Chapter 16

Pharmacokinetics of Anti-Cancer Drugs Used in Breast Cancer Chemotherapy

Swati Nagar*

Abstract

Pharmacokinetics of anticancer drugs used in breast cancer therapy are well established. This chapter reviews preclinical and clinical pharmacokinetics of the following drugs: cyclophosphamide, docetaxel, doxorubicin, 5-fluorouracil, methotrexate and tamoxifen. The absorption, distribution, metabolism and elimination of drugs are discussed in the context of breast cancer. The effect of age and menopause status on drug pharmacokinetics is evaluated. The important role of pharmacokinetic-pharmacodynamic modeling in understanding the phenomenon of chemo fog, memory deficit in breast cancer chemotherapy, is explored.

Introduction

Pharmacokinetics (PK), the study of the time course of drug absorption, distribution, metabolism and excretion, is a critical tool for optimization of drug therapy. Pharmacodynamics (PD) is the study of the pharmacologic effect (Fig. 1A). Pharmacokinetics and pharmacodynamic modeling are especially useful in clinical oncology, because anticancer drugs typically have narrow therapeutic windows. Further, drug exposure and clinical outcome are usually related. Thus, drug safety and efficacy need to be optimized to yield desired therapeutic outcome with the administered dosage, with minimal adverse effects. Pharmacokinetic-pharmacodynamic (PK-PD) evaluation of drugs allows this optimization (Fig. 1B).

The pharmacokinetics of anticancer drugs used in breast cancer therapy are well defined. The utility of PK studies in designing preclinical studies, human dosage regimen design and dose adjustment in special populations is explored with specific examples in this chapter. Future directions such as PK-PD evaluation of breast cancer drugs and the phenomenon of chemo fog are additionally discussed.

Pharmacokinetics of Anticancer Drugs Used in Breast Cancer Chemotherapy

Of the numerous anticancer drugs currently in clinical use, PK of drugs commonly used in breast cancer therapy (Fig. 2) are discussed below.

Cyclophosphamide

Cyclophosphamide is a prodrug that is activated via cytochrome P450 (CYP) enzymes to its active forms.[1,2] It is extensively metabolized to both active as well as inactive metabolites. Its elimination half life is 5-9 h and is shorter in children compared with adults.[3] The prodrug is not highly protein bound and renal excretion is low, possibly due to extensive reabsorption. With advances

*Swati Nagar—Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, USA. Email: snagar@temple.edu

Chemo Fog: Cancer Chemotherapy-Related Cognitive Impairment, edited by Robert B. Raffa and Ronald J. Tallarida

