An Overview and New Strategies to Improve Formulation Development of Anticancer Drugs

Sachin Kumar Yadav, Nayyar Parvez and Pramod Kumar Sharma

School of Medical and Allied Sciences, Galgotias University, GB Nagar, U.P.-203201, India

Abstract: Cancer is defined as a complex series of disease condition caused by persistent tissue injury and host-environment interactions. Generally anticancer drugs were delivered by the i.v. route which is the easiest way to achieve immediate and complete bioavailability of the drugs. However this route of administration could result in several side effects. Due to this reason, oral delivery of drugs is more considered. In this review we present a report on the general considerations about the cancer, profile of a cancer cell, types of cancer, anticancer therapy and the drug delivery systems to improve the oral bioavailability of anticancer drugs.

Key words: Cancer • New Drug Delivery System • I.V. • Bioavailability • Breast Cancer • Lung Cancer • Docetaxel • Taxotere

INTRODUCTION

Cancer is a disease condition which is caused by persistent tissue injury and interaction between host-environment. It can lead to a various genetic (Mutations), epigenetic (Loss of heterozygosity) and global transcriptome changes (Via inflammation pathways) due to repeated exposure of carcinogens such as tobacco, ultraviolet light and infections. It has been a great challenge to the health care professionals and scientists due to increased occurrence of cancer and worldwide prevalence during the last decade. About 45% increase in the global cancer deaths by 2030 were suggested by WHO statistics, of which 70% would be contributed from developing countries like India. Till the last couple of decades, the major portion of cancer therapy was based on parenteral route of administration. Oral route has gained major focus as compared to the parenteral route after looking at the quality of life and need of follow-up therapy after the diagnosis of the disease. Oral route is safe and most convenient route of drug delivery. Its main advantage is patient compliance. However design and development of oral drug delivery system have certain limitations in the choice of excipients, diverse properties of drug substances and principally, physiological barriers pose great challenge. Oral anticancer therapy affects many clinically relevant aspects such as:

A) Prolonged exposure of drugs to cancerous cells can be achieved by appropriate plasma drug concentration. This will increase the efficacy and decreases the side effects of the anticancer drugs.
B) The discomfort of injection is avoided by oral chemotherapy and it can also be conducted at home. The patient cooperation and their quality of life may be enhanced by this approach, which is an important issue and thus deserves high attention for any medical treatment.
C) The risks associated with intravenous infusion lines are avoided.
D) Due to avoidance of hospitalization, sterile manufacturing and trained personnel assistance, the treatment cost for the patient can be highly reduced.
E) Due to high level of ease in administration, oral therapy can also be explored in the segment of prophylactics [1].

General Consideration: Cancer isn’t just a single condition; it’s actually a complex collection of diseases that can arise in almost any tissue in the body. What characterizes full-blown cancer cells is that they’ve become decidedly anti-social, carrying on their activities without regard to the other cells and tissues around them. Most normal cells are monitored by a myriad of mechanisms that keep them working in cooperation with
Breast Cancer:

Breast cancer in women is currently a leading cause of cancer death among men in the United States and it is the most common malignancy. It is estimated that 241,740 men will be diagnosed with PCa and 28,170 men will die from PCa in 2012. Risk factors are however, will divide whenever they please, regardless of how much they crowd their neighbours. They’ll also move to places they don’t belong, attract blood vessels to themselves and stop obeying aging signals. In short, cancer cells misbehave and their mischief gives rise to tumours. Each cancer has its own unique pattern of bad behaviour determined by the tissue in which it was formed, the mutations the cells have adopted and the chemistry in an individual’s body. Because every cancer is unique, a treatment that works wonders for a leukaemia patient, for example, might do little or nothing for a woman with breast cancer. Even patients who have the same kind of cancer will have different responses to the same therapy, because the way the cancer arises and plays out depends on unique cellular events and the patient’s individual genome.

