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Therapeutic Importance of Biological Half-Life of Antineoplastic Agents- A Review

Running Title: Antineoplastic Agents and Their Pharmacokinetics

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Abstract Lung, prostate, and stomach cancer are the most prevalent cancers among males. Breast, colon, and cervical cancer are the most prevalent cancers among women. The literature also shows that patients suffering from cancer are increasing constantly, and hence the number of different chemotherapy treatments administered is increasing. The main objective of this review article is to summarize the effect of age on the half-life of some antineoplastic drugs belonging to the category of Topoisomerase inhibitors, alkylating agents, anthracyclines, purine analogs, antimetabolites, and N-nitrosoureas along with their pharmacokinetic properties. Literature indicates that highly bound antineoplastic drugs have higher differences in unbound drug concentrations among patients, and in some cases, the amount of concentration is not reflective of the unbound drug level and has an impact on pharmacokinetic parameters, including absorption, the volume of distribution, drug metabolism, and excretion. Protein binding affects the distribution and bioavailability of active drug substances.

Keywords Half-Life, Antineoplastic Agents, Pharmacokinetics, Cytochrome P450, Plasma Protein Binding

1. Introduction

Noncommunicable diseases (NCDs) have reached pandemic proportions around the world, as is widely acknowledged [1]. According to current epidemiological results, chronic respiratory disorders, cancer, diabetes, and cardiovascular disorders cancer are the main causes of noncommunicable diseases (NCDs) in Low Middle-Income Countries. According to World Health Organization, cancer is the leading cause of death in 2020, with an estimated 10 million fatalities, or about one in every six deaths. Cancer can arise in any cell type in the body. Cancer cells divide indefinitely, producing solid tumors or invading the bloodstream with aberrant cells. They can also spread from one part of the body to another through the process of metastasis. The main goals of chemotherapy are to treat cancer and improve the patient's quality of life [2]. Chemotherapy is one of the most challenging scientific issues since there has been minimal improvement in the overall cancer survival landscape over the recent decades. The lack of tumor selectivity is a present risk of most conventional anticancer chemotherapy drugs [3].

In the face of existing chemotherapy problems, a vital step toward improving cancer treatment is to target therapeutic molecules directly to tumor cells while avoiding injury to healthy tissues. Surgery, chemotherapy, radiation, targeted therapy, and immunotherapy are all forms of cancer treatment [4]. Traditional chemotherapy treats cancer with cytotoxic chemotherapeutic drugs. There are a number of commonly reported side effects and toxicity related to the drug, including bone marrow dysfunction, hematopoiesis dysfunction, hair loss, nausea, exhaustion, and vomiting. Chemotherapeutic drugs involve a mechanism that results in various adverse effects. Poor targeting and low bioavailability of chemotherapeutic agents are additional elements that lead to chemotherapy failure [5].

Understanding the concept of half-life helps to determine the elimination rates as well as steady-state plasma concentration for any specific therapeutic moieties. A significant pharmacological property has been considered as the drug's half-life in plasma or serum. The half-life of the drug concerns the amount of drug in plasma and depends on how quickly the drug is eliminated from the plasma. Different anticancer drugs have different half-lives. The rate of metabolism and elimination of the drug determines the drug's half-life. The half-life of drugs that are slowly metabolized will be longer. Drugs that are quickly metabolized have a shorter half-life [6]. The main objective of the review article is to design a more specific chemotherapeutic agent which exhibits desired therapeutic action in a minimum dose. A critical thrust towards improving cancer therapy which specially targets tumor cells without affecting healthy tissues.