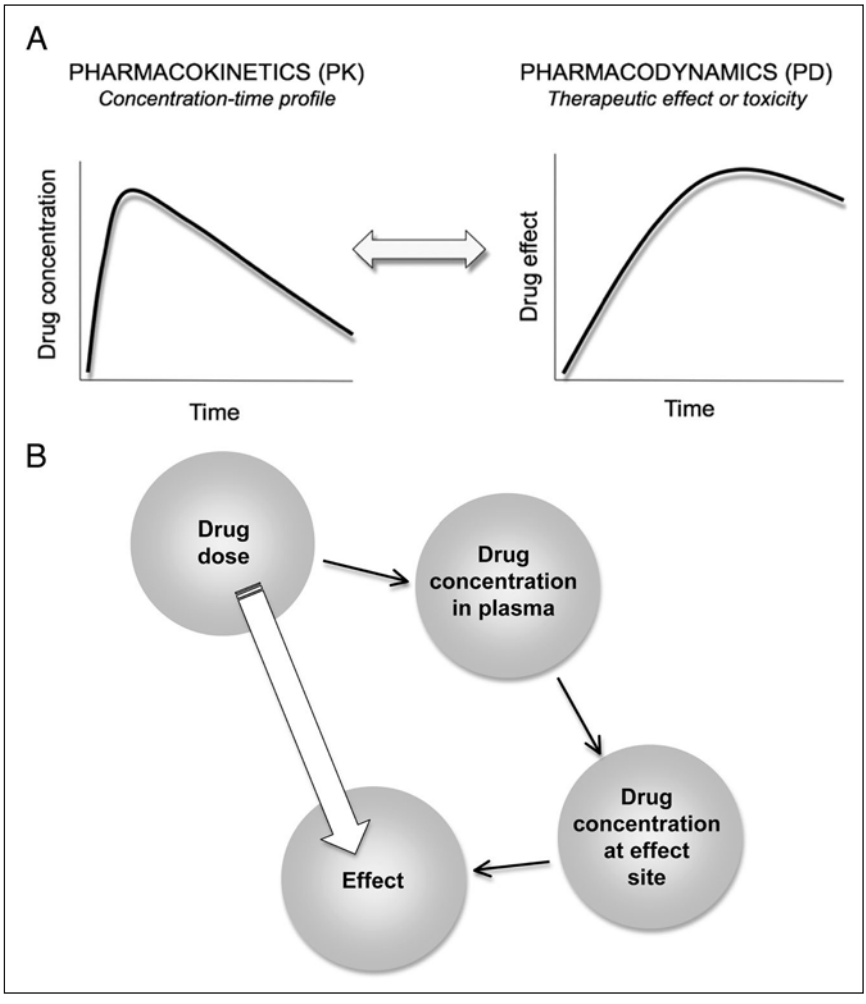

Figure 1. Pharmacokinetics studies the time-course of chemotherapeutic drug plasma concentration after a dose has been administered. Pharmacodynamics is the evaluation of the pharmacologic effect (therapeutic or toxic) that the drug elicits with respect to time (A). A PK-PD model uses a 'link' effect site compartment to relate the drug's concentration to its effect (B).

in bioanalytical methods, studies have recently focused on the PK of active metabolites instead of the inactive prodrug.[3] Large inter-individual variability has been noted in cyclophosphamide PK and CYP pharmacogenetics explains at least part of this variability.[1] Cyclophosphamide is known to cause autoinduction and is susceptible to drug-drug interactions because it is metabolized via CYPs.

Cyclophosphamide PK has been evaluated extensively in preclinical models. The role of CYP enzymes in the PK of cyclophosphamide was characterized in an elegant study utilizing cytochrome P450 reductase null mice.[4] In male wild-type mice, intraperitoneal doses of 100 and 300 mg/kg yielded areas under the plasma-time curve (AUCs) of 1560 and 8100 μg · min/ml respectively. The maximum plasma concentration (Cmax) was 38 and 181 μg/ml respectively at these doses. The intrinsic clearance of the drug was 6-fold greater in wild-type mice compared with the cyp-activity

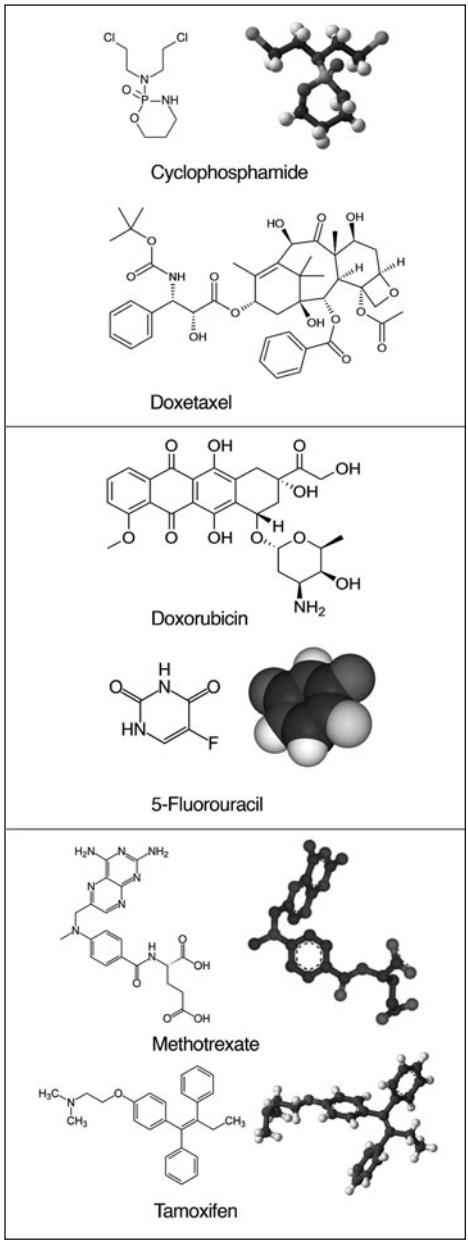

Figure 2. Chemical structures of cyclophosphamide (N,N-Bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide), docetaxel ((2R,3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5, 20-epoxy-1, 2, 4, 7, 10, 13-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate), doxorubicin ((8S,10S)-10-(4-Amino-5-hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione), 5-fluorouracil (5-Fluoro-1H-pyrimidine-2,4-dione), methotrexate ((2S)-2-[(4-{[(2,4-Diamino-7,8-dihydropteridin-6-yl)methyl](methyl)amino}phenyl)formamido]pentanedioic acid), and tamoxifen ((Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethyl-ethanamine).

