70-73).

A phase I/II trial by Rodman et al. (57) assessed the pharmacodynamics of continuous-infusion teniposide as a determinant of toxic and (or) oncolytic response in pediatric patients with ALL, lymphoma, or neuroblastoma. The systemic clearance of teniposide varied by ~10-fold, resulting in a comparable range of systemic exposures (Cp and AUC) among patients within the same dosage (Figure 5). Consequently, the ranges of corresponding Cp and AUC overlapped extensively across dosage groups, meaning that higher doses did not always produce greater systemic exposure. Importantly, the average systemic exposures (Cp) were significantly higher in responding patients (152 ± 74 mg/L) than in nonresponding patients (62 ± 28 mg/L; P < 0.005); therapeutic response was more probable in patients achieving greater systemic exposures, regardless of the dose administered (Figure 5). The incidence of severe mucositis also increased, in association with escalating sys-

Fig. 5. (Left) Steady-state teniposide concentrations at three incremental dose escalations depict wide variability and considerable overlap among groups, owing to pharmacokinetic variability; (right) relation of systemic teniposide exposure (μmol·L⁻¹·h⁻¹), irrespective of dose, and the proportion of patients experiencing therapeutic or toxic effects

Adapted, with data from Rodman et al. (57)
Clinical exposure and extent of pretreatment. Rodman et al. identified an intermediate serum concentration, at which the probabilities both of oncolytic response and of toxicity appeared to be acceptable. The proposed "window" of teniposide exposure has served as an initial target from which to further evaluate or optimize the efficacy of teniposide during phase II/III studies (59).

Additional studies (58, 59, 72, 73) have identified factors that affect the protein binding of teniposide and etoposide and, in turn, appear to influence clinical drug response. Hypoalbuminemia is correlated with a higher fraction of unbound (presumably active) etoposide and teniposide in plasma; hyperbilirubinemia also appears to increase the free fraction of etoposide. Hyperproteineinemia, occurring in patients with multiple myeloma, has been associated with more extensive protein binding of etoposide, which may diminish its therapeutic effects (74).

Both teniposide and etoposide undergo extensive hepatic metabolism and biliary excretion. Although the systemic clearance of total (bound and unbound) epido-phyllotoxin shows variable relation to clinical indices of hepatic function, e.g., increases of alkaline phosphatase and serum aminotransferases, the intrinsic (i.e., unbound) clearance of both drugs is clearly reduced in the presence of 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, although plasma concentrations of total drug are unchanged. For both etoposide and teniposide, increased exposures to free drug (unbound AUC) have been correlated with greater degrees of hematopoietic toxicity (58, 72). Clinical implications are that failure to account for free drug concentrations might obscure the detection of these pharmacodynamic relationships or of patients at increased risk of toxicity, if abnormal binding is present (43, 58).

The above studies of single-agent teniposide have established interpatient pharmacokinetic variability and defined pharmacodynamic relations between drug exposure (free or total AUC, clearance, or \(C_{p_{\text{um}}}\) and oncolytic or toxic responses (gastrointestinal and hematologic), providing a rationale for targeting systemic exposure in phase II/III studies of teniposide in more-complex, multiagent regimens. Because no relation has been discernable between outcome and absolute teniposide dose, systemic drug exposure appears to be the more useful intermediate end point by which to compare teniposide treatment regimens. These data underscore the confounding influence that pharmacokinetic variability may have on the definition of such end points as "maximum tolerated" or "minimally effective" doses.

Rodman et al. (59) recently reported experience with prospective escalation of teniposide systemic exposure (rather than dose), in conjunction with a phase I/II evaluation of an aggressive multiagent reinduction and maintenance therapy in relapsed pediatric ALL patients. Compared with an initial "full" pharmacokinetic study requiring 12 measured drug concentrations, Bayesian algorithms utilizing only three to five optimized sampling times were able to predict subsequent systemic exposures with adequate precision and bias. Dosage individualizations within increments of systemic exposure required a threefold range of dose, occasionally exceeding 150–200% of those currently accepted as conventional. Importantly, by minimizing the interpatient variability in targeted systemic exposures, escalation to 50% above the mean produced by previous regimens (1656 vs 1060 \(\mu\text{mol} \cdot \text{L}^{-1} \cdot \text{h}^{-1}\)) was accomplished without an increase in acute nonhematologic toxicities.

In pediatric acute nonlymphocytic leukemia patients, the pharmacokinetics of teniposide given in combination with amsacrine were similar to those in patients receiving teniposide alone, as was the incidence of severe mucositis in relation to teniposide systemic exposure, independent of amsacrine (75). Such findings are useful in designing multiagent regimens when overlapping toxicities are a potential concern.