2. Factors Affecting the Half-Life of Drugs

2.1. Dose

The effect of dose on antineoplastics pharmacokinetics has been reported to be similar to that of other drugs. Because of the increased use of antineoplastic agents at generally quite high doses, pharmaceuticals are tested over a wide range of doses during an early evaluation. It is critical to select the optimum drug dose in order to achieve a good therapeutic activity. The majority of anticancer drugs have a small therapeutic window and a strong dose-response relationship. Pharmacokinetic (PK) variability across individuals is common. The most important pharmacokinetics factor for anti-cancer drugs is the area under the plasma concentration versus time curve (AUC). A lower dose may not provide the desired treatment effect but may promote tumor growth, whereas a higher dose is hazardous to the patient's health. To reduce inter-individual variability, various methods for calculating anticancer drug doses have been used, such as Body surface area-based dosing, Glomerular filtration rate-based dosing, Phenotype-guided dosing, therapeutic drug monitoring, and toxicity-adjusted dosing methods. In that, body surface area-based (BSA) dosage fails to standardize systemic anticancer drug exposure, and other potential dosing techniques have their own set of drawbacks. The use of therapeutic drug monitoring (TDM) strategies for cytotoxic drugs in chemotherapy is strongly supported by existing research. The hormesis is also manifested in the dose-response relationship of numerous antineoplastic agents in a significant number of experiments. Calculating the proper dose will be made easier by modelling this behavior [7,8].

3. Metabolism by Cytochrome P450 Enzymes

Phase I processes are catalyzed by cytochrome P450 enzymes, a large superfamily of membrane-bound proteins largely present in the endoplasmatic reticulum. CYPs in the liver metabolize cyclophosphamide, ifosfamide, dacarbazine, procarbazine, tegafur, and thiotepa, and this activation process is essential for therapeutic effect. The cytochrome P450 families most involved in drug metabolism are CYP1, CYP2, and CYP3. Two major types may be distinguished among the phase I polymorphic cytochrome P450 enzymes that metabolize the xenobiotics. Class I enzymes including CYP2E1, CYP1A1, CYP1A2, and CYP3A4 metabolize pre-carcinogens and drugs. These are very conserved and perform several therapeutically significant roles. The highly polymorphic class II enzymes CYP2C9, CYP2B6, CYP2C19, and CYP2D6 are active in the metabolism of drugs but not pre-carcinogens. Phase II reactions combine phase I products to produce inactive polar compounds that are excreted by the kidneys and bile. Glutathione S-transferases (GSTs) and uridine diphosphate glucuronosyltransferases (UGTs) are phase II drug-metabolizing enzymes that use conjugation mechanisms to inactivate or activate anticancer medicines [9,10].

3.1. Anthracyclines

Anthracyclines are chemotherapeutic medications that disrupt nucleic acid (DNA and RNA) synthesis by inhibiting topoisomerases in cancer cells. They are used to treat different kinds of cancers like lung, breast, stomach, uterine, and ovarian cancer. The concomitant treatment of verapamil increased the elimination half-life of doxorubicin and lowered the rate of clearance, implying that verapamil inhibited doxorubicin metabolism. Furthermore, cyclosporin has been suggested to reduce the doxorubicin metabolism or excretion in cancer patients. Because cyclosporin and verapamil, which are both CYP3A substrates, increased doxorubicin plasma levels, one or more CYP3A enzymes may be involved in doxorubicin metabolism. The CYP3A inducers and inhibitors have an effect on the pharmacokinetics and pharmacodynamics of doxorubicin. Furthermore, calcium (ca^{++}) channel blockers and cyclosporin may affect the pharmacokinetics of doxorubicin and other antineoplastic agents by acting as P-glycoprotein inhibitors, for example, the P- glycoprotein-mediated biliary drug clearance. The combination of four P-glycoprotein inhibitors, cyclosporin A, verapamil, tetrandrine, and doxorubicin, has been suggested as a more beneficial strategy to improve drug concentration in brain areas and reduce drug toxicity [11]. Without cyclosporin, nausea and vomiting were increased and myelosuppression was noticed at 60% of the prescribed dosage of doxorubicin [12].

3.2. Epipodophyllotoxins

Epipodophyllotoxins are naturally occurring substances found in the root of the American Mayapple plant. Currently, several epipodophyllotoxin compounds are utilized to treat cancer. Etoposide and teniposide are two of them. They act as anti-cancer medications by creating a complex with topoisomerase II and DNA, which inhibits DNA synthesis. CYP3A4 is primarily responsible for catechol synthesis in the human liver via O-demethylation of teniposide and etoposide. Midazolam, erythromycin, and cyclosporin (CYP3A4) are all potent inhibitors of catechol synthesis from etoposide and teniposide. Although it is unknown how much 0- demethylation helps in vivo elimination of these compounds, catechol synthesis appears to have only a modest role in epipodophyllotoxins metabolism [13]. When anticonvulsive drugs (phenobarbitone or phenytoin) are administered concurrently, the clearance of etoposide and teniposide has been shown to be significantly enhanced [14,15]. Cyclosporin alters the etoposide pharmacokinetics in a concentration-dependent manner [16]. The area under the curve of etoposide increased by 80% and clearance decreased by 40% when cyclosporin was given at the same time. However, another CYP3A4 substrate, nifedipine, had no effect on the pharmacokinetics of etoposide [17].

