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Kinetics of Novel Drug Delivery in Cancer Chemotherapy

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AOO and MON designed the study. Author MON wrote the protocol and wrote the first draft of the manuscript. Authors AOO and MON managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Cancer, the uncontrolled proliferation of cells, is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which can affect any organ of people without regard to race, age or sex. Conventional chemotherapy has been successful to some extent in the treatment of cancer but their efficacy is limited by poor release pattern of drugs, poor bioavailability due to low water solubility or cell membrane permeability, high-dose requirements, adverse side effects, low therapeutic indices, development of multiple drug resistance and non-specific targeting. New drug-delivery technologies based on nanomaterials may be a ray of hope to overcome these challenges. The main goal of nanomedicine is to produce nanometre scale multifunctional entity, by engineering and designing the appropriate targeting agent which can diagnose, deliver the therapeutic agent, and monitor the treatment. Dendrimers have been investigated for encapsulation and controlled delivery of various anticancer drugs attributed to their high drug loading capacity, easy synthesis, stability, transdermal

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ability and oral drug-delivery potentials. Efficacy of cancer therapy may be enhanced by improved delivery kinetics. This review discusses the kinetics of drug delivery in cancer chemotherapy; which describes how the body handles anti-cancer drugs and accounts for their processes of absorption, distribution, metabolism and excretion.

Keywords: Kinetics; malignant; mutations; chemotherapy; nanomedicine.

1. INTRODUCTION

Cancer includes a range of diseases that arise as a result of the unrestricted growth of malignant cells, with the potential to invade or spread to other parts of the body [1]. These contrast with benign tumours, which do not spread. Cancer is caused by accumulated damage to genes due to chance or to exposure to a cancer causing substance. Cancer begins when cells acquire the ability to grow uncontrollably and ultimately invade and damage the body's normal tissues. Cancer development happens in multiple stages, from precancerous changes to malignant tumours. However, not all cancers form tumours, and different cancers can develop at different rates. Basic biology explains that almost all normal cells in the body live for a certain period of time and then die. This cellular life cycle allows the constant renewal of tissues to take place in the body; as new healthy cells replace old ones, maintaining the function of all the organ systems. The life expectancy of every cell is programmed into its genes; with a programmed cell death called apoptosis [2]. Dietary, environmental and other factors can change those genes, turning off apoptosis and causing the cell to multiply and grow continually [1]. The basic cause of sporadic (non-familial) cancers is DNA damage and genomic instability. A minority of cancers are due to inherited genetic mutations. The mutated cell comprises the very beginnings of a cancerous tumour, which under the right conditions will grow and spread. Although there is compelling evidence for multiple mutagenic events in the induction of cancers, there is also substantial evidence in support of non-mutagenic mechanisms [3].

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in [4]. Cancer-related deaths are projected to increase in the near future with estimation by the World Health Organization of about 13.1 million cancer-related deaths by the year [5]. Dietary choices and genes contribute differently at each of the stages of cancer development [6]. External risk factors for cancer development include infectious organisms, unhealthy diet, pesticides, environmental toxins, tobacco, radioactivity, X-rays and chronic inflammation, while internal factors includes inherited genetic mutations, immune conditions and hormones [7]. These factors may act together or in series to develop cancer [8]. Most cancers originate with genetic mutations in the cells of organs where the cells replace themselves at a rapid rate throughout life, such as the reproductive organs, the breast, the skin, the intestine, the colon and the bladder. An additional factor is the case in which the ''DNA repair systems'' are inadequate. These tissues reproduce their DNA more frequently than other cells do, making mistakes in replication more likely [9]. Mutations that lead to cancer also originate in parts of the body that are frequently exposed to toxins or high levels of hormones that enhance cell growth: the lungs, the colon, the prostate, the uterus and the ovaries. Mutations in one or more normal cells initiate cancer, and each division of the cell replicates mutated genes and accumulates additional genetic mutations [9]. If the body's defences do not target and eliminate that cell or group of cells, they go on and reproduce to form a primary tumour. Only a small percentage of mutated cells go through the steps of progression, invasion and metastasis [10]. A tumour suppressor gene directs the production of a protein that is part of the system that regulates cell division [11]. The tumour suppressor protein plays a role in keeping cell division in check. Like all genes, tumour suppressor genes may undergo a variety of mutations. When a tumour suppressor gene is mutated uncontrolled cell growth may occur [12]. However, most loss-of-function mutations that occur in tumour suppressor genes are recessive in nature [13]. Thus, in order for a particular cell to become cancerous, both of the cell's tumour suppressor genes must be mutated [14]. It is also proposed that the genetic basis of non-induced or spontaneous tumours, as well as cancers induced by non-mutagens, involves heritable changes in the regulation of gene expression [3].

