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Perspectives in Cancer Research

Clinical Pharmacology in Oncology. Recent Advances.

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IN THE past few years the pharmacology of anticancer drugs has been characterized by considerable development and evolution. This field encompasses topics as various as the mechanism of action, the structure–action relationship, the pharmacological disposition and the determination of the toxicity and efficacy of anticancer drugs. The characterization of the disposition includes the knowledge of the optimal route of administration, distribution patterns, metabolic pathways and routes of excretion. These parameters can be affected by physiologic or pathologic conditions of the host, such as age, organ dysfunction, therapy with other drugs and other modalities. Ideally, the clinician uses this information to select a dose and schedule of administration associated with the best efficacy and the lowest toxicity. It must be recognized, however, that cancer therapy remains far from that goal and that pharmacological information for an agent becomes available a long time after its empirical use. The purpose of this review is not to describe the pharmacology of each antitumor agent but, rather, to emphasize by selected representative examples the importance of these pharmacologic considerations. The reader is referred to appropriate reviews for further information [1, 2].

MECHANISM OF ACTION

Several drugs act through binding or reacting with DNA. Anthracycline antibiotics [3] and bleomycin [4] belong to this class of drugs. Alkylating agents and nitrosoureas have the ability to form covalent bonds with DNA [5]. Cisplatin generates a bivalent positive cation in aqueous solutions that can react with the nucleophilic sites of DNA [6]. Mitomycin C functions as an alkylating agent after being activated through quinone reduction [7]. The quinone ring also participates in the formation of free radicals, which have been implicated in the mechanism of action of these drugs [3].

A number of anticancer drugs interfere with the synthesis of the precursors of DNA and RNA. The case of cytosine arabinoside (ara-C) illustrates well how the understanding of the mechanism of action can lead to new therapeutic schedules. Ara-C is an analog of deoxycytidine; following phosphorylation into cytosine arabinoside triphosphate (ara-CTP), it acts as a competitive inhibitor of deoxycytidine triphosphate at the level of DNA polymerase [8] (Fig. 1). Ara-CTP is also incorporated into DNA, leading to the synthesis of a defective DNA. Two inactivating deaminases can act on ara-C and ara-C monophosphate respectively [8]. The product of the deamination of ara-C, uridine arabinoside, is the predominant species in plasma following the administration of ara-C. Finally, as an inhibitor of DNA synthesis, ara-C acts selectively during the S phase of the cell cycle [8]. Because of the rapid inactivation of ara-C and its phase-dependent

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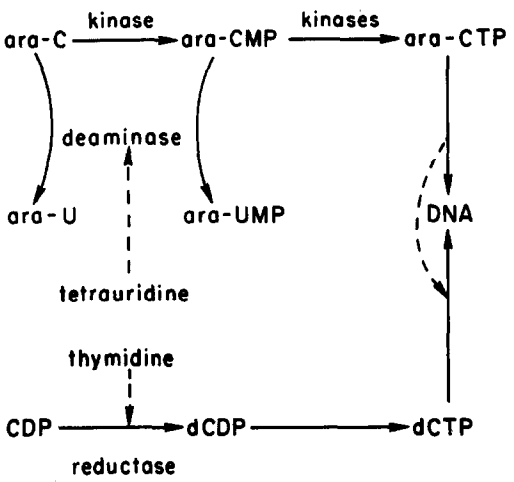

Fig. 1. Metabolism of ara-C. Ara-C: cytosine arabinoside; MP: monophosphate; DP: diphosphate; TP: triphosphate; C: cytidine; dC: deoxycytidine; ara-U: uridine arabinoside. --- Inhibition.

killing, the drug is usually given as a continuous infusion or by frequent bolus doses.

Resistance to ara-C can conceivably be related to decreased cellular uptake, reduced anabolism to ara-CTP, decreased intracellular retention of ara-CTP, increased catabolism, an alteration in DNA polymerase sensitivity or a modification of the relative amounts of ara-CTP and deoxycytidine triphosphate. One way to circumvent these resistance mechanisms is to increase the dose of ara-C. Rudnick *et al.* showed that the administration of 3–7.5 g/m^2 of ara-C is possible in man [9]. Toxicity including myelosuppression, gastrointestinal distress and central nervous disturbance was felt to be acceptable. Similar conclusions have been reached in a more recent study [10]. Of note, responses have been observed in patients refractory to treatment with anthracyclines and conventional doses of ara-C. In addition, responses have been noted in patients with meningeal leukemia. Pharmacokinetic data indicate that plasma concentrations remain higher for 3–12 hr than those obtained with a continuous infusion of ara-C at 100 mg/m^2 over 24 hr. A high degree of penetration into the central nervous system has been demonstrated [10].

