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Role of TDM-Based Dose Adjustments For AC/T Regimen Drugs Used In Breast Carcinoma

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Abstract:
Breast cancer, a prevalent and significant health issue among women, is influenced by genetic, environmental, and lifestyle factors. Treatment often involves the AC/T regimen (Adriamycin, Cyclophosphamide, and Paclitaxel), which presents dosage challenges due to toxicity and therapeutic window limitations. This review focuses on the role of Therapeutic Drug Monitoring (TDM) in optimizing AC/T regimen doses to enhance efficacy and reduce side effects. TDM's impact on improving clinical outcomes is discussed, especially with targeted therapies like tyrosine kinase inhibitors and immunosuppressants. Adriamycin's DNA intercalation, Cyclophosphamide's DNA alkylation, and Paclitaxel's microtubule stabilization illustrate varied mechanisms of action that benefit from TDM for dose personalization. This analysis highlights TDM's potential in reducing adverse effects while maximizing therapeutic impact in breast cancer treatment.

Keywords: Breast cancer, AC/T regimen, Adriamycin, Cyclophosphamide, Paclitaxel, Therapeutic Drug Monitoring (TDM), pharmacokinetics, targeted therapy, dose optimization.

INTRODUCTION:

Breast cancer is one of the many common and dangerous tumors that affect women. Numerous internal and external variables can contribute to the development and occurrence of breast cancer.[1-3] Its prevalence is associated with poor lifestyle choices, environmental variables, and social-psychological factors. Research indicates that between 5% and 10% of breast cancer cases are related to genetic abnormalities and family history, while 20% to 30% of cases are related to potentially modifiable variables.[4] Breast cancer begins in the cells of the breast. A malignant tumor is a cluster of cancer cells that can spread and kill surrounding tissue. It can also spread across the entire body. Sometimes, alterations in breast cells occur that stop them from proliferating or behaving normally. Breast disorders other than cancer could lead to cysts and abnormal hyperplasia. They could also lead to benign malignancies such as intraductal papillomas.[5]

On the other hand, mutations to breast cells can occasionally lead to breast cancer. The cells lining the ducts, or the tubes that transport milk from the glands to the nipple, are where breast cancer usually starts. One name for this subtype of breast cancer is ductal carcinoma. Cancer can also develop from the cells in the lobules, which are groups of glands that produce milk.[6,7] Such a malignancy is known as lobular carcinoma. It is possible for both ductal and lobular carcinomas to be in situ, meaning that the cancer is still concentrated in the original site and has not migrated to other tissues. Additionally, they could be invasive, meaning that they have penetrated into the tissues surrounding them.[8]

Additionally, less prevalent kinds of breast cancer can also occur. These consist of Paget disease in the breast, inflammatory breast cancer, and triple-negative breast cancer. Two rare types of breast cancer include soft tissue sarcoma and non-Hodgkin lymphoma.[9] Studies reveal that although breast cancer is rare, its frequency has been gradually increasing in China. The disease will affect more than 100 Chinese women out of every 100,000 by 2022, and 2.5 million women between the ages of 35 and 49 will be affected overall. Therefore, in order to reduce the incidence of breast cancer, study on risk factors is essential.[10] The most common disease in women worldwide and the primary cause of cancer-related deaths in women is breast cancer. In 2018, 2.09 million new cases of breast cancer were detected, and almost 630,000 people lost their lives to the disease. Although the incidence of breast cancer varies by region, it is on the rise. Despite the fact that the incidence of breast cancer (36.1/105) and death (8.8/105) are both comparatively low globally, China has the highest incidence of breast cancer (17.6% and 15.6%, respectively), ranking first globally and rising over the previous few years. Globally, the incidence of breast cancer is increasing along with the disease's burden, making it a major public health concern.[11] Breast cancer is a complex disease with significant genetic, environmental, and lifestyle/behavioral components. The goal of the current review was to better understand the worldwide epidemiology and risk factors for breast cancer in order to facilitate early identification. The primary risk factors for breast cancer are genetic factors, particularly family history; diet and obesity; as our nation's standard of living rises, women's diets tend to become increasingly high-fat; smoking and alcohol consumption; ionizing radiation; and residual factors, such as menstruation, breastfeeding, also can affect the occurrence of breast cancer. We should

make an effort to limit the effects of exogenous hormones on our bodies by avoiding wearing cosmetics containing estrogen on a regular basis. A great deal of discussion has centered around these appeals. Therefore, in order to guide clinical prevention and treatment, it is crucial to extensively investigate the risk variables for breast cancer utilizing meta-methods.[12]