As the group of abnormal cells continue to divide and spread forming a primary tumour, the tumour begins to grow its own blood vessels - **a**ngiogenesis, invade neighbouring tissue and interfere with organ function [15]. Cells break off the tumour and travel through the blood and lymph systems to organ systems outside the one in which the primary tumour developed - metastases. They lodge there continuing to divide and overtake healthy tissues. Specialized proteins stimulate the growth of new blood vessels to feed these new tumours, and other proteins extend the invasion of the primary tumour and metastases into adjacent tissues. As cancer cells grow, they cross boundaries that separate tissues and organs from one another. Specific tumours travel to specific tissues; for example prostate cancer usually spreads to the bone of the spine, while colon cancer usually spreads to the liver [16]. Once the tumour has grown and spread enough for symptoms to arise, they can cause internal bleeding, infection or organ failure. Failure to regulate or prevent such a spread of cancerous cells often leads to death of the patient [17].

There are several stages in cancer progression which is generally established with tumour size, extent of primary tumour and spread to other organs. Generally, tumours are classified based on their cell of origin instead of tissue site but histological classification includes six major categories namelycarcinoma, leukaemia, lymphoma, myeloma, sarcoma and mixed types [18]. Cancer therapies include, targeted therapies, immuno-therapies and hormone-therapies but are mostly limited to surgery, radiation, and chemotherapy or a combination of these options. All these methods risk damage to normal tissues or incomplete eradication of the cancer [19]. Conventional chemotherapy works primarily by interfering with DNA synthesis and mitosis, leading to the death of rapidly growing and dividing cancer cells. Chemotherapeutic agents are non selective and can also damage healthy normal tissues, causing severe unintended and undesirable side effects, e.g., hair loss, loss of appetite and nausea [20]. The severe adverse effects induced by X-rays and chemotherapeutic drugs on healthy tissues and organs are a major reason behind the high mortality rate of cancer patients [21]. Also, as the bio-accessibility of these drugs to tumour tissues is relatively poor, higher doses are required, leading to elevated toxicity in normal cells and an increased incidence of multiple drug resistance. Chemotherapy requires getting a drug to its specific target site in tissues where the drug performs its action [22]. Typically, the drug is introduced into the body-administration, sometimes far from this target site. The drug must move into the bloodstream-absorption and be transported to the target sites where the drug is needed-distribution. Some drugs are chemically altered (Metabolism) by the body before they perform their action, others are metabolized afterward, and still others are not metabolized at all. The final step is the removal of the drug and its metabolites from the body-excretion. Many factors, including a person's weight, age, genetic makeup, and kidney or liver function, can influence these kinetic processes and a better understanding of the kinetics of anti-cancer drugs will lead to improved outcome in cancer therapy [23].

2. CANCER CHEMOTHERAPY

The term chemotherapy connotes any use of chemicals to treat any disease (chemo- + -therapy). But it now refers to non-specific usage of intracellular poisons to inhibit mitosis, cell division. Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs-chemotherapeutic agents-as part of a standardized chemotherapy regimen [24]. Chemotherapy constitutes systemic therapy for cancer in that the drugs are introduced into the blood stream and are therefore in principle able to address cancer at any anatomic location in the body [25]. This systemic therapy is often used in conjunction with other modalities that constitute local therapy i.e. treatments whose efficacy is confined to the anatomic area where they are applied for cancer such as radiation therapy and/or surgery [26]. Cancer cells vary widely in their susceptibility to traditional chemotherapeutic agents. Many of the side effects of chemotherapy can be traced to damage to normal cells that divide rapidly and are thus sensitive to anti-mitotic drugs: cells in the bone marrow, digestive tract and hair follicles [27]. This results in the most common side-effects of chemotherapy like myelosuppression-decreased production of blood cells, hence also immunosuppression, mucositis-inflammation of the lining of the digestive tract, and alopecia (hair loss). As chemotherapy affects cell division, tumours with high growth rates such as acute myelogenous leukaemia and the aggressive lymphomas, including Hodgkin's disease) are more sensitive to chemotherapy, as a larger proportion of the targeted cells are undergoing cell division at any time [28].

