



Cancer Chemotherapy: A Review Update of the Mechanisms of Action, Prospects and Associated Problems

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Summary

Cancer is one of the leading causes of death in developed countries, responsible for about 25% of all deaths. On a yearly basis, 0.5% of the population is diagnosed with cancer. Treatment options include surgery, radiotherapy, and systemic therapies such as chemotherapy, endocrine therapy, and targeted agents. Conventional chemotherapeutic agents act by creating toxic effects on all dividing cells. The toxic by-products of some chemotherapeutic drugs are deposited mainly in the liver producing hepatotoxicity, leading to many side-effects like loss of appetite, nausea, vomiting, diarrhea, abdominal cramps and constipation, anemia, fatigue, hyperthermia, loss of hair, etc. In this review update, the benefits and problems of chemotherapy have been highlighted and the mechanisms involved in cancer formation, groups of chemotherapeutic agents, as well as method of chemotherapeutic administration, have been discussed.

Keywords: Cancer chemotherapy, cancer stem cells mechanisms of action, prospects side effects

1.0 Introduction

Cancer is one of the leading causes of death in developed countries, responsible for about 25% of all deaths. On a yearly basis, 0.5% of the population is diagnosed with cancer. Medically termed as a malignant neoplasm, cancer is an uncontrolled growth of abnormal cells in the body. This uncontrolled growth of cells can be attributed to

mutations in the signals that regulate the cell cycle of growth and division (Priya, 2012). Most cells remain in interphase, the period between cell divisions, during the cell cycle. The initial stage of the interphase, G1 (for the first gap) involving rapid growth, metabolic activity, and synthesis of RNA. Next, is the S phase (for DNA synthesis), where the cell continues to grow, and DNA gets replicated. In G2 (for the second gap), the cell continues to grow and prepares for cell division. Next is Cell division (mitosis) called as M phase (Rolz-Cruz and Kim, 2008).

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Cells that do not divide for long periods do not replicate their DNA and are in G₀. In normal cells, tumor suppressor genes act as braking signals during G₁ to stop or slow the cell cycle before the S phase. DNA repair genes are active throughout the cell cycle, particularly during G₂ after DNA replication and before the chromosomes prepare for mitosis (Preety, 2012). Cancer cells overcome the normal cell signaling process and become immortal. Apart from cell proliferation becoming uncontrollable, cells becoming resistant to apoptosis (programmed cell death) is another reason behind cancerous cells. In regards to mutations in tumor suppressors or activation of proto-oncogenes to oncogenes, the cell cycle gets disrupted, and the cells divide uncontrollably and grow into a lump called a tumor. (Tatarkova *et al.*, 2012).

In a benign tumor, the cells do not spread to other parts of the body and it is not called cancer. However, the cells may carry on growing at the original site and may cause a problem by pressing on other parts of the body. In a malignant tumor, the cells are able to spread to other parts of the body (Reeder and Vogel, 2007). Cancer will begin to grow in one part of the body. This is called primary cancer. If the cancer is not treated it may spread. If it spreads and grows in another part of the body, it is called secondary or metastatic cancer (Vlastos *et al.*, 2004)

Attempts to cure or palliate cancer employ 3 principal methods: surgery, radiotherapy, and chemotherapy. Differing from the operation and radiotherapy that emphasize the treatment of local tissues, chemotherapy is concerned with that of the whole body. Chemotherapy is the use of drugs to inhibit or kill proliferating cancer cells while leaving host cells unharmed, or at least recoverable (Soares and Johnson, 2007). The drugs are carried in the blood so they can reach cancer cells in most parts of the body. Chemotherapy drugs are usually given into a vein or by mouth. Sometimes they are given by injection under the skin, into the muscle, into the fluid around the spine or into a body cavity such as the bladder, or by the use of creams may for some skin cancers (Vitiello *et al.*, 2007). Chemotherapy drugs can't tell the difference between reproducing cells of normal tissues (like those that are replacing worn-out normal cells) and cancer cells. This means normal cells are damaged along with the cancer cells, and this causes side effects. For this reason, the range and effectiveness of chemotherapy become restricted. Each time chemotherapy is given, it involves trying to find a balance between destroying the cancer cells (in order to cure or control the disease) and sparing the normal cells to lessen unwanted side effects (Rolz-Cruz and Kim, 2008;

Smith and Dowsett, 2003). Determination of cancer type and cancer stage is a very important phenomenon for the success of chemotherapy (Kovacic, 2007). The growing capability of cancer cells to resist the chemotherapeutic drug is one of the main drawbacks of conventional chemotherapy (Johnstone *et al.*, 2000). Over-dosage in chemotherapy can produce many harmful effects in the patients.