Although Chinese researchers have already done so, in the current study we did a meta-analysis of breast cancer risk variables in Chinese women by compiling relevant literature from 2001 to 2021.[13] Our objective was to give Chinese women basic knowledge for preventing breast cancer. Breast cancer is the most common type of cancer diagnosed in women and a major worldwide health concern. Although the exact origin of breast cancer is still unknown, researchers have identified a number of risk factors that can increase a woman's chance of developing the disease. Understanding these risk factors is crucial for the early detection, prevention, and effective therapy of breast cancer [14]. Breast cancer is the most common cancer in women, accounting for more than 1 in 10 new cases diagnosed annually. It is the second most common cause of cancer-related mortality for women worldwide.

On the anatomy of the breast, milk-producing glands are situated in front of the chest wall. The ligaments connecting the breast to the chest wall support it, and they are supported by the pectoralis major muscle. The lobes that comprise the breast are grouped in a circle and number from 15 to 20. The fat covering the lobes determines the size and contour of the breasts. Every lobe is composed of lobules, which house the glands responsible for producing milk in response to hormone stimulation. Breast cancer develops gradually every time.

Most individuals find out they have their condition while undergoing routine screenings. Others might have breast changes in size or shape, nipple discharge, or an inadvertently detected breast lump. A tissue biopsy, imaging, especially mammography, and a physical examination are necessary for the diagnosis of breast cancer.[14]A diagnosis made early on improves survival rates. The tumor's inclination to spread lymphatically and hemologically is the cause of poor prognosis and distant metastases. This explains and emphasizes the value of breast cancer screening programs.[15] A risk factor is something that increases the chance of getting cancer. It could be a disease, drug, or habit. Most malignancies are caused by a combination of risk factors.

THERAPEUTIC DRUG MONITORING IN BREAST CANCER:

Since the discovery of the first anticancer medications, oncologists have faced challenges in determining the best way to administer a safe and effective dosage for these treatments, which frequently have a limited therapeutic window.[16] Toxicological deaths are uncommon, but toxic exposure is frequently fatal. Underdosing, however, can frequently happen and goes unnoticed due to dose calculation errors and the oncologists' required prudence.[17] Therapeutic drug monitoring (TDM) comprises individualized drug dosages or regimens to optimize therapeutic effects and reduce toxicity, as well as the measurement and interpretation of systemic drug concentrations in biologic fluids,[18] When it comes to adjusting the dosage of several drug classes—such as antibiotics, immunosuppressives, 5-8 antiepileptics,[19,20] and antiviral HIV treatment—in non-oncology settings, TDM has proven to be a significant resource.[21]

TDM has been demonstrated to enhance clinical outcomes in oncology patients undergoing high-dose leucovorin and fluorouracil (FU) infusional treatment for metastatic colorectal cancer, as well as in children getting high-dose methotrexate for acute lymphoblastic leukemia[22,23] and osteosarcoma[24] The only anticancer medication for which TDM is still regularly employed in clinical practice is methotrexate, and even then, drug doses are determined more for safety than for maximum anticancer efficacy.[25,26] Several factors, such as the absence of established therapeutic ranges and concentration-effect relationships, the frequent use of multidrug combinations with overlapping toxic and therapeutic effects, and the use of prodrugs or drugs with active metabolites, make it difficult to incorporate TDM into oncologic practice in the pretargeted therapy era.