Malignancies with slower growth rates, such as indolent lymphomas, tend to respond to chemotherapy much more modestly [24]. A major obstacle to successful chemotherapy is the development of cellular resistance to multiple structurally unrelated anticancer drugs. This phenomenon has been termed multidrug resistance (MDR), which occurs in a majority of cancer patients. MDR is mainly due to the over expression of ABC transporters which extrude chemotherapeutic drugs outside of cancer cells [29]. There are a number of strategies in the administration of chemotherapeutic drugs with a curative intent, to prolong life or to palliate symptoms: Induction chemotherapy is the first line treatment of cancer with a chemotherapeutic drug. This type of chemotherapy is used for curative intent [30]. Combined modality chemotherapy is the use of drugs with other cancer treatments, such as surgery, radiation therapy, or hyperthermia therapy [31]. Consolidation chemotherapy is given after remission in order to prolong the overall disease-free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission [30].

Intensification chemotherapy is identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used [30]. Combination chemotherapy involves treating a person with a number of different drugs simultaneously. The drugs differ in their mechanism and side-effects. The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity [30]. Neoadjuvant chemotherapy is given prior to a local treatment such as surgery, and is designed to shrink the primary tumour [30]. This is also given to cancers with a high risk of micro metastatic disease [32]. Adjuvant chemotherapy is given after a local treatment with radiotherapy or surgery. It can be used when there is little evidence of cancer present, but there is risk of recurrence [30].It is also useful in killing any cancerous cells that have spread to other parts of the body [33]. Maintenance chemotherapy is a repeated low-dose treatment to prolong remission [30]. Salvage chemotherapy or palliative chemotherapy is given without curative intent, but simply to decrease tumour load and increase life expectancy [30].

Chemotherapeutic drug absorption and clearance are influenced by multiple factors, including age, gender, metabolism, disease state, organ function, drug-to-drug interactions, genetics, and obesity, which has a major impact on the actual concentration of the drug in the person's bloodstream [34].

2.1 Drug Release Kinetics in Cancer Chemotherapy

There must be an adequate drug concentration in the body to allow for an effective dose at the tumour site. Among factors which affect the pharmacokinetics of a drug are the route of administration, the site of administration, body weight, tissue absorption, and the dose administered. When a chemotherapeutic agent enters the body, regardless of the route of administration, it undergoes absorption, separation into its constituent parts, metabolism and finally elimination [35].

2.1.1 Liberation

Liberation is the release of the active constituent of the drug from its formulation. Before a drug can be absorbed by the body and deliver its therapeutic effects, it needs to be in a form that can be absorbed by the body. This is true for all drugs except intravenous solutions and some true solutions. The drug needs to be in the form of a solution before it can be absorbed, so dissolution, and hence liberation, is the first step in the pharmacokinetics of a drug. Liberation determines availability, rate of absorption and onset of action. After it has been liberated from its formulation the drug diffuses to the site of absorption. If the drug is administered intravenously, however, it is able to immediately circulate around the body via the bloodstream [36].

2.1.2 Absorption

Once a drug is administered, drug absorption begins; the process by which the chemotherapy medicine enters the blood circulation [37]. Absorption factors including formulation, physicochemical properties, route of administration and the way the specific patient’s body processes drugs. Routes of drug administration include oral, sublingual, parenteral, nasal, transdermal, urogenital, rectal and ocular. Factors that influence drug absorption and bioavailability include permeation, which can include passive diffusion through the aqueous and lipid environment, and active transport, which comes into play in larger molecules [38].

In cases where the drug directly enters the bloodstream, absorption is likely to be more predictable and the drug's bioavailability is close to 100%. Drugs that are taken orally dissolve in the stomach, but only commence absorption once they enter the intestines. For a drug to reach the malignant cells it must cross several semi permeable membranes. Drugs can cross the membranes by active transport, pinocytosis, and passive diffusion [39].

2.1.3 Diffusion

Aqueous diffusion takes place across the interstitial space, endothelial blood vessel lining, epithelial membrane tight junctions and through aqueous pores.