null mice. Profound differences in the PK of cyclophosphamide between the two groups led to direct evidence of the critical role of CYP enzymes in cyclophosphamide disposition. A recent study developed a different genetically modified mouse model, again with no cyp activity.[5] The PK of cyclophosphamide was similar to previous reports in the wild-type mice. This study corroborated previous reports of the importance of CYP enzymes in cyclophosphamide PK.

Clinically, cyclophosphamide is administered orally or intravenously, most often in combination with doxorubicin, 5-fluorouracil, or adriamycin. Doses ranging from 100-600 mg/m^2 are administered to breast cancer patients[6] and its PK in humans is well established.[3] A study with 1 g/m^2 cyclophosphamide IV 1-h infusion in 29 Caucasian hematological cancer patients reported an AUC of 367 μg · h/ml and Cmax of 37 μg/ml. Drug clearance was estimated to be 6 L/h.[7] Another study was conducted in 51 Japanese breast cancer patients[8] and levels of cyclophosphamide as well as its 4-hydroxy metabolite were measured. The dose range was 600-1500 mg (300-750 mg/m^2), delivered as a one-hour IV infusion. Mean cyclophosphamide AUC was 775 μmol · h/L and a mean clearance of 4 L/h. The mean AUC for the 4-hydroxy metabolite was 9.4 μmol · h/L.[8]

Docetaxel

Docetaxel is a semi-synthetic analog of paclitaxel and is a cytotoxic antimicrotubule agent.[9] It exhibits complex PK in humans. Docetaxel is highly protein bound and α1-acid glycoprotein levels are found to predict docetaxel total clearance.[10] The drug is mainly metabolized by CYP3A4 and 3A5 and metabolites are eliminated fecally. Urinary elimination of the parent and metabolites is <10%.[11] CYP pharmacogenetics and docetaxel PK have been evaluated extensively, but the role of CYP polymorphisms in variable docetaxel disposition remains to be clearly defined.[10] Docetaxel is also a substrate for the efflux transporter P-glycoprotein.

Docetaxel PK has been evaluated in preclinical models, especially to delineate the role of efflux transporters and metabolizing enzymes in its disposition.[12] Docetaxel exhibits linear PK in mice.[13] It is highly protein bound and distributes well into most tissues. Like humans, docetaxel is metabolized and undergoes predominantly hepatobiliary elimination. Docetaxel (10 mg/kg) was dosed orally and IV in control and Pgp knockout mice in a recent study.[14] Oral docetaxel was well absorbed in control mice despite the presence of Pgp. It undergoes extensive first-pass metabolism resulting in poor oral bioavailability. Inhibition of its metabolism is a useful strategy to increase its AUC and exposure.

Clinically, docetaxel exhibited a total clearance of about 29 L/h/m^2 upon a 35 mg/m^2 weekly or 3-weekly schedule.[10] The elimination half-life was 15.6 h based on a 24 h sampling schedule. A mean AUC of 1.32 μg · h/ml was obtained, with a Cmax of 1.85 μg/ml. Studies in elderly patients did not show an effect of age on drug clearance.[15] Docetaxel dose adjustment is required in patients with liver function impairment.[10]

Doxorubicin

Doxorubicin is an anthracycline antibiotic that intercalates with DNA and inhibits topoisomerase II. It is delivered either as the free salt form or as a liposomal formulation.[16] Clearance as well as apparent volume of distribution is lower for liposomal doxorubicin compared with the free form. Doxorubicin is metabolized to cytotoxic doxorubicinol and inactive aglycones.[17] It is known to induce several CYP superfamily members.[18] It is a substrate for the efflux transporter P-gp.