Side-effects occur mostly when the chemotherapy damages the healthy cells that maintain the body's function and appearance. Different side-effects arise depending on the nature of the drug. For example, the Alkalyting agents and anti-metabolites directly damage DNA to prevent the cancer cells from reproducing; thus they can cause long-term damage to the bone marrow, which can eventually lead to acute leukemia. Similarly, Anthracyclines can permanently damage the heart if given in high doses for a long time. Other side effect includes symptoms of allergic reaction like fast heartbeat, itching or hives, swelling in the face or hands, swelling or tingling in the mouth or throat, chest tightness, and wheezing. Immune-suppression, Bone marrow suppression leading to anemia and thrombocytopenia. Another serious problem of immune-compromised patients, caecitis-infection of the gut-includes diarrhea, nausea, vomiting, fever, and distended abdomen, etc (Keidan *et al.*, 2009). Infertility arises in both female and male patients by some gonad toxic chemotherapeutic agents may also occur (Brydøy *et al.*, 2001). This review update, therefore, focused on problems and prospects associated with chemotherapy, addressing the mechanism involved in cancer formation, groups of chemotherapeutic agents as well as methods of chemotherapeutic administration.

2.0 Cancer

Medically termed as malignant neoplasm, cancer is an uncontrolled growth of abnormal cells in the body. This uncontrolled growth of cells can be attributed to mutations in the signals that regulate the cell cycle of growth and division (Priya, 2012). The cell cycle has 5 phases. Since cell reproduction happens over and over, the cell cycle is shown as a circle. All the phases lead back to the resting phase (G₀), which is the starting point. When a cell goes through the cell cycle, it reproduces 2 new identical cells. Each of the 2 cells made from the first cell can go through this cell cycle again when new cells are needed.

G₀ phase (resting stage): The cell has not yet started to divide. Cells spend much of their lives in this phase. Depending on the type of cell, G₀ can last from a few hours

to a few years. When the cell gets a signal to reproduce, it moves into the G1 phase.

G1 phase: The cell starts making more proteins and growing larger, so the new cells will be of normal size. This phase lasts about 18 to 30 hours.

S phase: The chromosomes containing the genetic code (DNA) are copied so that both of the new cells formed will have matching strands of DNA. This phase lasts about 18 to 20 hours.

G2 phase: The cell checks the DNA and gets ready to start splitting into 2 cells. This phase lasts from 2 to 10 hours.

M phase (mitosis): The cell actually splits into 2 new cells. This phase lasts only 30 to 60 minutes.

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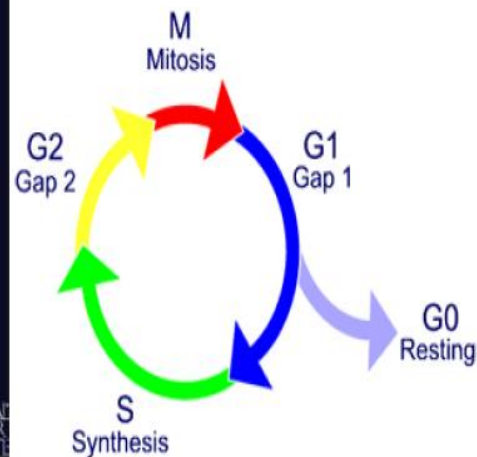
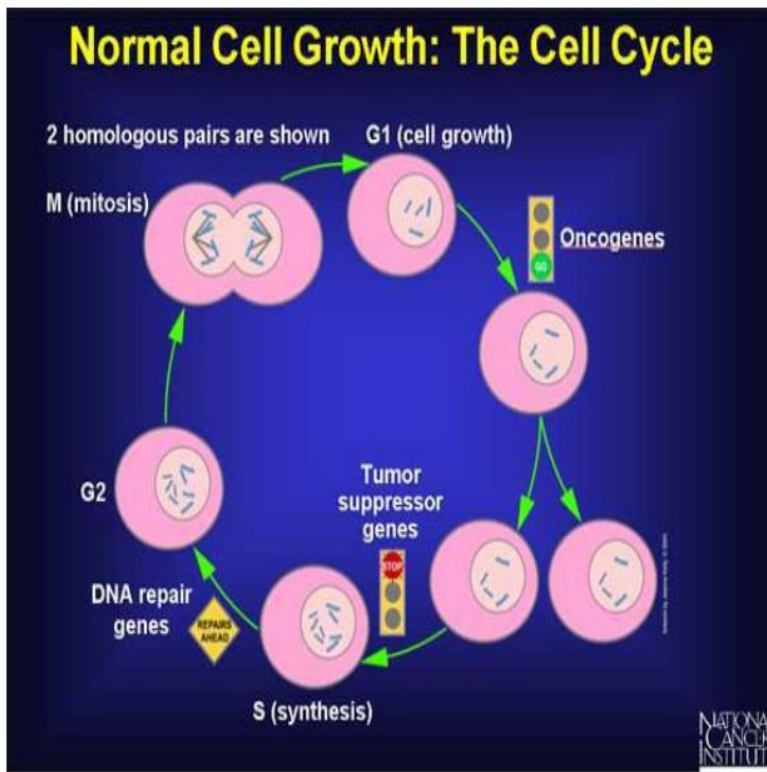