Mass transfer or diffusion is driven by Fick's Law [40]: which describes the molar flux due to diffusion as proportional to the concentration gradient. This is represented by the equation below:

Flux (J) (molecules per unit time) = $(C_1 - C_2) \cdot$ (Area ·Permeability coefficient) / Thickness

1. Where C_1 is the higher concentration and C_2 is the lower concentration
2. Area = area across which diffusion occurs
3. Permeability coefficient: drug mobility in the diffusion path
   - For lipid diffusion, lipid: aqueous partition coefficient -- major determinant of drug mobility
     - Partition coefficient reflects how easily the drug enters the lipid phase from the aqueous medium.
4. Thickness: length of the diffusion path [40]

Thus, the flux is shown to be equal to the negative diffusivity multiplied by the change in concentration divided by the change in distance.

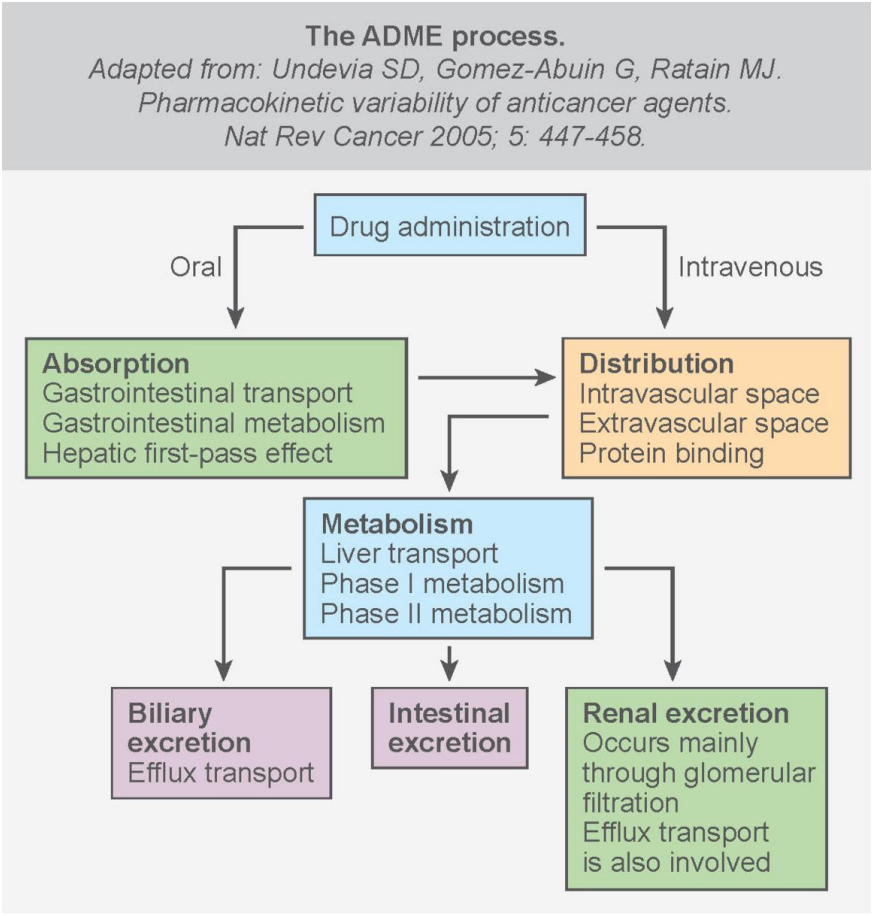

Fig. 1. Schematic diagram of the pharmacokinetic process

2.1.3.1 pH and the Henderson-Hasselbalch equation

Absorption of the drug depends on the dissolution rate, lipid/water solubility, blood circulation at the site of absorption, concentration at the absorption site and the area of absorbing surface [41]. The pH gradient across a membrane determines the absorption rate of the drug which is present in solution in both its ionized and unionized forms [42]. Non-ionized drugs cross lipid membranes more easily as they are more lipid soluble. The acid dissociation constant, pK_a value, of a drug is the pH at which the drug is 50% ionized, and is a constant value for each drug. The Henderson Hasselbalch equation developed independently by the American biological chemist L. J. Henderson and the Swedish physiologist K. A. Hasselbalch, [43] demonstrates the ratio of charged molecules to uncharged molecules at a certain environmental pH, as follows:

$$pH = pK_a + \log [[A-] / [HA]]$$

Where pK_a is the pH at which the drug is 50% ionized,

[A-] is the concentration of a conjugate base,

And [HA] is the molar concentration of an undissociated weak acid. A simplified version of this equation would be:

$pH=pK_a$ +log(charged/uncharged)

Therefore, if the pH of the drug's environment is known, the amount of drug likely to be in its uncharged state can be calculated [44].