Types of Cancer: Some of the cancers are discussed below:

Breast Cancer: Breast cancer in women is currently a leading cause of cancer-related death in humans and it is responsible for more than 1 million deaths each year. Lung cancer is the most common cause of cancer-related death worldwide in both the developed and the developing countries. Although many advances in its diagnosis and treatment, breast cancer remains a leading cause of cancer-related deaths among women. A majority (69%) of all breast cancer deaths occur in developing countries (WHO Global Burden of Disease, 2004) and it is estimated that, in 2012, there were more than 39,000 deaths from breast cancer in the United States alone [2]. The different stages of breast cancer, illustration of symptoms of breast cancer and cases of breast cancer related to age at diagnosis are shown in Figures 1, 2 and 3 respectively.

Prostate Cancer: Prostate cancer (PCa) is the second-leading cause of cancer death among men in the United States and it is the most common malignancy. It is estimated that 241,740 men will be diagnosed with PCa and 28,170 men will die from PCa in 2012. Risk factors are age, race, ethnicity and geographical location [3]. Different stages of prostate cancer are shown in Figure 4 and normal prostate and prostate cancers are shown in Figure 5.

Lung Cancer: Lung cancer is the most common cause of cancer-related death in humans and it is responsible for more than 1 million deaths each year. Lung cancer is broadly classified into two classes: non-small-cell lung carcinoma (NSCLC) and small-cell lung carcinoma.
Fig. 4: Different stages of prostate cancer

Fig. 5: Normal prostate and prostate cancer

Fig. 6: Stages of lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>93%</td>
</tr>
<tr>
<td>IIA</td>
<td>85%</td>
</tr>
<tr>
<td>IIIB</td>
<td>72%</td>
</tr>
<tr>
<td>IIIA</td>
<td>83%</td>
</tr>
<tr>
<td>IIIB</td>
<td>64%</td>
</tr>
<tr>
<td>IIIC</td>
<td>44%</td>
</tr>
<tr>
<td>IV</td>
<td>8%</td>
</tr>
</tbody>
</table>

Lung cancer treatment depends on the status of the patient, specific cell type of the cancer, the spread of the cancer [4]. Stages of lung cancer are shown in Figure 6.

**Gastric Cancer:** Gastric cancer occurs most frequently in the age group of 50-70 years and it is the second leading cause of death due to malignancy worldwide. The highest incidence of gastric cancer is in Japan, China, South America and Eastern Europe and the lowest in the United States. Gastric cancer is the third most common cancer in Kashmir only superseded by esophageal and lung cancer [5]. Percentage survival rate at different stages of gastric cancer is shown in Figure 7.
Profile of a Cancer Cell: Even though every cancer is different, there’s a shared set of behaviours that characterizes all cancer cells:

Uncontrolled Growth: Normal cells grow and divide when they get messages from the cells around them that it’s time to do so. Cancer cells, on the other hand, are able to jump-start growth by themselves and therefore can divide and make new copies of them independent of what’s going on in the cells around them. Lack of response to stop signals: A healthy cell will stop dividing when one of two things happens: it receives signals from nearby cells that the “neighbourhood” is crowded enough, or its cellular machinery is damaged. Ordinarily, a cell will take time out to repair problems. Cancer cells just keep on going, proliferating under conditions that would stop normal cells and making new copies of cells with damaged DNA.

Immortality: Almost all the cells in your body are programmed to stop functioning or commit suicide when cellular machinery is damaged beyond repair, when they’re infected by a virus, when there are too many cells, or when cellular functions begin to break down. An aging cell may simply stop dividing, or it may undergo a sequence of events called programmed cell death or apoptosis. Cancer cells ignore these stop signals and are thus able to expand their numbers.

Ability to Divide Infinitely: Healthy cells eventually stop dividing but continue to live. Their growth is stopped by the fact that their DNA is programmed to tolerate a certain number of replications and sends a “stop” signal when it’s reached its limit. Cancer cells evolve new ways to evade these signals. As a result, they continue to replicate, producing new cells that have miscopied or mutated DNA strands.