In preclinical studies doxorubicin (0.9 mg/kg dose in rats) was shown to exhibit biphasic PK profiles, with a distribution half life of 5-10 min and an elimination half-life of 29 h.[16] The clearance was about 120 ml/h/kg and the volume of distribution was 5 L/kg. A study in tumor-bearing mice utilized an IV dose of 6 mg/kg doxorubicin formulated in liposomes and yielded an AUC of 3.02 mg · h/ml.[19] The same dose given as free doxorubicin yielded a lower AUC (1.4 mg · h/ml) in tumor-bearing mice in an independent study.[20]

Clinical PK of doxorubicin is well established. Pegylated liposomal doxorubicin was administered as an IV infusion every 4 weeks to 15 patients with advanced solid tumors.[21] The PK profile was monophasic, with a long elimination half-life, low clearance and small volume of distribution. For a dose range of 30-50 mg/m^2, observed plasma AUC was 2513-4663 μg · h/ml, with Cmax in

the range of 19-35 μg/ml and systemic clearance estimate of 13 ml/h/m^2. Similar PK parameters were estimated in an independent study involving liver cirrhosis patients.[22]

5-Fluorouracil

5-fluorouracil (5-FU) is a pyrimidine analog that inhibits DNA synthesis. 5-FU must be converted to its active nucleotide for cytotoxic activity. It is administered IV and a continuous infusion achieves plasma concentrations of 0.5-0.8 μM.[23] 5-FU readily enters the cerebrospinal fluid. Urinary excretion of a single dose is low, about 5-10%. It is inactivated mainly in the liver via dihydropyrimidine dehydrogenase.

In tumor-bearing mice, an oral 13 mg/kg dose of 5-FU was reported to yield a plasma AUC of 55 ng · h/g.[24] In another study, free 5-FU administered IV (40 mg/kg) to control mice displayed one-comparment PK, with an AUC of 639 mg · min/L and an initial plasma concentration of 36 mg/L.[25] A dose of 100 mg/kg of 5-FU administered intraperitoneally to tumor-bearing mice yielded an AUC of 2922 mg/min/L and a Cmax of 124 μg/ml.

Clinical PK of 5-FU has been established in cancer patients. A study in 22 patients with upper gastrointestinal tract adenocarcinomas was conducted in order to establish an association between 5-FU toxicity and its plasma AUC.[26] A dose range of 315-560 mg/m^2 was administered as a 1-h infusion. Plasma AUC in the range of 147-405 mg · min/L was observed, with Cmax ranging from 2.8 to 6.8 μg/ml. The study concluded that increasing the infusion period for 5-FU administration decreased the AUC and therefore its toxicity. A subsequent larger study by another group enrolled 181 colorectal cancer patients.[27] The initial 5-FU dose was selected to attain a target AUC of 596 mg · min/L. However, this study concluded that 5-FU toxicity was not completely associated with its PK and other clinical correlates were necessary to understand its toxic profile.

Methotrexate

Methotrexate is an antifolate drug used in several cancers besides breast cancer.[23] After IV administration it displays triphasic plasma-time curves. About 50% of the drug is plasma albumin-bound. Metabolism is minimal and 90% of the drug is excreted unchanged in the urine. Methotrexate concentrations in the cerebrospinal fluid are low, but cytotoxic levels can be achieved in the CNS with high doses followed by leucovorin rescue.

Methotrexate PK has been reported in preclinical models and appears to be highly variable. For example, a 100 mg/kg intraperitoneal dose in mice yielded plasma AUC in the range of 156-207 μg · h/ml in one study.[28] Another study at a dose of 400 mg/kg i.p. however resulted in a plasma AUC of 238 μg · h/ml.[29] A recent study evaluated i.p. doses in the range 10-600 mg/kg in mice and reported AUCs at 267-12500 μg · h/ml.[30]

Methotrexate disposition was evaluated in 44 pediatric patients with acute lymphoblastic leukemia (ALL).[31] A high dose of 5 g/m^2 resulted in high plasma exposure of drug. The authors evaluated genetic polymorphisms in the human transporter multidrug resistance related protein 2 (MRP2; ABCC2) gene and found a significant gender—specific effect of the -24C > T polymorphism on methotrexate PK. Female patients with at least one copy of the -24T allele had significantly higher AUCs (measured between 36-48 h after start of infusion) than other patients.[31] Methotrexate population PK was evaluated in another study enrolling 79 pediatric ALL patients.[32] A 2-compartment model described drug PK, with a clearance estimate of 8.8 L/h and initial volume of distribution 17.3 L. A 24-h infusion of a 5 g/m^2 dose resulted in an AUC of 588 μg · h/ml. The population PK model made it possible to predict that below a threshold methotrexate level of 0.2 μM, folinic acid administration (delivered to minimize methotrexate-related toxicity) can be stopped.[32]

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator and is commonly used in hormone-responsive breast cancer therapy. The usual dose is 10 mg twice a day, but doses as high as 200 mg per day have been prescribed. It is readily absorbed upon oral administration, with steady-state levels reached at 4-6 weeks.[23] Tamoxifen is metabolized to oxidative metabolites (some of which

are active) via CYP enzymes, which undergo further Phase II glucuronidation and sulfation. The drug and its metabolites undergo enterohepatic recirculation and elimination is predominantly in the feces.