2.1.4 Distribution

Following intravenous administration or absorption, a drug distributes from the intravascular space to its target in the extra vascular space [37]. Most drugs bind to plasma proteins such as albumin. The amount of drug that moves to its target depends on how much drug binds to plasma proteins as only the free fraction of drugs is pharmacologically active [37].

The term volume of distribution (V_d), is the ratio between the amount of drug in the body and the concentration of the drug measured in blood or plasma [45]. This is shown mathematically as:

$$V_d = (\text{dose of drug}) / (\text{drug concentration})$$

Distribution tends to be uneven, however, due to variations in tissue perfusion, regional pH, tissue binding and the permeability of cell membranes. As the body is a dynamic, constantly changing environment, the drug is simultaneously being absorbed, distributed and eliminated. In order to produce a model that will demonstrate distribution, the body is divided into theoretical compartments [46]. The central compartment includes the blood in the blood vessels and organs that are well perfused such as the heart, lungs, kidneys and brain. If the drug has a tendency to bind to plasma proteins, most of the drug will remain within the bloodstream and the V_d value will be low.

The central volume V_c (volume of the central compartment) can be expressed as:

$$V_c = \text{Dose} / \text{Peak serum level}$$ [47].

Peripheral compartments consist of tissue compartments that are less well perfused. These include adipose tissue, muscle, skeletal tissue and peripheral organs. Even if the tissue itself has a high affinity for a drug, distribution will be slow across poorly perfused tissues [48]. The peripheral volume, V_t, is the totality of all the tissue spaces outside the central compartment. All drugs dissipate initially into the central volume and ultimately distribute into the peripheral volume. Therefore the sum of the central volume and the peripheral volume, Vt, make up the apparent volume of distribution, V_d .

Each drug has its own pattern of distribution within the body, with some drugs preferentially binding to adipose tissues or the extracellular fluid. Only unbound drug diffuses passively to the tissues where the drug exerts its pharmacological effects. Some parts of the body are more accessible to drugs than others. For example, entry of drugs to the brain is restricted by the blood-brain barrier [49]. The endothelial cells of brain capillaries possess tight junctions which slow the diffusion of water-soluble drugs and prevent unwanted substances such as bacteria and viruses from entering the brain. Factors that affect the volume of distribution include the pKa of the drug, its lipid solubility, drug-plasma protein binding, and the individual patient's characteristics such as age, sex, weight and general state of health [37].

2.1.5 Metabolism

Metabolism is a crucial step of drug disposition and can be a major source of pharmacokinetic variability. Hepatic uptake of drugs is mediated by transporter proteins through either passive

diffusion or active transport. Once in the liver, anticancer drugs undergo phase I and phase II reactions. Phase I reactions are oxidative or reductive reactions and result in the loss of pharmacological activity or the activation of inactive prodrugs such as capecitabine and tamoxifen. Phase II reactions conjugate phase I products to form usually inactive polar derivatives for renal and biliary elimination. Many of the genes that encode drug transporters and phase I and II enzymes are polymorphic, and as such are candidate sources of interindividual pharmacokinetic variability [37].

Metabolism may also change the physico-chemical properties of a molecule so that it may or may not become a substrate for one of the efflux pumps, such as the ABC transporters, including P-glycoprotein, the multidrug resistance proteins and the breast cancer resistance protein (BCRP) .This can lead to unwanted accumulation in normal tissues resulting in toxicity. These usually poor physico-chemical properties also determine whether a compound will be a substrate for one of the many influx transporters, such as the organic cation transporters or the organic anion transporters [50].

2.1.6 Excretion

The main routes of anti-cancer drug excretion are through the biliary tract and kidneys [37]. Variations in Absorption, Distribution, Metabolism and Excretion arise in cancer chemotherapy and the result is that many people do not receive the right dose to achieve optimal treatment effectiveness with minimized toxic side effects. Some people are overdosed while others are under dosed [51]. Therapeutic drug monitoring individualizes chemotherapy dosing by measuring the drug levels in blood plasma over time and adjust dose according to a formula or algorithm to achieve optimal exposure. This has been applied for drugs like Carboplatin [52] and busulfan [53].