Recruiting a Food Supply: All cells need to be fed by oxygen and nutrients in the blood. Ordinarily, the body’s systems carefully regulate the growth of new feeder blood vessels, a process called angiogenesis. A tumor of cancerous cells typically skirts these systems and independently signals the body to feed it, causing new vessels to grow into the tumor. This vascularization of a tumor marks one of the defining moments when a precancerous tissue crosses the line and becomes a true cancer.

Random Migration: In healthy tissues, the cells stay where they are, adhering to each other in structures that characterize the tissue and assist in its function. Mature cancer cells, in contrast, can let go of these molecular handholds and relocate to other parts of the body. This cell movement, called metastasis, is one of the most defining characteristics of malignance. The resulting eruption of tumors in distant parts of the body is what brings about the majority of deaths from cancer. Tumors in distant parts of the body is what brings about the majority of deaths from cancer. Taken together, these rogue qualities are considered the hallmarks of cancer. Precancerous cells may show uncontrolled growth and lack appropriate response to stop signals and so they may divide repeatedly. Each new division is subject to frequent genetic errors. When such cells proliferate, they continue to pass along their disruptive mutations and likely acquire new ones, eventually creating a cancerous tumor. Tumor cells often acquire the first five characteristics before they move out to other parts of the body. This helps explain why catching a cancer early is important: If you detect it before it has acquired all the hallmarks, you can prevent metastasis.

Anticancer Therapy: Anticancer therapy is one of the three pillars of cancer treatment along with surgical treatment and radiation therapy. Generally, anticancer drugs are divided into three categories: cytotoxic, biological and hormonal agents. Cytotoxic agents are the traditional therapies that damage cancer cells by interfering with DNA or its precursor, inhibiting the cellular division. However, this kind of agents has the great drawback of killing healthy cells along with cancer cells [6]. Major types of cytotoxic agents include alkylating agents [7, 8], antimetabolites [9] and plant alkaloid [10-12]. Biological agents or targeted agents include monoclonal antibodies [13-17] and cancer vaccines [18-21]. This therapy (Also called immunotherapy, biological response modifier therapy, or biotherapy) uses the body’s immune system to treat cancer. Hormonal therapy interferes with hormone-dependent pathways that promote the development or the growth of cancer cells and has an important role in treating breast and prostate cancers. It includes tamoxifen [22, 23] and aromatase inhibitors [24-26]. At present, most anticancer drugs are administered intravenously (i.v.).
The intravenous route is the most direct one and overcomes the variable absorption patterns of the gastrointestinal tract. It leads to immediate and complete bioavailability and therefore, accurate dosing. However, this route could be hazardous, because high concentration of the drug is delivered to normal tissues [27, 28]. I.V. chemotherapy regimens are designed to deliver the maximal tolerated dose of cytotoxic agent to kill cancer cells in a short period of therapy followed by a period of several weeks without administration [29]. Cisplatin, for example, since 1979 has become an important component in chemotherapy for its broad spectrum of antitumor activity. Unfortunately, this drug has several side effects because of its unspecific uptake into all rapidly dividing cells. For this reason, the tolerated doses are very low. The major side effects are nephrotoxicity, neurotoxicity, ototoxicity and myelosuppression [30]. In addition, the preparation of injectable formulations requires the use of specific pharmaceutical excipients, which may contribute to the toxicity of the final formulation. For example, paclitaxel (Taxol), approved for breast, prostate and lung cancers, is highly lipophilic requiring a particular excipient for its formulation composed of 1:1 blend of Cremophor EL polyethoxylated castor oil and ethanol, diluted with 5- to 20-fold in normal saline or dextrose solution before administration. However, many problems were reported related to the large amount of Cremophor EL necessary to deliver the required dose of paclitaxel. This excipient causes several hypersensitivity reactions, nephrotoxicity and neurotoxicity. Consequently, premedication with corticosteroids and antihistamine is used to increase safety and reduce the intensity of these kinds of reactions [31]. Furthermore, it was reported that this additive could modify the kinetics of the drug [32,33]. In the same way, in Taxotere, docetaxel is formulated with the non-ionic surfactant polysorbate 80 (Tween 80) which has been implicated in the occurrence of severe anaphylactic hypersensitivity reactions [34]. Furthermore, i.v. chemotherapy requires a hospital visit, nursing and a palliative treatment. Although the use of ambulatory pumps and indwelling catheters enable home-based i.v. chemotherapy, this kind of administration remains inconvenient for patients. It is painful, can lead to haemorrhage and in the long term it is often associated with infection, bleeding and venous thrombosis [35]. Generally, the patient shows sight of depression and anxiety he/she does not feel free and independent and his daily life is influenced by the medication schedule [36]. In this context, the oral chemotherapy becomes a very interesting alternative to the i.v. therapy. In several studies, patient preference for oral or i.v. treatment was studied directly in a randomized crossover trial, comparing an oral drug regimen versus i.v. treatment. The majority of patients at the end of the study chose to continue with the oral treatment. They found oral chemotherapy advantageous and it made them feel less sick. It helped them to face their illness better. The most important feeling elicited is the feeling of freedom. Patients can spend more time at home and the medication interfered less with the daily activities. Finally, from an economical point of view, the oral therapy is convenient because it limits the cost of hospitalization and the infusion equipment supplies [27, 35, 37-39]. Currently, 10% of cancer chemotherapy is provided to patients as an oral formulation, but the National Comprehensive Cancer Network predicts that by the year 2013 this percentage will jump to 25% [40].