In a randomized study of 45 adult patients, Ratani et al. (76) 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 about 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 infectious complications beyond acceptable values. 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 handicap phase II efficacy evaluations in patient populations having heterogeneous susceptibilities to etoposide hematotoxicity. These authors also evaluated the clinical practicality of this approach and concluded that, relative to optimization of dose on the first cycle, the utility of pharmacokinetic measurements during each cycle of therapy was minor. Their conclusion cannot be generalized to agents associated with greater intrapatient pharmacokinetic variability, for which follow-up serum sampling and Bayesian approaches may contribute substantially to improving model performance (2, 9).

Carboplatin Systemic Exposure, Thrombocytopenia, and Tumor Response

Egorin and coworkers have provided substantial evidence that determination of systemic exposure may be a more useful end point than administering the population average maximum tolerated dosage. Using adaptive control dosing approaches, this group has elucidated meaningful pharmacodynamic relations for several antineoplastic agents, including carboplatin (36, 37), hexamethylene bisacetamide (50), and menogaril (77). In a preliminary study (36), adult patients with refractory tumors and various degrees of renal dysfunction
were administered carboplatin at a fixed dosage of either 250 mg/m² or 150 mg/m² in patients with creatinine clearances <40 mL/min. The degree of thrombocytopenia, the major toxicity, was directly related to the AUC of the ultrafilterable (presumably active) fraction of platinum, but was also significantly influenced by the extent of prior cytotoxic therapy. In addition, correlations identified between creatinine clearance and carboplatin AUC permitted the development of a pharmacodynamic dosing algorithm, designed to produce predesignated changes in platelet count. Prospective evaluation (38) of this algorithm confirmed excellent agreement between intended and observed changes in platelet counts (r = 0.94 to 0.97). These data validated previous observations that had correlated thrombocytopenia with the extent of prior therapy and systemic exposure to carboplatin, whereas correlations with absolute dose intensity were notably absent.

From the above pharmacokinetic and pharmacodynamic models, Jodrell et al. (37) advanced to the important question of whether carboplatin systemic exposure was also related to oncolytic efficacy. In a retrospective study of advanced ovarian cancer patients, the significance of first-course carboplatin AUC (calculated from previously established associations with glomerular filtration rate), prior treatment, and performance status was examined in relation to various clinical outcomes (Figure 6). In this heterogeneous group of untreated and heavily pretreated individuals, all three variables (AUC, prior treatment, and performance status) were independent predictors of tumor response, thrombocytopenia, and leukopenia; pretreatment platelet count and leukocyte counts were also correlated with the degrees of thrombocytopenia and leukopenia, respectively. Importantly, there was a relation between carboplatin AUC and antitumor effects (e.g., complete or partial remission), which was best described by a sigmoid E_max model. This model indicated that response rates increased with increasing AUC until plateauing at the AUC range of 5–7 mg · mL⁻¹ · min⁻¹, corresponding to a maximum response rate of 30–50%. In contrast, the likelihood of thrombocytopenia and leukopenia continued to increase beyond this level of exposure, from an acceptable incidence to one approaching 100%. Therefore, carboplatin doses should be adjusted to achieve an AUC of ~5–7 mg · mL⁻¹ · min⁻¹ in ovarian cancer patients; further dose escalation would increase toxicity without significantly improving the likelihood of efficacy. This series of studies thus exemplifies the relatively rapid estimation of a proposed therapeutic range for further evaluation of carboplatin in ovarian cancer. Prospective confirmation of these data is needed before they can be widely extrapolated to all chemotherapy regimens for ovarian cancer.

Horwich et al. (39) likewise noted a relation between carboplatin AUC (≥4 mg · mL⁻¹ · min⁻¹) and antitumor efficacy, in germ cell tumor patients of good prognosis who were also receiving etoposide and bleomycin.

Refined dosing methodologies have improved carboplatin targeting by utilizing serum ⁹⁹ᵐTc-diethylenetriaminepentaacetic acid or ⁵¹ᵐCr-EDTA clearances to more reliably estimate the glomerular filtration rate; these values correlate more tightly with carboplatin clearance than do serum creatinine-based indices of renal function (78–81). In addition, the recent validation of a simplified scheme to estimate carboplatin AUC from only one or two carefully selected sampling times could facilitate larger-scale pharmacodynamic trials of carboplatin efficacy, in which detailed pharmacokinetic studies might otherwise be difficult (82).

