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

Pharmacokinetics of Anti-Cancer Drugs Used in Breast Cancer Chemotherapy

125

Pharmacokinetics of Anti-Cancer Drugs Used in Breast Cancer Chemotherapy

in bioanalytical methods, studies have recently focused on the PK of active metabolites instead of the inactive prodrug. Large inter-individual variability has been noted in cyclophosphamide PK and CYP pharmacogenetics explains at least part of this variability. 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. 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 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).