3. NEW APPROACHES TO DRUG DELIVERY IN CANCER CHEMO-THERAPY

Conventional chemotherapeutic agents accumulate both in normal and tumour cells due to non-specificity [54]. Parenteral drug administration may be associated with embolism, non-specificity and drug induced toxicity. Additionally, orally administered drug regimen is required to overcome biological barriers, protein binding and first pass metabolism to reach therapeutic concentrations in cancer cells [55].

3.1 Differential Targets in Novel Cancer the Rapeutics

Despite much progress made in categorizing the environmental causes and cellular and molecular biological basis for this dreaded disease, there is no precise understanding of the differences between a cancer cell and its normal counterpart. Effective cancer therapeutic systems exploit differences in the cancer cell milieu with the normal healthy cell otherwise high toxicity and adverse side effects will occur. Some of these loopholes include; pH, temperature, enzyme/substrates, antigens and antibodies [56].

3.1.1 pH response

The abnormal metabolism and protein regulation of tumour tissues form an acidic microenvironment that favours the proliferation of tumour cells. This pH abnormality is widely exploited in tumour-targeted delivery. In the acidic microenvironment of tumours, nanocarrier structures can be changed by chemical bond dissociation or charge reversal for specific drug release. This has been applied, for instance, to overcome the resistance of breast cancer to doxorubicin, which is a most widely used anti-cancer drug [57]. Other numerous pH-responsive, intelligent nanoparticle delivery examples have been developed [58-59].

3.1.2 Temperature response

The temperature of tumour tissues is slightly higher than that of surrounding normal tissues. This temperature difference has been applied in temperature-responsive drug delivery to tumours. Lv et al. developed a novel polymer system for intelligent drug release; the developed system is based on molecular recognition and phase transition temperature response [60]. Talelli et al. developed biodegradable thermo sensitive polymeric micelles for the stable encapsulation of hydrophobic oleic-acid-coated super paramagnetic iron oxide nanoparticles [61].

3.1.3 Enzymatic response

Some enzymes are only present or are more concentrated in tumour cells than normal ones. Their specific binding with enzyme substrates can be employed to achieve the intelligent response of targeting drugs [62-63]. An enzyme-responsive conjugate was shown to improve the

delivery of a pi3k inhibitor to prostate cancer cells [64].

3.1.4 Antigen response

Similar to enzymes, the special identification and connection between antigens and antibodies has been exploited for the design of active targeting drug delivery. Ding et al. utilized the specific binding between a receptor and a ligand to realize targeted drug delivery. The authors combined immune nanoparticles containing the death receptor 5 monoclonal antibody (DR5 mAb) and nanoparticles carrying kappa oxazine (DTIC) to form the composite nanoparticle DTIC NP-DR5 mAb. The drug-loading nanoparticles accumulate in tumour cells due to the specificity of the monoclonal antibody and DR5 recognition effect in the body. This system is also a good example of the combined therapy of immune therapy and chemotherapy [65].

3.2 Carrier-Mediated Combination Drug Delivery

By delivering two of more drugs simultaneously using a carrier-mediated drug delivery system the combination system can generate synergistic anticancer effects and reduce individual drug related toxicity [66]. Carrier-mediated drug delivery systems can offer many advantages over delivery of physical mixture of multiple drugs. The advantages include:

(1) Prolonged drug circulation half-life mediated by the carrier,
(2) Reduced nonspecific uptake,
(3) Increased accumulation at the tumour site through passive enhanced permeation and retention (EPR) effect and/or active targeting by incorporation of targeting ligands [67],
(4) Predominantly endocytotic uptake with the potential to bypass mechanisms of multidrug resistance [68], and,
(5) Ratiometric dosing, that is, ability to tailor the relative ratios of each agent based on its pharmacological disposition. Also a single delivery system carrying multiple drugs in the same platform can lead to synchronized and controlled pharmacokinetics of each drug, resulting in improved drug efficacy, single formulation with improved solubility and bioavailability, and so forth [69]. When carrier-mediated systems containing multiple drugs come to fruition as novel drug delivery systems in general cancer therapy it can also be adapted to metastatic breast cancer treatment, which requires aggressive therapy [70].