The last ten years have seen a significant shift in the "drug scape" of oncology, and with the introduction of targeted medicines with distinct pharmacokinetic (PK) and dosage properties, the usefulness and viability of TDM should be reexamined.[27] The majority of tyrosine kinase inhibitors (TKIs) are oral medications used once a day at predetermined doses as the primary agent. Although administered intravenously, monoclonal antibodies (mAbs) have lengthy elimination half-lives that are expressed in weeks or months.[28,29] Even the so-called "old" targeted medicines, such bicalutamide and tamoxifen, which are steroid receptor inhibitors, are continuously administered orally. Because of these variables, it is technically feasible to use a single trough-level measurement to estimate the steady-state exposure of these new compounds.

ADRIAMYCIN

Regression in various neoplastic conditions has been observed with the use of Adriamycin, including acute leukemia, Wilms' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, Hodgkin's and non-Hodgkin's type lymphomas, bronchogenic carcinoma, thyroid carcinoma, hepatomas, and ovarian carcinoma. The precise mode of Adriamycin 's action is yet unknown and complicated. By intercalating with DNA, Adriamycin inhibits the synthesis of macromolecules. In addition to inhibiting topoisomerase II's progression, this also relaxes DNA supercoils to facilitate

transcription. After breaking the DNA chain for replication, Adriamycin stabilizes the topoisomerase II complex, preventing the DNA double helix from being resealed and therefore halting the replication process.
The exact mechanism of action of Adriamycin is unknown, however it is thought to be connected to its capacity to bind to DNA and impede the production of nucleic acids. Studies on cell cultures have revealed fast chromatin binding and cell penetration, as well as mutagenesis and chromosomal abnormalities. They have also shown fast reduction of mitotic activity and nucleic acid synthesis. Adriamycin suppresses the immune system. It suppresses the titre of hemolytic and hemomagglutinating antibodies in mice given sheep red blood cells as an immunization. Similar data in humans suggests that doxorubicin is a potent immunosuppressive drug that wears off quickly. Adriamycin is a cytotoxic medication that is not phase- or cell cycle-specific.
Adriamycin 's affect on myeloid cell proliferation appears to be connected to its harmful effects on bone marrow. Adriamycin 's cardiotoxicity is most likely mediated by a variety of mechanisms. It is likely that cardiotoxicity is not directly associated with the inhibition of cardiac muscle replication, even though doxorubicin does prevent DNA synthesis in cardiac muscle in animal systems. Some evidence points to the production of free radicals as the cause of the unknown damage to the heart muscle. Furthermore, without compromising its antitumor efficaciousness, our observations imply that concomitant treatment of Vitamin E and other free radical acceptors may reduce cardiotoxicity in experimental animal systems.

a. Pharmacokinetic properties:
Adriamycin 's absorption rate is less than 5%, making it unsuitable for oral use. Pharmacokinetic studies demonstrate that considerable tissue binding and fast plasma clearance occur after injecting normal or radiolabelled doxorubicin hydrochloride intravenously. There is no information on Adriamycin's plasma-protein binding. Adriamycin does not cross the blood-brain barrier.
Adriamycin 's metabolism and excretion are still unknown. The liver is primarily responsible for the drug's metabolism, producing adriamycinol and other aglycone metabolites. It is important to remember that a number of the metabolites are carcinogenic. Whether any are more cytotoxic than the original chemical is unknown, though. Elevated metabolite concentrations show up quickly in plasma and go through a phase of distribution with a quantifiably brief first half-life. Patients with aberrant liver function may have poor metabolism.
Adriamycin and its metabolites exit the plasma according to a triphasic pharmacokinetic pattern, with a mean half-life of 12 minutes for the first phase, 3.3 hours for the second phase, and 29.6 hours for the extended third phase.
Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4%-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40%-50% of the administered dose being recovered in the bile or the faeces in seven days. Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues.