Formulations of Anticancer Drugs

Conventional Formulations for Cancer: Different conventional formulations for cancer have been developed. Some of them are:

Intravenous Formulations: Combination of telmisartan with cisplatin controls oral cancer cachexia in Rats. The effect of combination of telmisartan with cisplatin was studied in oral cancer cachexia induced by applying 0.5% 4-nitroquinoline-1-oxide (4-NQO) in propylene glycol to tongue, thrice a week for 8 weeks. From 8th to 22nd week, cisplatin (0.23mg/kg, i.v.) was administered once in three weeks and telmisartan (5mg/kg/day, p.o.) was administered daily [41].

Oral Formulations: Some examples of approved oral chemotherapy drugs are listed in Table 1 [42]. The list of oral cytotoxic drugs in development are enlisted in Table 2.

New Drug Delivery System for Cancer: Different NDDS formulations for the treatment of Cancer were developed and available in the market. NDDS formulations generally include liposome, microspheres, micelles, nanoparticles, neosomes, lipoproteins, cellular carriers etc. Some NDDS formulations for Cancer are given below:
Table 1: Some examples of approved oral chemotherapy drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Form</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altretamine</td>
<td>Hexalen</td>
<td>Capsules</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Targretin</td>
<td>Capsules</td>
<td>Cutaneous T cell lymphoma</td>
</tr>
<tr>
<td>Capetictine</td>
<td>Xeloda</td>
<td>Coated tablets</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Chloraminophene</td>
<td>Capsules</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Vepesid</td>
<td>Capsules</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Zavedos</td>
<td>Capsules</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Lomustine</td>
<td>Belustine</td>
<td>Capsules</td>
<td>Brain, lung and colon cancer</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Alkelaran</td>
<td>Coated tablets</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Lysodren</td>
<td>Capsules</td>
<td>Adrenal carcinoma</td>
</tr>
</tbody>
</table>