3.3. Vinca Alkaloids

Catharanthus roseus and other vinca plants produce anti-mitotic and anti-microtubule alkaloids known as vinca alkaloids. Vinca alkaloids are used to treat cancer. These alkaloids act by binding to tubulin and preventing it from polymerizing into microtubules, which prevents cell division during metaphase. Some of these compounds include vinblastine, vincristine, vindesine, and vinorelbine. In the treatment of malignant disorders, vincristine is given intravenously. Vincristine metabolism is at least partially mediated by cytochrome P450 3A4 [18]. Concomitant nifedipine treatment significantly reduced vincristine clearance and the elimination of half-life. Other CYP3A inducers and vinca alkaloids interactions are clinically relevant [19]. CYP3A subfamily enzymes biotransformed vindesine into one major metabolite. This metabolite's structure was unknown. The CYP3A subfamily is involved in hepatic metabolism since vinblastine, vincristine, and vinorelbine all showed a severe inhibitory effect on vindesine metabolism. Additionally, known CYP3A subfamily inhibitors such as erythromycin and ketoconazole decreased the metabolism of vinblastine [20].

3.4. Cyclophosphamide

It is a chemotherapeutic prodrug that converts into its active metabolite by cytochrome P450 (CYP) metabolism. Cyclophosphamide acts by inhibiting cancer cells in the body by forming crosslinks with and between DNA strands at the guanine N-7 position. To examine the cyclophosphamide toxicokinetics and to determine the significance of hepatic P450 metabolism on the pharmacokinetics of the drug in vivo, researchers used the Cytochrome P450 Reductase Null (HRN) animal, which had virtually no hepatic cytochrome P450 activity [14]. HRN mice had a 6-fold lower in vitro metabolism and intrinsic clearance of CPA than wild-type mice. This shift in CPA metabolism was mirrored in vivo, with significant differences in CPA and its metabolite pharmacokinetics. The HRN mice's Cmax, plasma area under the curve (AUC), and half-life are enhanced, respectively at a cyclophosphamide dose of 100 mg/kg. Similar effects were reported at a dose of 300 mg/kg. These findings back up the hypothesis that hepatic metabolism is the main route for CPA elimination. Although at differing rates, the HRN animals produced the principal CPA metabolites, 4-hydroxycyclophosphamide (4-OH-CPA), and 3-dechloroethylcyclophosphamide. At 100 mg/kg, 4-hydroxycyclophosphamide's half-life increased by 1.8 times, its Cmax decreased by 1.7 times, but its area under the curve (AUC) remained the same [11]. In adults, cyclophosphamide pharmacokinetic variability has been demonstrated to alter therapy efficacy and toxicity. Children show the same kinds of variations as adults [21]. It's a prodrug that needs cytochrome P450 (CYP450) enzymes to work [22]. Hepatic blood flow variations, cirrhosis-related hepatocellular loss, patient-to-patient variation in the expression of CYP450 enzyme families, and dietary factors all have an effect on the metabolism of cyclophosphamide. It also occurs at varying rates in children and adults. Hepatic enzyme-inducing drugs like phenobarbitone and prednisolone increase their metabolism, while inhibitors like phenobarbitone decrease their metabolism [21].

4. Plasma Protein Binding

Therapeutic drug monitoring's major purpose is to allow for drug dosage individualization based on individual differences in drug metabolism and/or excretion rates. Proteins are not filtered by glomeruli, the protein-bound drug has no effect and is not excreted. As a result, it is gradually discharged. The bound drug does not reach tissues, is not metabolized, and has no pharmacologic activity. Plasma protein binding will decrease drug transverse across the cell membrane, decrease drug metabolism and excretion, prevent crossing the blood-brain barrier, placental barrier, and the glomerulus, serve as a reservoir, release more drugs to maintain equilibrium, prolong the duration of action, change the half-life, and decrease the volume of distribution. Latter is a function of tissue protein binding. Thus, the distribution of highly albumin-bound drugs will be limited to blood volume. The significance of estimating bound and free plasma concentrations of chemotherapeutic medicines in clinical practice has been convincingly proven for various key drugs during the last few decades.