Figure 1: a. The cell cycle; b. Cell cycle phase

Source: (Preety, 2012).

Cancer cells overcome the normal cell signaling process and become immortal. Apart from cell proliferation becoming uncontrollable, cells becoming resistant to apoptosis (programmed cell death) is another reason behind cancerous cells. In regards to mutations in tumor suppressors or activation of proto-oncogenes to oncogenes, the cell cycle gets disrupted, and the cells divide uncontrollably. Normal cells remain in the area where they

belong and do not spread to other parts of the body. Cancer cells disregard this principle and spread through the body in a process called metastasis. These include direct invasion and destruction of the organ of origin, or spread through the lymphatic system or bloodstream to distant organs. The immune system consists of a group of cells called white blood cells that recognize and destroy "foreign" material in the body such as bacteria, viruses, and unfamiliar or abnormal cells. Cancer cells manage to slip through this detection system without triggering the immune system to start fighting, either at the primary cancer site, in the blood vessels, or at the site of the distant spread (Priya, 2012)

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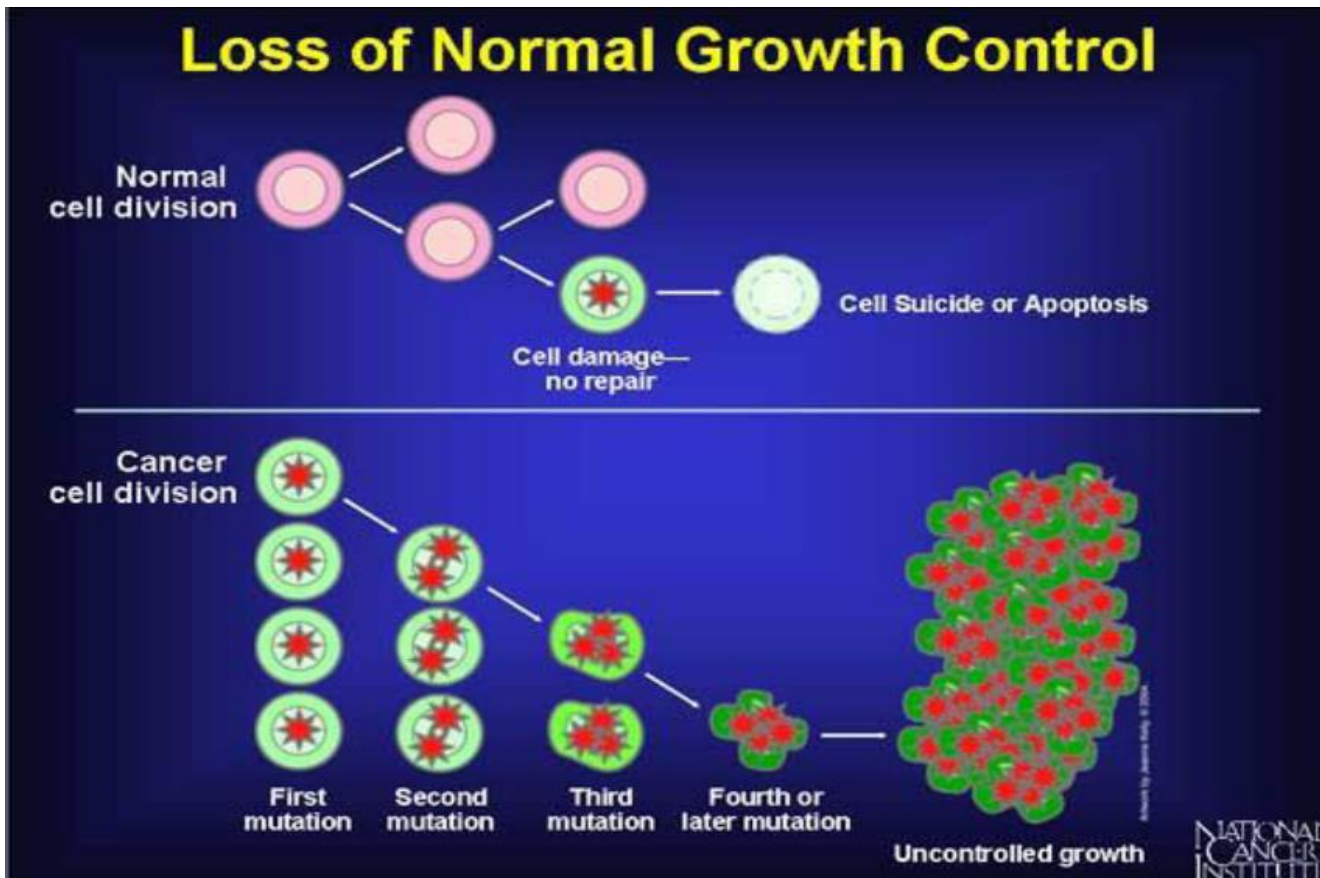