Table 2: List of oral cytotoxic drugs in development

<table>
<thead>
<tr>
<th>Agent</th>
<th>New strategies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (Ptx)</td>
<td>Ptx/ cyclosporine A</td>
<td>P-gp inhibitor, similar bioavailability with daily dosing schedule.</td>
</tr>
<tr>
<td></td>
<td>Ptx-HP.β-CD-nanoparticles</td>
<td>Bioavailability ~ 80%</td>
</tr>
<tr>
<td>Docetaxel (Dtx)</td>
<td>Dtx/ Ritonavir</td>
<td>CYP450 inhibitor, increment of systemic exposure by 50 fold</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Standard Hycamtin for i.v.</td>
<td>Less toxicity</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Lipid nanocapsules loaded SN38</td>
<td>Permeability improvement across caco-2-cells</td>
</tr>
</tbody>
</table>

A) Amphiphilic micelles of poly(2-methyl-2-carboxytrimethylene carbonate-co-D,L lactide)-graft-poly(ethylene glycol) for anti-cancer drug delivery to solid tumours.

B) Liposomal paclitaxel formulation for the treatment of breast and ovarian cancer.


D) Doxorubicin HCl liposomal injection was the first liposomal encapsulated anticancer drug to receive clinical approval.

E) Development of targeting lonidamine liposomes that circumvent drug-resistant cancer by acting on mitochondrial signaling pathways [4].

Self-Emulsifying Drug Delivery Systems for Cancer: Different SEDDS formulations for Cancer are available in the market.

I) Self-emulsifying drug delivery systems (SEDDS) was developed for the improvement of the stability of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) after released from poly (d,l-lactide-co-glycolide) (PLGA) wafer [43].

II) Self-nanoemulsifying drug delivery systems of tamoxifen citrate were developed for breast cancer treatment. The drug delivery encounters problems of poor water solubility and vulnerability to enzymatic degradation in both intestine and liver [44].

III) Self-microemulsifying drug delivery system (SMEDDS) improves anticancer effect of oral 9-nitrocamptothecin on human cancer xenografts in nude mice. 9-NC is an orally active agent being developed for the treatment of pancreatic cancer and other solid tumors [45].

Formulation Issues with Anticancer Drugs

Inadequate Aqueous Solubility: From a physico-chemical point of view, major anticancer drugs are sparingly water-soluble, making it difficult to formulate them efficiently. Improving the apparent solubility of such substances might only solve one aspect of the problem but it is a starting point to design efficient pharmaceutical formulations. In this context, different strategies were used to improve anticancer drug solubility by using pharmaceutical excipients, drug delivery systems or chemical reactions to form prodrugs. Concerning pharmaceutical excipients used for the solubilization of anticancer drugs, water miscible co-solvents, such as ethanol, methanol, methane chloride or acetonitrile, 14 mM in isopropanol [46] and water-insoluble organic solvents, such as oils, triglycerides, vitamin E, or their associations are generally used. Furthermore, micelles, liposomes, micro and nanocapsules, dendrimers, emulsions, microemulsions and nano-emulsions were largely used to increase apparent water solubility of anticancer drugs [47-49]. One strategy to improve anticancer drug aqueous apparent solubility is to use cyclodextrins, which are macromolecules composed of...
cyclic oligosaccharides of D-(+)-glucopyranose units, all in chair conformation, linked by α-(1,4)-glucosidic bonds. Complexation of poorly water-soluble drugs with natural or chemically modified cyclodextrins represents an interesting strategy for increasing their apparent water solubility [50-54] and offers further possibilities for their pharmaceutical formulation ranging from conventional to colloidal dispersions [39, 55-57], for review see [55, 58-60]. Interactions generally occur between cyclodextrins and lipophilic molecules or lipophilic groups on the guest molecules resulting in the formation of drug and/or cyclodextrin complexes [55-57, 61]. These complexes can be much more water-soluble than the lipophilic molecule [62]. So far, cyclodextrins were used to increase the solubility of the poorly water-soluble drugs to increase their bioavailability. However, the hydrophilic external surface can represent a drawback, because it can result in a lack of affinity for the biological barriers [63]. In this context, researchers focused their interest in the cyclodextrin derivatives and in particular in the advantages of the cyclodextrins encapsulated into colloidal carriers. Duchene et al. [62] showed the increase of loading capacity of poly (isobutyl cyanoacrylate) nanospheres by employing hydroxypropyl-β-cyclodextrin (HP-b-CD) and the possibility of the spontaneous formation of either nanocapsules or nanospheres by nanoprecipitation of amphiphilic cyclodextrin diesters. In the recent years, the use of cyclodextrins has been successfully applied to increase the encapsulation of different lipophilic drugs [64], such as benzophenone, tamoxifen, paclitaxel [55, 65] and saquinavir [66].