4.1. Binding Proteins

Plasma protein binding, with the exception of inert, lipid-soluble drugs that can interact with complexes of lipoprotein globulins via the lipid component, usually indicates the interaction of a drug's ionized polar or non-polar groups with the protein's analogous groups. The majority of anticancer medicines are weak acids or bases [23].

The majority of acidic medicines bind to human serum albumin (HAS), and several drug binding sites have been recognized [24,25]. When a medication binds to one of these sites, it has no effect on the functions of other binding sites. Basic drugs, on the other hand, bind to plasma proteins more than human serum albumin. The α1-Acid glycoprotein (AAG; orosomucoid) is a significant binder for several basic drugs [26]. In cancer patients, the binding of various anticancer medicines to plasma proteins is changed. In these patients, the predominant alterations in drug binding proteins are an increase in α1-Acid glycoprotein and a decrease in human serum albumin concentration. Although it is raised in numerous neurodegenerative and carcinogenic disorders, the action of α1-Acid glycoprotein remains unknown. A healthy person's plasma contains more α1-Acid glycoprotein, and males appear to have slightly higher α1-Acid glycoprotein levels than females. Human serum albumin levels may be lower in cancer patients, with greater plasma volume and a longer half-life. In some pathological circumstances, plasma protein binding reduces, resulting in an increase in free fraction and a decrease in half-life [24].

4.2. Binding of Anticancer Drugs

Protein binding of antineoplastic agents like bleomycin and thiotepa varies, but the drugs like teniposide and vinblastine are bound to proteins present in the plasma. The differences in plasma protein binding of antineoplastic agents are usually less amount in metabolically healthy patients. As a result, protein binding is a crucial factor to consider while monitoring therapeutic drugs [27,28]. Highly bound anticancer medicines have higher differences in unbound drug concentrations among patients and it is helpful to monitor the drug concentration in cancer patients. they are the most suitable candidates for unbound drug concentration monitoring. In some circumstances, the amount of drug present in plasma does not correspond to the level of the unbound drug [24].

4.3. Protein Concentration-Dependent Binding

The half-life of various antineoplastic agents based on their plasma protein binding is shown in table 1. Etoposide binds 95% in patients with normal serum albumin and bilirubin, and teniposide binds even more strongly, with >98% bound to plasma proteins, resulting in a longer half-life [29]. The only antineoplastic agents for which unbound concentrations are measured and the relationship between therapeutic effects and the unbound drug has been thoroughly examined are platinum-containing anticancer medications such as cisplatin, carboplatin, and oxaliplatin. Nucleophiles attack these agents immediately, exchanging one or both chloride ligands to generate high to low-molecular molecular weight complexes. After gradual infusion of cisplatin intravenously, 65 to 98 percent of platinum was identified in the plasma of patients. The amount of protein binding also causes decreased urine excretion and increased platinum tissue accumulation. Unbound and total carboplatin concentration-time profiles are similar throughout the first six hours after drug administration, unlike cisplatin, and the distribution half-life is similar for different species [24].

Table 1. Half-life of antineoplastic agents with respect to plasma protein binding

Antineoplastic agents	% Unbound	Half-life (Hours)
Amsacrine	3	2.63
Brequinar	2	13-18
Carboplatin	10	2.0±0.2
Chlorambucil	1	1.3±0.9
Cisplatin	<5	0.5±0.1
Cyclophosphamide	87	7.5±4.0
Cytarabine	87	2.6±0.6
Docetaxel	<2	14±705
Doxorubicin	15-25	26±17
Etoposide	4	8.1±4.3
5-Fluorouracil	>95	0.2±0.07
Ifosfamide	45	3.8-8.6
Irinotecan	65	12±3.0
Melphalan	71-80	1.4±0.2
6-Mercaptopurine	81	0.9±0.4
Methotrexate	54	7.2±2.1
Teniposide	<1	9.0±3.0
Thiotepa	90	2.1±0.4
Topotecan	79	3.5±1.5
Trimetrexate	2	13.0±5.0
Vinblastine	<1	29±12
Vinorelbine	12	45±12

