Chemotherapy and selective toxicity

In present scenario various type of treatments are available for cancer such as chemotherapy, radiotherapy, surgery, and immunotherapy. The management of cancer through non selective drug therapies often results in deleterious effect on the normal healthy human cells which can result in other adverse side reactions on different parts of the body(2012). The new area of focus in treatment of cancer is by administering drug by selective toxicity. The main goal of an anti cancer drug is to kill the growing cancer cells. However, there are some normal human cells which multiply rapidly and are affected by these anti cancer drugs which may produce various side effects mainly in formation of blood cells in bone marrow, formation of germ cells in reproductive organs, endothelial cells in digestive system and hair follicles. Selective toxicity in simple terms can be defined as the property of toxic substance to harm or kill a particular species of cells (i. e cancer cells) without producing any harmful effect to normal cells even if the two species are present in very close proximity. For example – If an anti cancer drug ‘ aminoglutethimide’ is administered, it will act non-selectively by killing normal human cells along with the targeted cancer cells and may produce toxic effects like- hepatotoxicity, hypothyroidism and skin rash. However, another anti-cancer drug ‘ anastrozole’ will act selectively and will only target cancer cells, leaving normal cells unaffected. However side effects such as bone weakness, sweats and diarrhea have been observed in very few cases. Due to this reason selective toxicity is a preferred chemotherapy for the treatment of cancer. Selective toxicity may be achieved through devising drug regimens based on pharmacokinetic data(Zubrod, 1978). It is advantageous because there are less chances of normal human cell to be affected by drug thus leading to lesser side effects(2012).

Part II

Chemotherapy

Currently, cancer treatment mainly is done through surgical removal of tumor, radiation therapy, and chemotherapy. The selection of therapies depends on the severity and type of cancer. The most common and first line treatment for cancer is chemotherapy(Chidambaram et al., 2011). In Chemotherapy, drug intervenes with the ability of cancer cells to divide and reproduce and thus prevent tumor growth. It also makes them cytotoxic causing apoptosis and hence shrinking of tumor. There are various side effects associated with chemotherapy, e. g- alopecia, nausea and vomiting, fatigue, hearing impairment, neutropenia, thrombocytopenia, anemia, loss of appetite, bowel movement problems, depression (Today, 22-July-2009). The existing chemotherapy produces symptomatic relief by inducing cytotoxicity in the cancer cells however it also leads to cytotoxicity in normal human cells as well. Thus it causes various side effects e. g. infections, nausea, vomiting, fatigue, anemia, inflammatory disorders etc. (Feick, 2012).

Limitations of chemotherapy

Most of the anti-cancer drugs are hydrophobic in nature for which we require solubilizing solvent for product formulation. These solvents are toxic in nature and may be harmful if used for chemotherapy. Poor selectivity of anti-cancer drugs may lead to improper functioning of normal human cells and may induce adverse reactions, free radicals, inflammatory factors causing various side effects. Various anti- cancer drugs are unable to enter the cancerous cells due to which their pharmacological activity is inhibited. Thus

drug administered to patient may not produce any therapeutic effects and this phenomenon is known as multi-drug resistance.

1 Selective drug targeting

As the growth rate of cancer cells is more rapid than the growth of normal cells, cancer therapies use combination of radiation therapy as well as chemotherapy including use of catheters so as to decrease the size of cancer and thereafter excision of tumor by surgery. But they possess many side effects as discussed earlier, hence there is a need for the introduction of new strategies and techniques to curb this problem(Brannon-Peppas and Blanchette, 2012).

1. 1 To overcome lack of selectivity of cancer drugs

The efficacy of the treatment of the cancer is directly proportional to the ability of the drug to selectively target the cancer cells thus improving the life expectancy of the patient. Artemisinin is commonly used for the treatment of breast cancer; however it is non-selective in nature. In order to improve the selectivity of drug, analogues of artemisinin and holotransferrin is used in the treatment of breast cancer. The cancer cells are destroyed by dihydroartemisinin by inducing cytotoxicity in cells in the presence of ferrous iron. The concentration of iron is increased in the cancer cells by inducing protein i. e. holotransferrin (which increases the concentration of ferrous iron thus activating dihydroartemisinin)(Singh and Lai, 2001).