b. Therapeutic drug monitoring and target concentration intervention of Adriamycin:
Based mostly on information gathered in a meta-analysis released in 1998 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), the efficacy of Adriamycin -containing regimens in the adjuvant therapy of early breast cancer has been determined. For early stage breast cancer, the EBCTCG gathers primary data on all pertinent research, including published and unpublished, and updates these analyses on a regular basis. In the adjuvant chemotherapy trials, overall survival (OS) and disease-free survival (DFS) were the main outcomes. The meta-analyses facilitated the comparison of doxorubicin-containing regimens with CMF as an active control (6 trials including 3510 patients) and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) vs no chemotherapy (19 studies including 7523 patients).
The EBCTCG meta-analysis included six randomized studies that contrasted CMF with regimens containing Adriamycin. An evaluation was conducted on 3510 women who had axillary lymph node-related early breast cancer; almost 70% of the women were premenopausal and 30% were postmenopausal. There had been 1348 fatalities and 1745 initial recurrences at the time of the meta-analysis. Studies showed that regimens incorporating Adriamycin are efficacious and maintain at least 75% of the previous CMF adjuvant impact on DFS.

CYCLOPHOSPHAMIDE
Breast cancer, sarcoma, multiple myeloma, and other neoplasms are among the conditions for which cyclophosphamide is mainly prescribed. Nitrosophosphamide is a nitrogen mustard that works by alkylating cells to prevent cancer. This exercise examines the benefits of cyclophosphamide as an agent for the treatment and management of neoplastic disorders by an interprofessional team, including its indications, contraindications, mechanism of action, and other important details. The use of cyclophosphamide in the treatment of severe multiple sclerosis is also noted.
Nitrogen mustard drugs, such as cyclophosphamide, work by alkylating DNA molecules. The cyclophosphamide metabolizes to an active form that can prevent protein production by DNA and RNA crosslinking and is not phase-specific to the cell cycle. The phosphoramide mustard that is produced when cyclophosphamide is metabolized by liver enzymes such cytochrome P-450 is primarily responsible for the drug's antineoplastic actions.

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Cyclophosphamide is initially converted to hydroxycyclophosphamide by hepatic enzymes, which is then metabolized to aldophosphamide. Aldophosphamide cleaves to provide acrolein and phosphoramide mustard, the active alkylating agent. At the guanine N-7 site, the phosphoramide metabolite creates cross-links both within and between neighboring DNA strands. These changes are irreversible and ultimately result in cell death that is predetermined. Apart from its antimitotic and antineoplastic properties, cyclophosphamide exhibits selectivity for T cells and suppresses the immune system. Lower dosages of cyclophosphamide have demonstrated potential for use in the selective immunomodulation of regulatory T cells, whereas higher dosages are employed in the eradication therapy of malignant hematopoietic cells. In the CSF and peripheral blood, the medication increases the release of Th2 cytokines such IL-4 and IL-10 while decreasing the secretion of interferon-gamma and IL-12. Owing to these effects, cyclophosphamide is seen as a useful supplement to regimens for tumor vaccination, management of post-transplant alloreactivity, and therapy of immune-mediated diseases, including certain types of vasculitis. A number of potential mechanisms of action for cyclophosphamide's immunomodulatory effects have been proposed by various research, while the exact mechanism remains unclear.

a. Pharmacokinetic properties

A mixed function microsomal oxidase system biotransforms cyclophosphamide primarily in the liver to active alkylating metabolites. These metabolites prevent malignant cells that are vulnerable to fast cell division from growing. Elimination half-life (t½) after IV injection is 3–12 hours, and total body clearance (CL) is 4–5.6 L/h. Throughout the therapeutic dose range, pharmacokinetics is linear. The kinetics of cyclophosphamide were described by saturable elimination in tandem with first-order renal elimination after a ninety-minute infusion at a dose of 4.0 g/m2. Protein binding accounts for around 20% of cyclophosphamide and does not vary with dosage. Over 60% of certain metabolites are linked to proteins. Total bodily water (30 to 50 L) is roughly represented by the volume of distribution.