5. Effect of Age on the Half-Life of the Anticancer Drug

Pharmacokinetic properties include absorption, the volume of distribution, drug metabolism, and excretion are influenced by age. Blood cells, plasma composition, serum protein profile, and all influence the volume of distribution (Vd). Up until the age of 85, total body fat is increased and a decrease in body water is common. Between the ages of 30 and 80, the amount of fat increases from 15% to 30% of body weight, while intracellular water declines from 42 percent. These modifications lead to a lower volume of distribution (Vd) of aqueous-soluble drugs like anthracyclines while increasing the volume of distribution (Vd) of fat-soluble drugs like carmustine (BCNU). Therefore, the half-life is increased by the increase in the volume of distribution (Vd).

5.1. Topotecan

Topotecan is a drug that acts by inhibiting topoisomerases and it is used to treat ovarian, cervical, and small cell lung carcinoma. Hypoalbuminemia has a lower influence on the unbound fraction and toxicity in the elderly than irinotecan. The half-life of topotecan is 3 hours and renal elimination accounts for 40%, and bile concentration also plays an important role.

5.2. Methotrexate

Methotrexate is an antimetabolite of an antifolate type that acts by inhibiting dihydrofolate reductase and also has an immunosuppressive effect and is used to treat breast, leukemia, lymphoma, lung cancer, osteosarcoma, and gestational trophoblastic disease. Elderly patients should take extreme precautions since oral methotrexate has a blood bioavailability of 50–60%, due to the considerable variability of GIT absorption. It is eliminated completely by the kidneys and binds to plasma proteins up to 50%. While methotrexate is distributed in fluid volume, which declines with age, the percentage of unbound drug and Volume of distribution are not significantly different in younger (25–50 years) and aged (60–80 years) patients using methotrexate for rheumatoid arthritis. The renal clearance of free and total methotrexate increased as the elimination half-life increased, most likely due to impaired renal function in the old-aged group [30].

5.3. Cyclophosphamide

Cyclophosphamide is an alkylating agent that acts by inhibiting or preventing the multiplication of cancer cells in the body and is used to treat various kinds of cancers like sarcoma, lymphoma, breast, and ovarian, and small cell lung cancer. Cyclophosphamide is absorbed orally with an actual bioavailability of about 100%, with 20% of the drug bound to plasma proteins. Cyclophosphamide is inactive until it is converted to 4-hydroxy-cyclophosphamide in the liver, which is then degraded to generate phosphoramide mustard, the final alkylating agent. Cyclophosphamide is mostly excreted as metabolites, with about 5–25% of the unaltered drug passing via urine [30]. The active metabolites of cyclophosphamide have steep dose-response curves, and age-related changes in the liver may influence efficacy and toxicity. Due to cyclophosphamide's slower hepatic clearance, prolonged half-life, and presence and inactivation of its active metabolite 4-hydroxy-cyclophosphamide, patients with moderate hepatic impairment do not experience any changes in their overall exposure to the active metabolites. Hypoalbuminemia increases plasma concentration and reduces the half-life of the active ingredient. It also increases the risk of dementia, a significant ifosfamide side effect [31].

5.4. Ifosfamide

Ifosfamide is an alkylating anticancer medicine that is used to control and treat cancers such as non-Hodgkin lymphoma, sarcoma, and lung cancer. Ifosfamide is a structural isomer of the widely used alkylating chemical oxazaphosphorine cyclophosphamide. It's a prodrug' that needs to be biotransformed to become cytotoxic. The amount of body water decreases with age, and because ifosfamide is a water-soluble medication, the volume of distribution should be lower. In contrast, the volume of distribution of ifosfamide has been found to be higher in elderly patients [32]. Ifosfamide has a half-life of 3.85 hours in individuals under 60 years old and 6.03 hours in those over 60 years old, respectively. Hypoalbuminemia leads to increased plasma concentration and a shorter half-life for the ifosfamide, and it's also a risk factor for dementia, a possible ifosfamide adverse effect [33].