Fig 2: Cell division: normal cell vs. cancerous cell

Source: (Preety, 2012).

2.1 Cancer Stem Cell (Csc)

A recent American Association for Cancer Research (AACR) workshop defined CSC as a malignant cancer cell with a stem cell phenotype (Clarke *et al.*, 2006). Whilst the CSC hypothesis does not specifically address the mechanisms of malignant transformation, it has been suggested that CSCs are the malignant counterparts of normal adult tissue SCs which, due to dysregulated signaling pathways, are unable to maintain stem cell homeostasis. As well as the normal SCs, also CSCs are thought to reside at the top of the lineage hierarchy and give rise to differentiated cells, which themselves have no potential for self-renewal, and therefore do not contribute significantly to tumor growth. Due to their long life, SCs remain in a tissue for longer periods compared to their differentiated progeny, thereby making them more likely to acquire transforming mutations. Additionally, it is generally accepted that SCs are more resistant to apoptosis and DNA damage and they are

therefore more likely to survive to any insults (Crocker and Allan, 2008). Whilst being quiescent in normal tissue, SCs are able to maintain their pool by undergoing asymmetric cell division during biological processes such as the occurrence of tissue damage. During this process, a SC divides asymmetrically to generate an identical daughter cell that is committed to differentiation. It has been suggested that in this way CSCs generate the different cell types within a tumor, leading to tumor self-renewal as well. Specific signaling pathways are involved in embryogenesis processes, leading to the development of various organs. We are talking about several key pathways, such as sonic Hedgehog, Notch, PTEN, BMI-1, WNT, and p53. During the development of cancer an alteration of these pathways occurs and this event could lead to dysregulation of SC self-renewal and contribute to tumor proliferation (Molofsky *et al.*, 2004). The SC pool is also tightly regulated by signaling pathways from the microenvironment of the SC niche, and several of these pathways, including Hedgehog and WNT, have been implicated in carcinogenesis (Korkaya *et al.*, 2009). This may have very important implications in therapeutic interventions, including explanation for the development of chemoresistance. A role for CSCs in

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propagating and maintaining metastases has been proposed (Miki *et al.*, 2007). The different hypothesis that the dedifferentiation of mature cells to a more pluripotent state could be a potential mechanism for the development of SC-like features by cancer cells, cannot be dismissed.