Mercaptopurine, Intracellular 6-TGN Metabolite, Leukopenia, and Outcome in ALL

A cytotoxic and immunosuppressive purine antagonist utilized primarily in the maintenance therapy of ALL, mercaptopurine is actually a prodrug that undergoes extensive intracellular uptake and biotransformation. The cytotoxic effect of mercaptopurine is primarily attributed to intracellular metabolites (6-TGN), the ultimate intracellular accumulation of which is determined by the relative activities of competing pathways of enzymatic metabolism, one of which exhibits genetic polymorphism (64, 83–85). The activity of thiopurine methyltransferase (TPMT), one of the enzymes largely

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**Fig. 6.** Models developed by the modified Hill equation, for the relationship between carboplatin AUC and the likelihoods of therapeutic response in advanced ovarian cancer (A), ≥ grade 1 thrombocytopenia (C), ≥ grade 3 thrombocytopenia (B), and grade 3 leukopenia (C) in previously treated (A) and untreated (B) patients

Adapted, with permission, from Jodrell et al. (37)
responsible (in addition to xanthine oxidase) for inactivating mercaptopurine, is inherited as an autosomal codominant trait, with 1 in 300 individuals inheriting a deficiency in TPMT activity. Individuals deficient in TPMT activity accumulate higher intracellular concentrations of 6-TGN, ostensibly because more mercaptopurine is available for activation through alternative pathways of biotransformation (84). In clinical studies TPMT-deficient patients develop extensive toxicity, unless substantial reductions in mercaptopurine dosage are made (86, 87).

Considerable pharmacokinetic variability has been observed, not only in the plasma concentrations of parent mercaptopurine after oral administration, but also in the intracellular accumulation of active metabolites at a given level of plasma exposure (27, 31, 64). Erythrocytes are generally accepted as an adequate surrogate for assessing the chronic intracellular accumulation of 6-TGN in normal and leukemic cells, largely because leukemic blasts are not available after the first 4-6 weeks of ALL therapy. Correlations between mercaptopurine dose (or plasma pharmacokinetics) and hematopoietic toxicity have generally been poor or absent (31, 64, 88, 89), but pharmacodynamic studies in childhood ALL have demonstrated strong correlations between erythrocyte 6-TGN concentrations and both toxic and therapeutic responses (Figure 7). Patients who accumulate relatively high amounts of erythrocyte 6-TGN appear to be at greater risk of experiencing neutropenic complications (19), whereas pediatric ALL patients who have low erythrocyte 6-TGN concentrations may have a higher probability of disease relapse (51).

Several treatment protocols for childhood ALL titrate mercaptopurine dosage to the point of slight neutropenia; however, the majority of regimens utilize combinations of myelosuppressive chemotherapy, making it difficult or impossible to determine which drug is being dosed excessively (19, 30, 70). In addition, these regimens often limit the maximum dose of mercaptopurine that can be given, which may prevent the accumulation of adequate intracellular 6-TGN, potentially placing patients at an increased risk of relapse (27, 64, 90). Routine screening for TPMT activity is feasible and can help to identify subsets of patients at increased risk for excessive accumulation of 6-TGN; however, because few individuals are TPMT deficient, these efforts may have a relatively low yield. Monitoring erythrocyte 6-TGN concentrations, in conjunction with leukocyte counts, is a more rational approach to individualizing mercaptopurine dosage requirements in ALL combination regimens; these end points also provide useful information for assessing oral absorption or compliance problems (86-88).

In conclusion, as exemplified here, many antineoplastics meet criteria supporting TDM as a means of optimizing therapy. In particular, these criteria include extensive pharmacokinetic variability and relatively narrow therapeutic indices. The effective application of TDM to anticancer therapy hinges on adequate understanding of how drug concentrations relate to antineoplastic efficacy or toxicity. At present, the determination of reliable relationships between drug concentration (or systemic exposure) and clinical effect remains a major challenge. The number of defined pharmacodynamic relationships is increasing, largely as a consequence of improved pharmacodynamic study designs that assess interpatient pharmacokinetic variability. Dosing strategies that target levels of antineoplastic systemic exposure are clinically feasible and promise to facilitate the identification of optimal levels of treatment intensity for several anticancer drugs. Considering the favorable impact that TDM has had on the pharmacotherapy of other diseases and the expanding number of anticancer drugs with defined pharmacodynamic relationships, we deem the utilization of TDM a rational strategy to optimize the use of selected anticancer drugs.

Supported in part by Cancer Center CORE Grant P30 CA21785, Solid Tumor Project Grant NCI 5PO1 23069, Leukemia Program Project Grant P01 CA20180, National Institutes of Health E-37 CA36401; by a Center of Excellence grant from the State of Tennessee; and by American Lebanese Syrian Associated Charities (ALSAC).

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CLINICAL CHEMISTRY, Vol. 39, No. 11(B), 1993 2429