Intestinal Transit: After its oral administration, the active drug has to reach the intestinal absorption site. So far, multiparticulate drug delivery systems (DDS), including micro and nanoparticulate systems, were employed to improve the intestinal absorption of hydrophilic [67, 68] or hydrophobic drugs [39, 40]. In this context, the use of different kinds of polymers such as polysaccharides (chitosan or dextran), acrylic copolymers (Eudragit), phospholipids or cellulosic derivatives [cellulose acetate phthalate CAT or cellulose acetate trimellitate CAP and hydroxypropyl methylcellulose phthalate (HPMCP)], confer to these particulate systems adequate gastroresistant properties [69, 70]. If they pass intact through the stomach they can reach the small intestine where these DDS should release their drug content. For some drugs, the transit time through the intestine can be too short leading to incomplete absorption, resulting in low bioavailability and poor efficacy. Because the transit time in the gastrointestinal tract can be inadequate, many researchers have sought to enhance the duration available for absorption by rendering the dosage form mucoadhesive. The phenomenon of mucoadhesion results from the combined effects of different mechanisms depending on the nature of the dosage form as well as the polymers used [71-74]. The use of mucoadhesive DDS can (i) result in increased local drug concentrations, which is favorable to absorption, (ii) improvement of the effectiveness of the drugs by maintaining the plasma drug concentration at the therapeutic levels for prolonged periods of time and (iii) in some cases restricting absorption to a specific site in the intestine [75, 76]. Such dosage forms may be beneficial for the oral delivery of anticancer drugs impaired by low intestinal permeability.

Drug Metabolism and Efflux Pumps in the Intestinal Wall: The metabolism of anticancer drugs and/or their efflux in the intestinal wall during the absorption process represents another problem arising when an anticancer drug is orally administered. Consequently, cancer cells became resistant to the drugs [77]. It has been demonstrated that the expression and the activity of ABC transporters and the metabolite CYP450 enzyme expressed in the gastrointestinal tract could seriously impair the bioavailability of anticancer drugs [78-80]. Physiologically, ABC transporters have an important role in body defence; they are recognized for their ability to modulate the normal absorption, distribution, metabolism, excretion and toxicity of xenobiotics [81-83]. In this situation, an important strategy to achieve an efficient oral chemotherapy may exist in the concomitant delivery of inhibitors of the ABC transporters and CYP450 with the aim of increasing the drug bioavailability [38, 84]. However, the inhibition of the metabolism mechanisms may simultaneously influence the distribution and the bioavailability of other xenobiotics, leading to unwanted side effects.

CONCLUSION

Most of the marketed anticancer drugs are available as I.V. formulations. And due to this patient feels difficulty by I.V. route. Different fields of science are working to improve oral delivery of anticancer drugs. Many problems must to be solved. The achievement of suitable pharmacokinetic profiles and the toxicity issues
are probably the most important limitations for the oral administration of anticancer drugs. In the case of i.v. chemotherapy, the hospitalization enables the monitoring of the treatment directly by the health care provider, which is not possible with the oral chemotherapy. In this review we aim to define the different marketed formulations of anticancer drugs and also the drugs which are in development.

ACKNOWLEDGEMENT

All authors thankfully acknowledge, School of medical and allied sciences, Galagotias university for providing infrastructure for completing this review.

REFERENCES