3.3 Nanomedicine for Cancer Therapy

Significant progress has been made in the development of drug delivery devices, for localized cancer treatment. Such devices have also been shown to have the potential to reduce the side effects associated with bulk chemotherapy and radiotherapy [71]. Several innovative methods of drug delivery are being introduced to cancer therapy. A wide range of nanoscale compounds based on synthetic polymers, proteins, lipids, and organic and inorganic particles have been employed for cancer treatment. The Different types of advanced drug delivery approach like polymeric Nano capsules, nanoparticles, liposomes, nanoemulsion, microsphere, microcapsules, hydrogels has been expressed utilizing bioactive and plant extracts. These novel systems offer a number of advantages, such as protection from degradation in the bloodstream, better drug solubility, enhanced drug stability, targeted drug delivery, decreased toxic side effects and improved pharmacokinetic drug properties [71].

Nanomedicine is a rapidly developing area that is revolutionizing cancer diagnosis and therapy. Nanoparticles have unique biological properties given their small size (diameter within 1–100 nm) and large surface area to volume ratio, which allows them to bind, absorb and carry anticancer agents, such as drugs, DNA, RNA, and proteins, along with imaging agents with high efficiency. Nanocarriers used in chemotherapy can be classified into two major types designed for targeted or non-targeted drug delivery: vehicles that use organic molecules as a major building block material and those that use inorganic elements (usually metals) as a core. Organic nanocarriers are comprised of liposomes, lipids, dendrimers, carbon nanotubes, emulsions, and synthetic polymers [71].

4. KINETICS OF TUMOR TARGETING BY NOVEL AGENTS

Nanoscale drug delivery architectures are able to penetrate tumours due to the discontinuous, or “leaky,” nature of the tumour microvasculature, which typically contains pores ranging from 100 to 1000 nm in diameter. The microvasculature of healthy tissue varies by tissue type, but in most tissues including the heart, brain, and lung, there are tight intercellular junctions less than 10 nm. Therefore, tumours within these tissue types can be selectively targeted by creating drug delivery nanostructures greater than the intercellular gap

of the healthy tissue but smaller than the pores found within the tumour vasculature [72].

Through precise control of the drug carrier architecture, the release of the drug can be tuned to achieve a desired kinetic profile. Three of the most common kinetic profiles are zero order, first order, and Higuchi [73]; these are expressed mathematically in the following equations. The delivery of most drugs is accomplished through oral administration or by injection and follows first order kinetics. The ideal release profile for most drugs would follow a steady release rate so that the drug levels in the body remain constant while the drug is being administered. More recent transdermal drug delivery mechanisms follow the Higuchi model [72]. As shown subsequently, nanostructured polymeric and silica nanoparticles are being developed as drug carriers which achieve near zero order kinetics [74].

Zero order: $D_t = D_0 + K_0t$

First order: $\ln D_t = \ln D_0 + K_1t$

Higuchi order: $D_t = D_0 = K_Ht^{1/2}$

Where D_t is the amount of drug released at time t, D_0 is the initial amount of drug released, result of initial rapid release,

$k_0$is the zero-order release constant,

k_1 is the first-order release constant, and

k_H is the Higuchi release constant.

Though nanoparticles are promising drug carrier systems, their poor oral bioavailability, instability in circulation, inadequate tissue distribution, and toxicity are some limitations to practical application that remain unresolved [75].

5. CONCLUSION

Current challenges of anticancer drug development include the site specific delivery with low systemic toxicity. The pharmacokinetics of a drug after administration is usually defined by its absorption, distribution, metabolism and elimination. Pharmacokinetics considerations are important in determining the proper chemotherapeutic dosing. For years doses were based on the patient's body surface area, but there is high inter-patient variability in plasma drug exposure and drug clearance. Methods have been proposed either to reduce pharmacokinetic variability among patients or to decrease other sources of inter-patient variability such as errors in dose calculation or drug manufacturing. An ideal dosing calculation considers the metabolic pathway of each drug, estimates the activity of involved enzymes and calculates the dose. Focus of such novel approaches is based on cancer treatment with innovative methods. Consequently, these promising technologies offer new opportunities for cancer treatment with minimal/lower toxicity to normal cells.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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