Another way to increase the effect of ara-C is to decrease the deamination process by using an agent such as tetrauridine [8] or to decrease the competition with deoxycytidine triphosphate. Thymidine has been shown to induce an inhibition of the reduction of cytidine diphosphate into deoxycytidine diphosphate (Fig. 1) and *in vitro* data suggest that the sensitivity of cultured tumor cells to ara-C is increased by thymidine [11]. In a trial of a combination of ara-C and thymidine, a 47% total response rate was achieved in patients refractory to conventional doses of ara-C [12]. Thus a thorough evaluation and manipulation of the mechanism of action of ara-C has lead to new effective ways of administering this drug.

ROUTE OF ADMINISTRATION AND DISTRIBUTION

The route of administration is an important factor with regard to the access of a drug to different organs. Obviously, intravenously injected drugs have the easiest access to most tissues. This is not the case for orally administered drugs, which must cross both the gastrointestinal mucosae and the hepatic filter before reaching the general circulation.

Wide variations of absorption have been described for a number of drugs. Melphalan is widely used in the treatment of ovarian cancer and myeloma and as adjuvant therapy in breast cancer. Although the absorption of this drug is uniform in laboratory animals, considerable variability in absorption by humans has been reported [13, 14]. Some authors have found that the fraction of melphalan absorbed is higher after a meal [13], whereas others recommend administration in an empty stomach in order to minimize the number of substances to which melphalan might bind [14]. Erratic absorption has also been shown for thiotepa [15], hexamethylmelamine [16] and 5-fluorouracil [17]. In the latter case the bioavailability could be largely influenced by the first-pass hepatic metabolism of the drug. Increasing the dose of 5-fluorouracil results in an increase of bioavailability, probably because of the saturation of the hepatic metabolism. In contrast, other drugs exhibit a decrease of their bioavailability at higher doses. For example, plasma concentrations and urinary excretion of methotrexate are similar after oral or i.v. administration of 0.1 mg/kg, whereas after an oral dose of 10 mg/kg only 10% are absorbed [18]. A similar phenomenon has been described for 6-mercaptopurine [19]. It is believed that these drugs, which are analogs of natural substances, are absorbed at low doses by means of an active transport mechanism. At higher doses the same compounds are absorbed more slowly by passive diffusion [20]. In addition, drug absorption can be modified by functional and anatomic abnormalities of the gastrointestinal tract, which are frequent in cancer patients. With the development of rapid and sensitive methods of determination of plasma concentrations for various drugs, the clinician has an elegant tool to monitor drug absorption.

A rather new route of administration of chemotherapeutic agents is the large-volume intraperitoneal administration. Usually, drugs

are given in a small volume as a single intraperitoneal injection. In the approach developed at the National Cancer Institute [21–24], peritoneal dialysis catheters are implanted into the abdominal cavity; drugs are given in a large amount (2 l) of fluid, which is either exchanged several times (8 exchanges over 36 hr) or instilled daily without drainage for 3–5 days. The rationale supporting this technique relies on considerations predicting slow passage of hydrophilic drugs from the intraperitoneal space to the systemic circulation, and thus a substantial difference between intraperitoneal and plasma concentrations and clearances [21]. The peritoneal cavity and tumor are exposed to higher drug concentrations than other tissues, which are exposed to the drug through the systemic circulation. Large volumes of fluid ensure exposure of the entire peritoneal surface. In trials with intraperitoneal administration of 5-fluorouracil, the maximal intraperitoneal concentration achieved is about 10 times higher than the highest plasma concentration obtained after intravenous administration. Intraperitoneal drug concentrations decline slowly with a half-life time of 1.6 hr, compared to the intravenous bolus drug half-life of 10–20 min [23]. Toxicity is acceptable, although cases of chemical and bacterial peritonitis have been observed. Similar conclusions have been reached in trials with high-volume intraperitoneal administration of methotrexate and adriamycin [23, 24]. The place of this new treatment modality vs more classical approaches remains to be evaluated.