After cyclophosphamide is activated, 4-hydroxycyclophosphamide is produced, and this compound is in balance with its ring-open tautomer, aldophosphamide. Aldehyde dehydrogenases have the ability to oxidize 4-hydroxycyclophosphamide and aldophosphamide, resulting in the inactive metabolites 4-ketocyclophosphamide and carboxyphosphamide, respectively. Phosphoramide mustard and acrolein are the active metabolites that are produced when aldophosphamide undergoes β-elimination. Other proteins, such as albumin, can accelerate this spontaneous conversion. By side chain oxidation, less than 5% of cyclophosphamide may be directly detoxified, producing the inert metabolites 2-dechloroethylcyclophosphamide. High doses cause a decrease in the parent compound's proportion cleared via 4-hydroxylation, which causes patients' cyclophosphamide elimination to be non-linear. It seems that cyclophosphamide stimulates its own metabolism. After repeated dosing at 12- to 24-hour intervals, auto-induction causes an increase in total clearance, an increase in the production of 4-hydroxyl metabolites, and a shorter t1/2 value. The main forms of excretion for cyclophosphamide are metabolites. After IV treatment, 10–20% are eliminated unaltered in the urine and 4% are eliminated in the bile. After administering cyclophosphamide intravenously for an hour to individuals with renal impairment, the pharmacokinetics of the drug were ascertained. The findings showed that when renal function declined, so did the systemic exposure to cyclophosphamide.

b. Therapeutic drug monitoring and target concentration intervention of Cyclophosphamide:

Following a one-hour intravenous infusion in patients with renal impairment, the pharmacokinetics of cyclophosphamide were ascertained. The findings showed that when renal function declined, so did the systemic exposure to cyclophosphamide. Comparing the moderate renal group (CrCl of 25 to 50 mL/min), the severe renal group (CrCl of 10 to 24 mL/min), and the hemodialysis group (CrCl of < 10 mL/min) showed increases in mean dose-corrected AUC of 38%, 64%, and 23%, respectively, over the control group. Given that the severe group's exposure increased significantly ($p>0.05$), individuals with severe renal impairment need to have their toxicity constantly monitored.

Four individuals undergoing long-term hemodialysis had their cyclophosphamide dialyzability examined. Dialysis clearance, which is determined by the difference between the arterial and venous blood flows, averaged 104 milliliters per minute in dialysate. This is within the drug's metabolic clearance range of 95 milliliters per minute. During hemodialysis, a mean of 37% of the cyclophosphamide dosage was eliminated. Patients on hemodialysis had an elimination halflife (t1/2) of 3.3 hours, which is 49% shorter than the 6.5 hours to t1/2 recorded in uremic patients. Cyclophosphamide may be dialyzable based on factors such as decreased half-life (t1/2), greater clearance during dialysis compared to metabolic clearance, high extraction efficiency, and substantial drug elimination during dialysis.

PACLITAXEL

Paclitaxel a novel antimicrotubule drug stabilizes microtubules by blocking depolymerization and encourages microtubule formation from tubulin dimers. The usual dynamic reconfiguration of the microtubule network, which is necessary for critical interphase and mitotic cellular processes, is inhibited as a result of this stability. Furthermore, during the cell cycle, paclitaxel causes aberrant microtubule arrays or "bundles" and numerous microtubule asters during mitosis.

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a. Pharmacokinetic properties:

In sensitive cancer cells, paclitaxel stabilizes microtubule polymerization, which causes mitotic arrest and apoptotic cell death. The various mechanisms responsible for resistance to paclitaxel are multifaceted and include efflux mediated by PgP (MDR1, ABCB1) and other ABC transporters (efflux systems), changes in the way paclitaxel binds to tubulin (due to overexpression or mutations in tubulin), adjustments to cellular apoptotic signals, and CYP3A4 and CYP2C8's detoxification of paclitaxel. The resistance mechanisms to taxanes that are associated with microtubule-associated proteins (MAP) are the most significant.