Early preclinical studies reported a lack of detectable tamoxifen concentration at low doses. Slow-release pellets containing 5 or 25 mg tamoxifen were administered subcutaneously to mice, but no plasma drug levels were detectable even after 2 weeks of treatment.[33] Daily s.c. injections of 1000 μg or i.p. 25-100 mg/kg doses resulted in plasma concentrations of 0.21-0.51 μM. In another study, single high dose of tamoxifen in mice (200 mg/kg oral) resulted in detectable levels of parent drug as well as metabolites 4-hydroxytamoxifen and *N*-desmethyltamoxifen.[34] Parent drug plasma AUC was 15.9 μg · h/ml in mice. Metabolite formation in rats was found to be more representative of human metabolism, suggesting that rats rather than mice might be a better preclinical model for tamoxifen disposition studies.

Tamoxifen PK has been well documented in humans.[35-40] In a clinical trial including 34 postmenopausal metastatic breast cancer women, 20 mg tamoxifen was administered daily for 6 weeks.[38] Median concentrations of 107 ng/ml parent, 200 ng/ml *N*-desmethyltamoxifen and 3 ng/ml for 4-hydroxy tamoxifen were observed. High-dose tamoxifen PK was evaluated in 34 male patients with hormone-refractory metastatic prostate cancer.[36] Tamoxifen at 16 mg/m^2/day was administered and yielded an average steady-state concentration of 2.96 μM. Results from a large clinical trial involving 24 international centers and a total of 357 patients were recently published.[35] Tamoxifen alone (20 mg/day) was administered to 111 postmenopausal women with early stage breast cancer. The geometric mean steady-state trough plasma concentration of tamoxifen was 95 ng/ml, while that of *N*-desmethyltamoxifen was 265 ng/ml. A dose range study (1-20 mg/day tamoxifen) was conducted recently in pre as well as postmenopausal women (total n = 120).[39] Median tamoxifen concentration ranged from 7.5 to 83.6 ng/ml in serum and 78.2-744.4 ng/ml in breast tissue. This study further quantitated levels of the 4-hydroxy, *N*-desmethyl and *N*-didesmethyl metabolies in serum, normal breast tissue and breast cancer tissue. Finally, 32 postmenopausal breast cancer patients on 20 mg/day tamoxifen were enrolled in a PK study and a steady-state plasma drug AUC of 3.04 mg · h/L was reported.[37]

Pharmacokinetics in Special Populations: Age and Menopause Status

Age related physiologic changes can alter the PK-PD of a drug. Age therefore becomes an important consideration before starting systemic chemotherapy in breast cancer patients.[41] Drug absorption is affected with age due to decreased gastrointestinal motility, decreased digestive enzyme secretion and decreased blood flow.[42,43] Changes in body composition, decrease in total body water and lower body mass all contribute to altered drug distribution. Hepatic metabolism may be affected with age due to a decrease in liver mass, hepatic blood flow and enzyme function.[41] Tumor biology additionally changes with age.[44] These age-related changes in drug PK-PD also play a critical role in drug-drug interactions, especially in the older patient who is more likely to be on numerous drugs at a given time. Pharmacokinetic data have been collected in elderly breast cancer patients. In some cases, decreased drug clearance has been noted, while other studies have not found a significant effect of age on drug PK.[41,44] It is nevertheless critical to take into account patient age when making decisions regarding chemotherapy drug selection, dosing, single versus combination therapy and therapeutic monitoring for toxicity or adverse events.