5.5. Melphalan

Melphalan is a nitrogen mustard alkylating agent that acts by alkylating the DNA nucleotide guanine that results in inhibiting DNA and RNA synthesis and it is used to treat various myeloma (a type of cancer of the bone marrow). Melphalan is also used to treat a specific kind of ovarian cancer. Melphalan's oral absorption is unpredictable and incomplete, with a bioavailability of 25–89%, and it's likely to be even worse for the elderly. It is degraded spontaneously in plasma. Melphalan is only partially excreted by the kidneys, so it is advised to alter the dosage: use 85% of the usual dose for renal clearance rates of 60 ml/min, 75% for those of 45 ml/min, and 70% for those of 30 ml/min. Regarding dosage modifications in liver disease, there is no information. Thus, older patients have a longer half-life of melphalan [34].

5.5. Carmustine

Carmustine (BCNU) is a fat-soluble N-nitrosoureas substance that acts by inhibiting DNA replication and transcription that rapidly crosses the blood-brain barrier. This implies that the volume of distribution in the elderly may increase considerably, increasing half-life in adults with approximately double the fat content of younger people. Clinical studies provide evidence that older people frequently receive inadequate doses, notwithstanding the probability that this is the scenario. About 60-70 percent of the dosage is excreted in the urine after 96 hours, and recommendations for dose modification have been provided [35].

5.6. Gemcitabine

Gemcitabine is an antimetabolite that acts by inhibiting the process of DNA replication and it is used to treat pancreatic, breast, lung, and bladder carcinomas and has a wide range of activity and its plasma protein binding is 10%. Despite the fact that there is no relationship between pharmacokinetic parameters and toxicity, gemcitabine is more likely to produce skin toxicity and renal failure in those with creatinine levels above 1.6 mg/dL, making it difficult to provide accurate dose recommendations. In individuals with renal or hepatic impairment, however, caution is advised. Age and sex influence the overall renal elimination and half-life of gemcitabine, with men having a longer half-life as they get older [35].

5.7. Fludarabine

Fludarabine is a purine derivative that acts by inhibiting ribonucleotide reductase and DNA polymerase. The active metabolite 2-fluoro-ara-A is formed rapidly and its elimination half-life is about 6.8–12.5 hours. Fludarabine associated with neutropenia is closely proportional to total body clearance, AUC, and elimination half-life in individuals with renal impairment, with a half-life of up to 24 hours reported. Dose modifications may be necessary for people with renal impairment [36,37].

5.8. Idarubicin

Idarubicin is an antileukemic anthracycline medication. It attaches to DNA and prevents DNA unwinding by interfering with topoisomerase II. Idarubicin is an orally given medication with poor bioavailability (30%) and age-independent pharmacokinetics. It is expected to be less harmful to the heart than doxorubicin. Idarubicin is largely eliminated through the hepatobiliary system, but it is also excreted through the kidneys to a lesser extent, and it has a prolonged half-life of elimination, particularly for the active metabolite idarubicinol. Total plasma clearance is markedly reduced in patients with renal impairment, dosage adjustment is required [38]. Patients with acute myeloid leukemia under the age of 60 were compared to those over 60 who were both given an idarubicin regimen at 8 and 12 mg/m^2, respectively. Idarubicinol has a significantly prolonged half-life (60 vs 41 hours) and a 50% decrease in renal clearance in aged people. Despite the fact that the elderly and non-elderly received different doses, their exposure was similar, and the necessity for dose adjustment in the elderly, despite the fact that no guidelines exist [39].

6. Conclusions

World Health Organization (WHO) also expressed concern about the incidence of cancer which is constantly increasing and it has been expected to continue with the number of new cancer cases. The relationship between administered dosage, age, tissue concentration, metabolism, protein binding, therapeutic activity, and/or toxicity remains highly complicated. However, evidence of the pharmacokinetic properties of most antineoplastic agents in diverse situations may be found in various preclinical studies. Protein binding affects the bioavailability and distribution of active drugs and serves as a barrier to drug passage across biological membranes and barriers. Because of the high molecular weight of the drug-protein complex, precautions should be taken to improve therapeutic activity, and it also has an impact on the drug's elimination from the body.

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