Organ distribution is another important parameter for the disposition of a drug. Distribution to the central nervous system (CNS) represents a specific situation. Infiltration of the meningeal structures is commonly observed in leukemias, lymphomas and, as shown more recently, in small cell cancer of the lung [25]. Brain metastases are frequent in melanoma, and lung and breast cancer. Therapy against meningeal disease can be administered directly into the meningeal space. Methotrexate is commonly used in that situation, but ara-C and thiotepa can also be administered safely by intrathecal or intraventricular injection [26, 27]. Most of the time, however, CNS therapy is a part of systemic treatment and drugs that penetrate the CNS are needed. This penetration can be obtained by forcing the blood–brain barrier with high concentrations of drug. As already mentioned, this can be done for ara-C. Systemic high doses of methotrexate also reach significant concentrations in the cerebrospinal fluid [28]. However, at conventional doses the ability of an agent to cross the blood–brain barrier is related to its lipid solubility [29]. Nitrosoureas are lipid-soluble compounds that have been used in the treatment of CNS tumors. However, their activity remains limited and their is a need for new active drugs against CNS disease. Because of the high antitumor activity of quinone derivatives such as anthracyclines and mitomycin C, attempts have been made to incorporate this structure into compounds with optimal properties to penetrate the CNS. Diaziquone (AZQ) presents these characteristics and has been shown to be active on intracerebrally implanted murine tumors, to penetrate into the cerebrospinal fluid in man and to exhibit significant antitumor activity against recurrent primary and metastatic tumors of the brain [30, 31].

Although a good correlation is found between chemical structure, pharmacokinetic data and clinical activity in the case of AZQ, this is not always the case. Cerebrospinal fluid levels of VM-26 are negligible; however, a 51% objective response rate against brain tumors has been reported with this compound [32]. For cisplatin the ratio of cerebrospinal fluid over plasma concentrations never exceeds 0.04 [33]; in contrast to these findings, 4 complete and 5 partial responses have been seen among 22 patients with brain tumors [34]. These discrepancies are possibly clarified by the observations reported by Stewart *et al.* [35]. While the low passage of cisplatin to the cerebrospinal fluid is confirmed, these authors have detected potentially cytotoxic concentrations in tumor samples obtained at autopsy or surgery. Thus the ability to enter the cerebrospinal fluid is not always correlated with the ability to enter the tumor tissue. Such a phenomenon might be related to the local disruption of the blood–brain barrier and might implicate that classical conceptions in brain pharmacology must be reviewed.

METABOLISM AND EXCRETION

Metabolic conversion of anticancer drugs can be a part of an inactivation process, but is sometimes a requirement for activity. As explained previously, ara-C must be phosphorylated to exert its cytotoxic activity; cyclophosphamide is inactive by itself and is first hydroxylated by the microsomal mixed-function oxygenase system [28] (Fig. 2); the resulting product, 4-hydroxycyclophosphamide, suffers spontaneous opening of its ring structure to generate aldophosphamide. This compound is split into phosphoramide mustard and acroleine. It is generally accepted that phosphoramide mustard exerts the cytotoxic action of cyclophosphamide, whereas acroleine is responsible for the hemorrhagic cystitis associated with the drug [28]. The knowledge of the

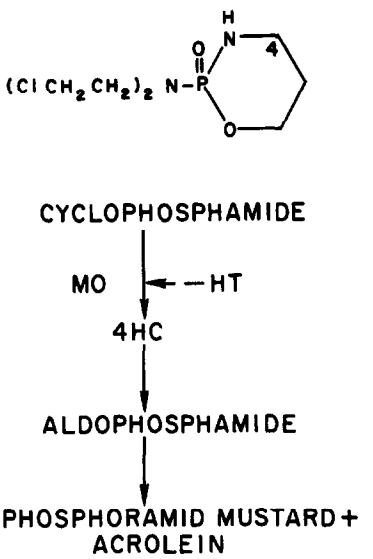

Fig. 2. Metabolism of cyclophosphamide. 4HC: 4-hydroxy-cyclophosphamide; MO: mixed function oxidase enzymes; HT: hyperthermia. --- Inhibition.

metabolism of cyclophosphamide has lead to attempts to prevent the urotoxicity of this compound. Sulfhydril-containing agents, such as *N*-acetyl-cysteine, have the property of inactivating acroleine following direct combination; *N*-acetyl-cysteine has indeed been shown to reduce urotoxicity but also the antitumor activity of cyclophosphamide [28]. Another sulfhydril compound, sodium-2-mercaptoethane sulfonate (mesnum), can decrease the urotoxicity of cyclophosphamide in animals without affecting the antitumor activity, possibly because mesnum is not taken up by tissues, but quickly and completely eliminated via the kidney [36]. The clinical utility of mesnum has been suggested by Scheef *et al.* [36]. Since the formation of acrolein from 4-hydroxycyclophosphamide occurs in the urines themselves and is eased by an increased pH, diuretics acidifying the urines such as furosemide might be more protective than alkalinizing diuretics [37]. However, these measures have not gained wide acceptance, probably because urotoxicity can be prevented in most patients by maintaining an adequate hydration and urinary flow [28].