Comparing the effect of dihydroartemisinin and holotransferrin on the cancerous as well as normal human breast cancer cells from Figure 1 it can be inferred that combination targeted therapy resulted in to a better

treatment of breast cancer. Also mortality of normal breast cells is very less compared to the cancer cells(Singh and Lai, 2001).

Control

holotransferrin dihydroartemisinin holotransferrin + dihydroartemisininC: UsersTarun KakkarDownloadssakshibcc. jpg

Figure Treatment of human breast cancer cells by holotransferrin and dihydroartemisinin(Singh and Lai, 2001).

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Figure Effect of holotransferrin and dihydroartemisinin on normal human breast cells(Singh and Lai, 2001).

In another type of target mediated therapeutic action folate receptors are used for selective targeting of drug. Folate receptors are G protein coupled receptors present in cell membrane and are involved in cell growth and development. These receptors are over produced in cancer cells and are absent in normal human cells. Thus the folic acid which is an agonist of folate receptor is conjugated with drug to be targeted (which are antibodies), radio opaque agents, low molecular synthetic drugs, protein toxins etc. This is novel method of drug targeting as it seems to possess minimal side effects and also shows much better pharmacological activity(Elnakat and Ratnam, 2006).

2. To improve aqueous solubility of drug

The anti-cancer drugs are poorly soluble in nature, thus possesing low bioavailability and reduced pharmacological activity. Nano drug delivery system (NDDS) is current research focus for enhancing the bioavailability of the poorly soluble these drug(Chen et al., 2011). In NDDS therapeutic index of the drug is improved by altering the surface properties of drug molecules or by combining drug with drug carriers e. g. doxorubicin which is widely used anticancer drug suffers from various side effects such as cardiovascular and bone-marrow toxicity. So, in order to improve the selectivity of doxorubicin with cancer cells it was conjugated with dextran and then encapsulated with chitosan nanoparticles. This combination may help to reduce the size of tumor and to overcome the side effects caused due to conventional doxorubicin(Mitra et al., 2001). The selectively targeting of the nanoparticles is done either passively or actively to cancerous sites. In passive targeting the nanoparticles of the drug are accumulated in the tumor which is based on the difference in the interstitial pressure of blood vessels in tumor compared to that pressure in normal blood vessels. Liposomes, micelles, dendrimers, synthetic polymers are used as drug carriers for targeting the drug(Allen and Cullis, 2004, Nathanson and Nelson, 1994). However, in active drug targeting the drug is conjugated with ligands, anitbodies, nucleic acid which targets the drug to a specific site thus it bypasses any accumulation of nanoparticles in nonspecific sites(Lavasanifar et al., 2002). The drug present in the nanoparticles adhere to the tumor cells by endosome dependent mechanism(figure 3) which cutouts the endothelial efflux pump and thus increases the intracellular concentration of drug molecules(Chidambaram et al., 2011).

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Figure . Endosome dependent mechanism of actively targeted nanoparticles(Chidambaram et al., 2011)

3. To overcome multi drug resistance

A same cancer disease can be caused by different genes and factors; this phenomenon is known as heterogeneity. It is significant because heterogeneous induction of disease makes it difficult to understand which type of diagnosis and therapy is to be used to cure a specific type of cancer. One way of treating the heterogeneous state of cancer is by administering combinatorial drug therapies. In this method, various drugs are used for targeting different genes and factors. It has been found to be useful in some cases however not in every case, as they mainly target drugs related to cancer dividing cells and not the non-dividing cancerous cells. So therefore future area of research mainly focus on drug development for inhibiting the non-dividing cancer cells (Bhatia et al., 2012).