Choice of therapy (chemotherapy, hormone therapy, monoclonal antibody) for breast cancer depends on the cancer status, i.e., stage (early versus metastatic), estrogen/progesterone receptor status (positive versus negative) and human epidermal growth factor receptor 2 (Her2/neu) status (positive versus negative). Menopause status—whether a woman is premenopausal, perimenopausal, or postmenopausal—also dictates choice of breast cancer therapy. For example, aromatase inhibitors improve the outcome for early-stage breast cancer in postmenopausal women, but should not be given to premenopausal women as they may stimulate tumor growth.[45,46] Relative amounts of estrogen hormones depend on menopausal status and it remains to be studied whether differential levels of estrogens would alter the PK of an administered drug. Tamoxifen has been shown

to increase estrogen hormone clearance.[47] Estrogens are glucuronidated and sulfated in humans and might interact via these common metabolic pathways with drugs that are also substrates for glucuronidation and sulfation (e.g., tamoxifen). The picture is further complicated by genetic polymorphisms in sulfating and glucuronidating enzymes and their effects on hormone and drug metabolism.[48-52]

Pharmacokinetics of Anticancer Drugs and Memory Deficit as a Pharmacodynamic Endpoint

There is renewed interest in the evaluation of memory deficit as a result of breast cancer chemotherapy. Several reports have recently evaluated cognition in relation to chemotherapy.[53-56] There is debate as to whether any cognitive deficit is associated with chemotherapy, or is instead correlated with stress, hormone changes and age in the older patient. Further, mechanisms underlying cognitive deficits are not yet understood. To date, there have been no studies correlating pharmacokinetics of anticancer drugs with cognition as a pharmacodynamic endpoint. Such studies will be critical to discern the role of PK in any memory deficits due to chemotherapy. It is conceivable that differential effect site drug (or active metabolite) concentrations will correlate with altered cognitive endpoints. Furthermore, study design of such PK-PD studies must incorporate effect site (e.g., brain) drug concentrations instead of only evaluating plasma drug levels.

Conclusion

Pharmacokinetics of drugs used in breast cancer therapy have been evaluated in detail. Memory deficit due to breast cancer chemotherapy is a new area of research. PK-PD studies correlating memory deficit to effect-site anticancer drug concentrations have not been conducted to date. Such studies will be critical in understanding the phenomenon of chemo fog, its underlying mechanisms and in designing therapeutic regimens to minimize these adverse effects.

References

1. Ekhart C, Doodeman VD, Rodenhuis S et al. Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide. Pharmacogenet Genomics 2008; 18(6):515-23.
2. Roy P, Yu LJ, Crespi CL et al. Development of a substrate-activity based approach to identify the major human liver P-450 catalysts of cyclophosphamide and ifosfamide activation based on cDNA-expressed activities and liver microsomal P-450 profiles. Drug Metab Dispos 1999; 27(6):655-66.
3. de Jonge ME, Huitema AD, Rodenhuis S et al. Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet 2005; 44(11):1135-64.
4. Pass GJ, Carrie D, Boylan M et al. Role of hepatic cytochrome p450s in the pharmacokinetics and toxicity of cyclophosphamide: studies with the hepatic cytochrome p450 reductase null mouse. Cancer Res 2005; 65(10):4211-7.
5. Gu J, Chen CS, Wei Y et al. A mouse model with liver-specific deletion and global suppression of the NADPH-cytochrome P450 reductase gene: characterization and utility for in vivo studies of cyclophosphamide disposition. J Pharmacol Exp Ther 2007; 321(1):9-17.
6. Bang SM, Heo DS, Lee KH et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000; 89(12):2521-6.
7. Xie H, Griskevicius L, Stahle L et al. Pharmacogenetics of cyclophosphamide in patients with hematological malignancies. Eur J Pharm Sci 2006; 27(1):54-61.
8. Nakajima M, Komagata S, Fujiki Y et al. Genetic polymorphisms of CYP2B6 affect the pharmacokinetics/pharmacodynamics of cyclophosphamide in Japanese cancer patients. Pharmacogenet Genomics 2007; 17(6):431-45.
9. Fulton B, Spencer CM. Docetaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of metastatic breast cancer. Drugs 1996; 51(6):1075-92.
10. Baker SD, Sparreboom A, Verweij J. Clinical pharmacokinetics of docetaxel: recent developments. Clin Pharmacokinet 2006; 45(3):235-52.