The liver is the major site of drug detoxification and a major site of drug excretion. Hepatic metabolic transformations usually result in the production of more polar compounds that are not reabsorbed through the renal tubular and intestinal epithelium [38]. These transformations are usually carried out by non-specific enzymes and involve two steps: first, a reactive group is added to the molecule through oxidation, reduction or hydrolytic processes; these active groups can then be conjugated to radicals such as glucuronic acid or sulfate [38]. The metabolism of adriamycin has been well investigated [3] (Fig. 3) and provides a good example of these various metabolic steps. Reduction of the side-chain into an alcohol derivative is carried out by the cytosolic aldoketoreductase; hydrolysis can consist of demethylation of the methyl group in the C4 position and cleavage of the sugar moiety. This cleavage follows spontaneous rearrangements of the semiquinone free radicals resulting from the reductive action of the microsomal NADPH cytochrome P450 reductase. Finally, glucurono- and sulfo-conjugation can occur at the C4 position of the demethoxy derivatives. Adriamycin and daunorubicin represent classical examples of the various metabolic pathways that can occur for a given class of drug.

Excretion of anticancer drugs and their metabolites occur primarily in urine and bile. The routes of excretion of the major antineoplastic drugs are summarized in Table 1 [7, 19, 32, 39–43]. Drugs like methotrexate and cisplatin are directly excreted into the urines; others are metabolized and subsequently excreted by the kidneys. Cyclophosphamide and ara-C belong to this class of drugs. The anthracyclines and vinca alkaloids are excreted primarily by the liver. Asparaginase is an example of drug of which negligible amounts are found in bile and urines; it is probably cleared by the reticuloendothelial system. Substantial amounts of actinomycin D are encountered in bile and urines. 5-Fluorouracil is metabolized to various products including CO_2, which is eliminated by the lung. It must be mentioned that whereas urine is directly available for analysis, the study of the biliary excretion is more difficult and relies on animal

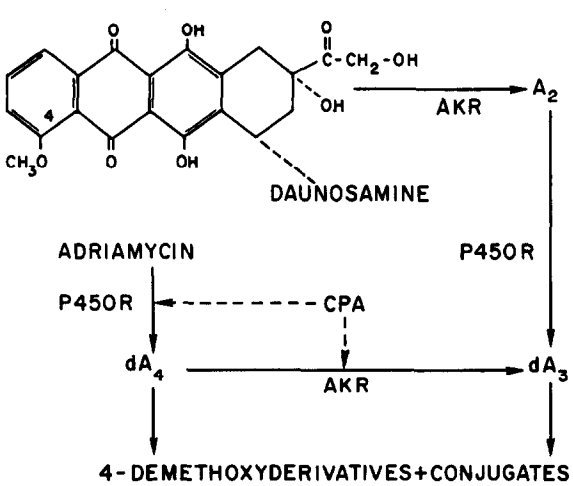

Fig. 3. Metabolism of adriamycin. A_2: adriamycinol; dA_4: 7-deoxyadriamycin aglycone; dA_3: 7-deoxyadriamycinol aglycone; P450R: NADPH cytochrome P450 reductase; AKR: aldoketoreductase; CPA: cyclophosphamide. --- Proposed inhibitory effect of pretreatment with CPA in rats.

Table 1. Major route of elimination of some antineoplastic drugs

Renal	Metabolic*	Biliary†	Mixed‡
Methotrexate	6-thioguanine	anthracyclines	actinomycin D
Nitrosourea	cyclophosphamide	mitomycin C	VP-16
Cisplatin	6-mercaptopurine	vincristine	VM-26
Bleomycin	DTIC	vinblastine	
	procarbazine	vindesine	
	5-fluorouracil		
	cytosine arabinoside		

*Metabolites are excreted subsequently through various routes.
†Biliary excretion may be preceded by hepatic metabolism.
‡Combination of renal, metabolic and/or biliary elimination.

data or relatively exceptional patients such as those with external biliary drainage. In these patients, however, liver function abnormalities frequently exist and the validity of the information may be questioned.