Cytochrome P450 (CYP) enzymes, primarily CYP3A4 and CYP2C8, mediate the biotransformation of paclitaxel. CYP2C8 catalyzes the selective hydroxylation of paclitaxel at the 6-position, resulting in the major metabolite 6α-hydroxy-paclitaxel (M5), with a high affinity and metabolic rate. Paclitaxel also becomes 30-p-hydroxyphenyl-paclitaxel (M4) when it is hydroxylated at the C13 side-chain of the molecule. The possible activation or inhibition of CYP3A4 has a significant impact on the hydroxylation of paclitaxel. When administered at the standard intravenous infusion rate over a period of 1 or 3 hours, paclitaxel displays nonlinear pharmacokinetics (as opposed to 24-hour infusions). Paclitaxel's nonlinear PK is brought on by saturable transport, saturable drug binding, and interactions with the solvent that forms micelles, cremophor EL (CrEL).

It has been proposed that CrEL may prevent PgP-mediated biliary secretion, induce lipoprotein dissociation that modifies protein binding, and change paclitaxel distribution through entrapment in micelles. Consequently, as CrEL concentrations rise, the free percentage of paclitaxel falls. It has been demonstrated that paclitaxel has a high distribution volume of about 60 L/m2. It has been calculated that paclitaxel has a terminal half-life of 8 to 12 hours and a maximal elimination capacity of 36 μmol/Lh over a 3-hour infusion at a dose of 175 mg/m2, with an intra-individual variability of 18% and an inter-individual variability of 37%.

b. Therapeutic drug monitoring and target concentration intervention of Paclitaxel

Major toxicities associated with paclitaxel include suppression of the bone marrow (neutropenia, anemia, thrombopenia), acute or chronic neurotoxicity leading to cumulative peripheral paresthesias or hypesthesias, or arthralgia and myalgia, respectively, and less common but potentially severe acute CrEL-associated hypersensitivity reactions. Paclitaxel scheduling on a weekly basis rather than a three-weekly basis has gained traction in several clinics because of its relative simplicity, quicker infusion times, easy monitoring, favorable clinical efficacy, and potential for lower toxicity.

A Phase 3 Intergroup trial, conducted by the Cancer and Leukemia Group B [CALGB], Eastern Cooperative Oncology Group [ECOG], North Central Cancer Treatment Group [NCCTG], and Southwest Oncology Group [SWOG], randomly assigned 3170 patients with node-positive breast carcinoma to receive adjuvant therapy with Paclitaxel or no further chemotherapy after four courses of doxorubicin and cyclophosphamide (AC). Women with histologically positive lymph nodes after mastectomy or segmental mastectomy and nodal dissections participated in this multicenter investigation. The purpose of the 3 x 2 factorial trial was to determine the safety and effectiveness of three distinct doxorubicin (A) dose levels as well as the impact of adding Paclitaxel and administering it after AC therapy was finished. Following stratification based on the number of positive lymph nodes (1-3, 4–9, or 10+), patients were randomly assigned to receive 600 mg/m2 of cyclophosphamide and 60 mg/m2 of doxorubicin (on day 1), 75 mg/m2 (in 2 divided doses on days 1 and 2), or 90 mg/m2 (in 2 divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every three weeks for four courses of chemotherapy. Or they could receive no additional chemotherapy or Paclitaxel 175 mg/m2 as a 3-hour infusion every three weeks for four more courses. Patients who had segmental mastectomies before to the research were to undergo breast irradiation upon recovery from treatment-related side effects. Patients whose tumors tested positive for tamoxifen were to receive further tamoxifen treatment (20 mg daily for 5 years).

CONCLUSION:

The cornerstone of cancer patients' treatment is pharmacological therapy. Even though systemic drug concentrations for many antineoplastics vary greatly between patients, body size-based dosing is still the most used method. In certain situations, therapeutic drug monitoring (TDM) is utilized for a small number of antineoplastics. The appropriateness of concentration-based dosage in oncology is a complex matter that involves several factors, one of which is the lack of a systematic evaluation of exposure-response connections in the regulatory approval process. TDM is a multi-step, complicated, service-level intervention that requires a multidisciplinary team that includes clinical and laboratory personnel. Clinicians' decision-making over dosage must alter if they are to adopt TDM. Examining TDM in cancer requires taking the necessity of changing practices into account.

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