11. Clarke SJ, Rivory LP. Clinical pharmacokinetics of docetaxel. Clin Pharmacokinet 1999; 36(2):99-114.
12. Schellens JH, Malingre MM, Kruijtzer CM et al. Modulation of oral bioavailability of anticancer drugs: from mouse to man. Eur J Pharm Sci 2000; 12(2):103-10.
13. Sparreboom A, van Tellingen O, Nooijen WJ et al. Preclinical pharmacokinetics of paclitaxel and docetaxel. Anticancer Drugs 1998; 9(1):1-17.
14. Bardelmeijer HA, Ouwehand M, Buckle T et al. Low systemic exposure of oral docetaxel in mice resulting from extensive first-pass metabolism is boosted by ritonavir. Cancer Res 2002; 62(21):6158-64.
15. ten Tije AJ, Verweij J, Carducci MA et al. Prospective evaluation of the pharmacokinetics and toxicity profile of docetaxel in the elderly. J Clin Oncol 2005; 23(6):1070-7.
16. Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. Clin Pharmacokinet 2003; 42(5):419-36.
17. Kivisto KT, Kroemer HK, Eichelbaum M. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. Br J Clin Pharmacol 1995; 40(6):523-30.
18. Zordoky BN, El-Kadi AO. Induction of several cytochrome P450 genes by doxorubicin in H9c2 cells. Vascul Pharmacol 2008; 49(4-6):166-72.
19. Charrois GJ, Allen TM. Drug release rate influences the pharmacokinetics, biodistribution, therapeutic activity and toxicity of pegylated liposomal doxorubicin formulations in murine breast cancer. Biochim Biophys Acta 2004; 1663(1-2):167-77.
20. Hong RL, Huang CJ, Tseng YL et al. Direct comparison of liposomal doxorubicin with or without polyethylene glycol coating in C-26 tumor-bearing mice: is surface coating with polyethylene glycol beneficial? Clin Cancer Res 1999; 5(11):3645-52.
21. Fujisaka Y, Horiike A, Shimizu T et al. Phase 1 clinical study of pegylated liposomal doxorubicin (JNS002) in Japanese patients with solid tumors. Jpn J Clin Oncol 2006; 36(12):768-74.
22. Varela M, Real MI, Burrel M et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46(3):474-81.
23. Chabner BA, Ryan DP, Paz-Ares L et al. Antineoplastic Agents in Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill, 2001.
24. Ooi A, Ohkubo T, Higashigawa M et al. Plasma, intestine and tumor levels of 5-fluorouracil in mice bearing L1210 ascites tumor following oral administration of 5-fluorouracil, UFT (mixed compound of tegafur and uracil), carmofur and 5′-deoxy-5-fluorouridine. Biol Pharm Bull 2001; 24(11):1329-31.
25. Jin Y, Li J, Rong LF et al. Pharmacokinetics and tissue distribution of 5-fluorouracil encapsulated by galactosylceramide liposomes in mice. Acta Pharmacol Sin 2005; 26(2):250-6.
26. Grem JL, Quinn M, Ismail AS et al. Pharmacokinetics and pharmacodynamic effects of 5-fluorouracil given as a one-hour intravenous infusion. Cancer Chemother Pharmacol 2001; 47(2):117-25.
27. Gusella M, Crepaldi G, Barile C et al. Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. Ann Oncol 2006; 17(11):1656-60.
28. Song JG, Nakano S, Ohdo S et al. Chronotoxicity and chronopharmacokinetics of methotrexate in mice: modification by feeding schedule. Jpn J Pharmacol 1993; 62(4):373-8.
29. Ohdo S, Inoue K, Yukawa E et al. Chronotoxicity of methotrexate in mice and its relation to circadian rhythm of DNA synthesis and pharmacokinetics. Jpn J Pharmacol 1997; 75(3):283-90.
30. Lobo ED, Balthasar JP. Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice. J Pharm Sci 2003; 92(8):1654-64.
31. Rau T, Erney B, Gores R et al. High-dose methotrexate in pediatric acute lymphoblastic leukemia: impact of ABCC2 polymorphisms on plasma concentrations. Clin Pharmacol Ther 2006; 80(5):468-76.
32. Plard C, Bressolle F, Fakhoury M et al. A limited sampling strategy to estimate individual pharmacokinetic parameters of methotrexate in children with acute lymphoblastic leukemia. Cancer Chemother Pharmacol 2007; 60(4):609-20.
33. DeGregorio MW, Wilbur BJ, Coronado E et al. Serum tamoxifen concentrations in the athymic nude mouse after three methods of administration. Cancer Chemother Pharmacol 1987; 20(4):316-8.
34. Robinson SP, Langan-Fahey SM, Johnson DA et al. Metabolites, pharmacodynamics and pharmacokinetics of tamoxifen in rats and mice compared to the breast cancer patient. Drug Metab Dispos 1991; 19(1):36-43.
35. Dowsett M, Cuzick J, Howell A et al. Pharmacokinetics of anastrozole and tamoxifen alone and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer 2001; 85(3):317-24.
36. Bergan RC, Reed E, Myers CE et al. A Phase II study of high-dose tamoxifen in patients with hormone-refractory prostate cancer. Clin Cancer Res 1999; 5(9):2366-73.