Renal or hepatic dysfunction are common in cancer patients and may be related to several mechanisms [42]. The tumor may directly infiltrate or compress the biliary or urinary tract; amyloidosis, hypercalcemia and paraproteinemic nephropathy are examples of indirect effects. Treatment itself may induce renal or hepatic abnormalities. Various drugs are direct nephro-or hepatotoxins (Table 2). Treatment can induce indirect complications, such as uric acid nephropathy. Other treatment modalities such as radiation therapy and especially other drugs (e.g. aminoglycosides, amphotericin B) are other causes of renal or hepatic impairment. Guidelines are available for dose reduction in case of renal or hepatic failure [39, 42], but in many cases the choice of dose remains a matter of clinical experience. In addition, when organ failure is due to the tumor itself, regular doses may be indicated, provided that adequate supportive care is available during the toxic period.

Table 2. Nephro- and hepatotoxicity of some anticancer drugs

Nephrotoxic drugs	Hepatotoxic drugs
Methotrexate	methotrexate
Cisplatin	cytosine arabinoside
Nitrosoureas	6-mercaptopurine
Streptozotocin	6-thioguanine
Mithramycin	mithramycin
	streptozotocin
	asparaginase

PLASMA LEVELS AND PHARMACOKINETIC MODELS

Plasma levels are more and more frequently determined in conjunction to phase I and II trials. Since these studies are very demanding in terms of professional and technical resources, it is important to question their interest. Blood level monitoring has an established value in the treatment of epilepsy and infectious diseases, and can be correlated with efficacy and toxicity. This stage has not yet been reached in oncology [44]. Variations in tumor sensitivity are probably more important than variations in blood levels in explaining the success or failure of a given treatment. One might expect a better correlation between blood levels and toxicity. For example, clinical data indicate that the cardiotoxicity of adriamycin is reduced by decreasing peak plasma levels. This was first suggested by Weiss *et al.*, who used a weekly regimen at a dose of 20 mg/m^2 [45]. More recently, in a trial where adriamycin was administered as a continuous infusion of 60 mg/m^2 over 24–96 hr, cardiotoxicity, assessed by several parameters including endomyocardial biopsy, was significantly less severe than that observed in patients receiving the drug by i.v. bolus. Antitumor activity appeared to be maintained. The peak plasma levels were significantly decreased by increasing the infusion time. In contrast to a decreased cardiotoxicity, myelosuppression was similar with both regimens [46]. The lack of relationship between blood levels and myelosuppression has also been noted in the case of marcellomycin, a new anthracycline recently investigated in our laboratory. This drug has been introduced into clinical trials on the basis of reduced hematological toxicity in animal and *in vitro* models [47]. In contrast, phase I clinical trials have revealed that myelosuppression is the dose-limiting toxicity in man [47, 48]. In addition, myelosuppression appears to be erratic. These inter- and intraspecific differences in toxicity could conceivably be related to pharmacological differences. Qualitatively, murine and human metabolisms appear to be similar; however, lower peak levels and areas under the plasma curve for the parent drug were found in humans, where myelosuppression is more marked [49, 50]. On the contrary, higher values were observed for a polar metabolite, but

the relative toxicity of this metabolite is unknown. Among humans wide variations in plasma peaks and areas under the curve have been found for the parent drug and various metabolites, but without correlation with toxicity [50]. The failure to find such correlations in this study and others might be related to the small number of patients, the unknown effect of the parent drug vs metabolites, the fact that local drug distribution, uptake and metabolism are not measured and variations of sensitivity of the different target tissues.

There are, however, examples where drug blood level monitoring is useful. Its use in evaluating the bioavailability of orally administered drugs has already been mentioned. Modification of pharmacokinetic parameters in case of renal or hepatic dysfunction can give information about the route of elimination of a drug and can provide a basis for dose adjustment. A classical application of blood level monitoring is the administration of high-dose methotrexate. In the study reported by Stoller *et al.* methotrexate was given at doses ranging from 50 to 250 mg/kg over a 6-hr period. All patients received intravenous hydration, bicarbonate and rescue with leucovorin. Toxicity was observed only in patients with 48-hr methotrexate levels higher than 9×10^{-7} M. Blood levels were much more reliable than changes in serum creatinine [51]. It has been subsequently shown that an earlier determination of methotrexate levels is as effective in calculating the leucovorin dose and avoiding excessive toxicity [52].