37. Hutson PR, Love RR, Havighurst TC et al. Effect of exemestane on tamoxifen pharmacokinetics in postmenopausal women treated for breast cancer. Clin Cancer Res 2005; 11(24 Pt 1):8722-7.
38. Ingle JN, Suman VJ, Johnson PA et al. Evaluation of tamoxifen plus letrozole with assessment of pharmacokinetic interaction in postmenopausal women with metastatic breast cancer. Clin Cancer Res 1999; 5(7):1642-9.
39. Kisanga ER, Gjerde J, Guerrieri-Gonzaga A et al. Tamoxifen and metabolite concentrations in serum and breast cancer tissue during three dose regimens in a randomized preoperative trial. Clin Cancer Res 2004; 10(7):2336-43.
40. Kisanga ER, Gjerde J, Schjott J et al. Tamoxifen administration and metabolism in nude mice and nude rats. J Steroid Biochem Mol Biol 2003; 84(2-3):361-7.
41. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. Cancer Control 2007; 14(1):32-43.
42. Yuen GJ. Altered pharmacokinetics in the elderly. Clin Geriatr Med 1990; 6(2):257-67.
43. Baker SD, Grochow LB. Pharmacology of cancer chemotherapy in the older person. Clin Geriatr Med 1997; 13(1):169-83.
44. Hamberg P, Verweij J, Seynaeve C. Cytotoxic therapy for the elderly with metastatic breast cancer: a review on safety, pharmacokinetics and efficacy. Eur J Cancer 2007; 43(10):1514-28.
45. Ortmann O, Cufer T, Dixon JM et al. Adjuvant endocrine therapy for perimenopausal women with early breast cancer. Breast 2009; 18(1):2-7.
46. Utsumi T, Kobayashi N, Hanada H. Recent perspectives of endocrine therapy for breast cancer. Breast Cancer 2007; 14(2):194-9.
47. Levin J, Markham MJ, Greenwald ES et al. Effect of tamoxifen treatment on estrogen metabolism in postmenopausal women with advanced breast cancer. Anticancer Res 1982; 2(6):377-80.
48. Sparks R, Ulrich CM, Bigler J et al. UDP-glucuronosyltransferase and sulfotransferase polymorphisms, sex hormone concentrations and tumor receptor status in breast cancer patients. Breast Cancer Res 2004; 6(5):R488-98.
49. Nagar S, Remmel RP. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene 2006; 25(11):1659-72.
50. Nagar S, Walther S, Blanchard RL. Sulfotransferase (SULT) 1A1 polymorphic variants *1, *2 and *3 are associated with altered enzymatic activity, cellular phenotype and protein degradation. Mol Pharmacol 2006; 69(6):2084-92.
51. Gjerde J, Hauglid M, Breilid H et al. Effects of CYP2D6 and SULT1A1 genotypes including SULT1A1 gene copy number on tamoxifen metabolism. Ann Oncol 2008; 19(1):56-61.
52. Ohtake E, Kakihara F, Matsumoto N et al. Frequency distribution of phenol sulfotransferase 1A1 activity in platelet cells from healthy Japanese subjects. Eur J Pharm Sci 2006; 28(4):272-7.
53. Nelson CJ, Nandy N, Roth AJ. Chemotherapy and cognitive deficits: mechanisms, findings and potential interventions. Palliat Support Care 2007; 5(3):273-80.
54. Jenkins V, Atkins L, Fallowfield L. Does endocrine therapy for the treatment and prevention of breast cancer affect memory and cognition? Eur J Cancer 2007; 43(9):1342-7.
55. Palmer JL, Trotter T, Joy AA et al. Cognitive effects of Tamoxifen in premenopausal women with breast cancer compared to healthy controls. J Cancer Surviv 2008; 2(4):275-82.
56. Jim HS, Donovan KA, Small BJ et al. Cognitive functioning in breast cancer survivors: a controlled comparison. Cancer 2009; 115(8):1776-83.