Another area where the knowledge of plasma levels is important is the tumor stem cell assay. Potentials and limitations of this test have been recently reviewed [53]. The *in vitro* drug concentration must be related to achievable levels in plasma; otherwise the test may be insensitive or non-specific. Usually, tumor cells are exposed to one-tenth of peak plasma levels for 1 hr; the importance of the metabolites must not be neglected either, since it has been shown, for example in the case of adriamycin and chlorambucil, that metabolites can be active species [54, 55]. The knowledge that a drug such as cyclophosphamide requires activation to be active is of obvious importance for the use of this drug *in vitro*. Thus extensive pharmacological information is required for the interpretation of the tumor stem cell assay.

Models are important tools in pharmacology [56]. A model is basically a set of equations describing the concentration of a drug as a function of time. Usually the behavior of a drug is described separately in different fractions of the body, or compartments. These do not necessarily correspond to anatomic regions. Drug administration and elimination occur most of the time in a central compartment; the drug distributes itself among this central and one or several peripheral compartments. For each compartment a basic differential equation that describes the injection, elimination and transfer processes can be written and subsequently solved by integration. The equation must satisfy the rule that the net change for a compartment equals the sum of all inputs minus the sum of all outputs. The most important parameters that can be derived from a model are the volume of distribution, half-life times, clearance rate and area under the curve. The apparent volume of distribution indicates the extent of distribution of a drug. Since a drug can be stored or bound on different structures of the body, it is not unusual that the volume of distribution is larger than the plasmatic volume or even than the total body volume. The half-life times and clearance rates describe the rate of elimination at which the drug is cleared from a given compartment. The area under the plasma curve is a composite parameter that takes into account peak concentrations and half-life times; it represents the total exposure of the compartment to the drug. In addition to their descriptive value, models can be used to test a theoretical hypothesis prior to clinical application. This approach has been used for the development of the large-volume intraperitoneal therapy [21].

PHARMACOLOGICAL INTERACTIONS

Interactions are conceivable between 2 drugs or 1 drug and another treatment modality. A classical example of drug–drug interaction is the increased toxicity of 6-mercaptopurine in patients receiving concomitant allopurinol [1]. Streptozotocin has been shown to modify the pharmacokinetics and to increase the toxicity of adriamycin [57]. The interaction between adriamycin, cyclophosphamide and hyperthermia has been studied in our laboratory. In a clinical trial of this combined therapy in soft tissue sarcomas it has been found that the amount of adriamycin aglycones was lower in euthermic patients whereas hyperthermic patients had values closer to those encountered in patients treated with adriamycin alone [58]. This phenomenon could reflect an effect of hyperthermia on the disposition of adriamycin. Our investigations have not shown any effect of hyperthermia on the uptake and metabolism by rat liver preparations [59], but Skibba *et al.* have demonstrated that, again in rats, hyperthermia decreases the bile flow and the excretion of adriamycin and its metabolites when heat is applied for a sufficient period of time [60].

On the other side, hyperthermia reduces the activation of cyclophosphamide [58, 61]. Since cyclophosphamide can inhibit the NADPH cytochrome P450 reductase, probably through acrolein [62], the inhibition of the activation of cyclophosphamide by hyperthermia could result in an increased production of adriamycin aglycones. We have indeed shown that cyclophosphamide pretreatment in rats reduces the conversion of adriamycin to 7-deoxyadriamycinol aglycone by liver microsomes [63] (Fig. 3). All these data suggest a complex interaction between hyperthermia, cyclophosphamide and adriamycin.

CONCLUSIONS AND FUTURE PROSPECTS

The ultimate goal of pharmacology is to provide safe and active drugs. Antineoplastic agents usually have a narrow therapeutic index, and therefore the level of understanding of their behavior must be high to exploit even minimal differences of action between normal and tumor cells. This explains the difficulty and length of these studies, and the delay before clinical applications. Although not directly related to clinical practice, it is important to study the mechanism of anticancer drugs since, in some cases, like ara-C, this approach can provide ways to circumvent resistance to a drug or to reach more easily specific regions of the body, such as the brain and meningeal space. Drug plasma concentration monitoring is already useful in evaluating drug absorption and interpreting the tumor stem cell assay. In specific situations, such as treatment with high-dose methotrexate, these data help in designing therapy and rescue with an antidote. Blood drug levels and pharmacokinetic models will probably be increasingly used to understand drug toxicity and efficacy, but this will need better information on drug metabolism, local distribution, uptake by tumor and normal cells and the concentration–effect relationship. All these parameters will have to be investigated for single drugs but also for multidrug combinations, combined treatment modalities and high-dose therapy. Clearly, the field of clinical pharmacology provides the oncologist with ample room for fruitful investigations.

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