In 1997 Bonnet and Dick first isolated the CSCs in leukemic cells expressing SC marker CD34 and afterwards, also, in other solid tumors (Bonnet and Dick, 1997). Classically, SCs are defined by their two main characteristics: self-renewal and pluripotency (Quintana *et al.*, 2008). Experiments performed on human acute myeloid leukemia and solid tumors show that CSC have three functional characteristics: transplantability, tumorigenic potential to form tumors when injected into nude mice; distinct surface markers; ability to recreate the full phenotypic heterogeneity of the parent tumor (Clarke, 2007). In characterizing normal and CSCs the problem is that these cellular populations are rare and the absence of specific cell surface markers represents a challenge to isolate and identify pure SC populations (Hill, 2006)

2.2 Cancer Cell Metabolism

Glucose is one of the most important energy sources of proliferating cells. In the first step of energy production, glucose is metabolized by glycolysis to pyruvate. Under aerobic conditions, pyruvate is oxidatively decarboxylated by the pyruvate decarboxylase complex inside the mitochondria to form acetyl Coenzyme A (acetyl-CoA). Acetyl-CoA is then completely oxidized to CO₂ by the tricarboxylic acid (TCA) cycle. This process provides NADH, which is oxidized during mitochondrial respiration to generate high amounts of ATP through oxidative phosphorylation (OXPHOS). Under anaerobic conditions, pyruvate can be reduced ('fermented') to lactate by lactate dehydrogenase (*LDH*). This process of glucose fermentation is less efficient in generating ATP than the TCA cycle (Lunt *et al.*, 2011). In the early 1920s, Warburg first noticed that cancer cells consume more glucose than normal cells leading to increased production of lactic acid even in the presence of sufficient amounts of oxygen (designated as 'aerobic glycolysis'). This phenomenon is known as the "Warburg effect" (Vander *et al.*, 2009).

Higher glucose uptake in tumors is used diagnostically for cancer detection by monitoring the incorporation of [¹⁸F]-labeled deoxyglucose (FDG) in FDG-positron emission

tomography. So far, underlying mechanisms for the altered metabolic program in cancer cells are still not completely elucidated. Changes in the tumor's microenvironment, such as limited availability of oxygen and nutrients, may influence the metabolic switch from OXPHOS to aerobic glycolysis (Vander, 2011). In addition, various genetic alterations in pathways regulating cell metabolism have been identified during the past years. These include for example the *PI3K* (phosphatidylinositol-3-kinase), *HIF* (hypoxia-inducible factor), *p53*, *c-Myc*, *Ras*, *AMPK* (AMP-activated protein kinase) and *LKB1* (liver kinase B1) pathways, as well as overexpression of glucose transporters (*Glut*), hexokinase (*HK*) and other key enzymes involved in glycolysis. Stimulated by the *c-Myc* oncogene, cancer cells exceedingly utilize glutamine as a carbon and nitrogen source as well as for the generation of ATP (Lunt *et al.*, 2011).

Cancer cells adapt to the metabolic requirements of tumor growth by alterations in the activity of pyruvate kinase (*PK*) (Mazurek *et al.*, 2005). *PK* catalyses the rate limiting, ATP-generating step of glycolysis, in which phosphoenolpyruvate (PEP) is converted to pyruvate. Surprisingly, cancer cells express high levels of the less efficient embryonic M2 isoform of *PK* (*PKM2*), resulting in the inhibition of glycolysis and reduced production of ATP. The advantage for cancer cells lies in the fact that intermediates of glycolysis accumulate and are available for alternative metabolic pathways. Rapidly dividing cells need biosynthetic intermediates for cell duplication during proliferation.

Channeling glucose to aerobic glycolysis instead of OXPHOS enables the cell to export acetyl-CoA to the cytosol in form of citrate for the construction of fatty acids, to supply glycolytic intermediates for nonessential amino acid production, and to provide ribose-5-phosphate from the pentose phosphate pathway (PPP) for nucleotide synthesis. Additionally, the pentose phosphate pathway promotes the production of NADPH as an important cofactor that supplies reducing equivalents for many enzymatic reactions (Cairns *et al.*, 2011). NADPH is also a key antioxidant required to control levels of reactive oxygen species (ROS) produced exceedingly during rapid cell proliferation (Cairns *et al.*, 2011). Therefore, the altered cancer cell metabolism is likely to constitute a growth advantage to rapidly proliferating cancer cells (Vander *et al.*, 2009).

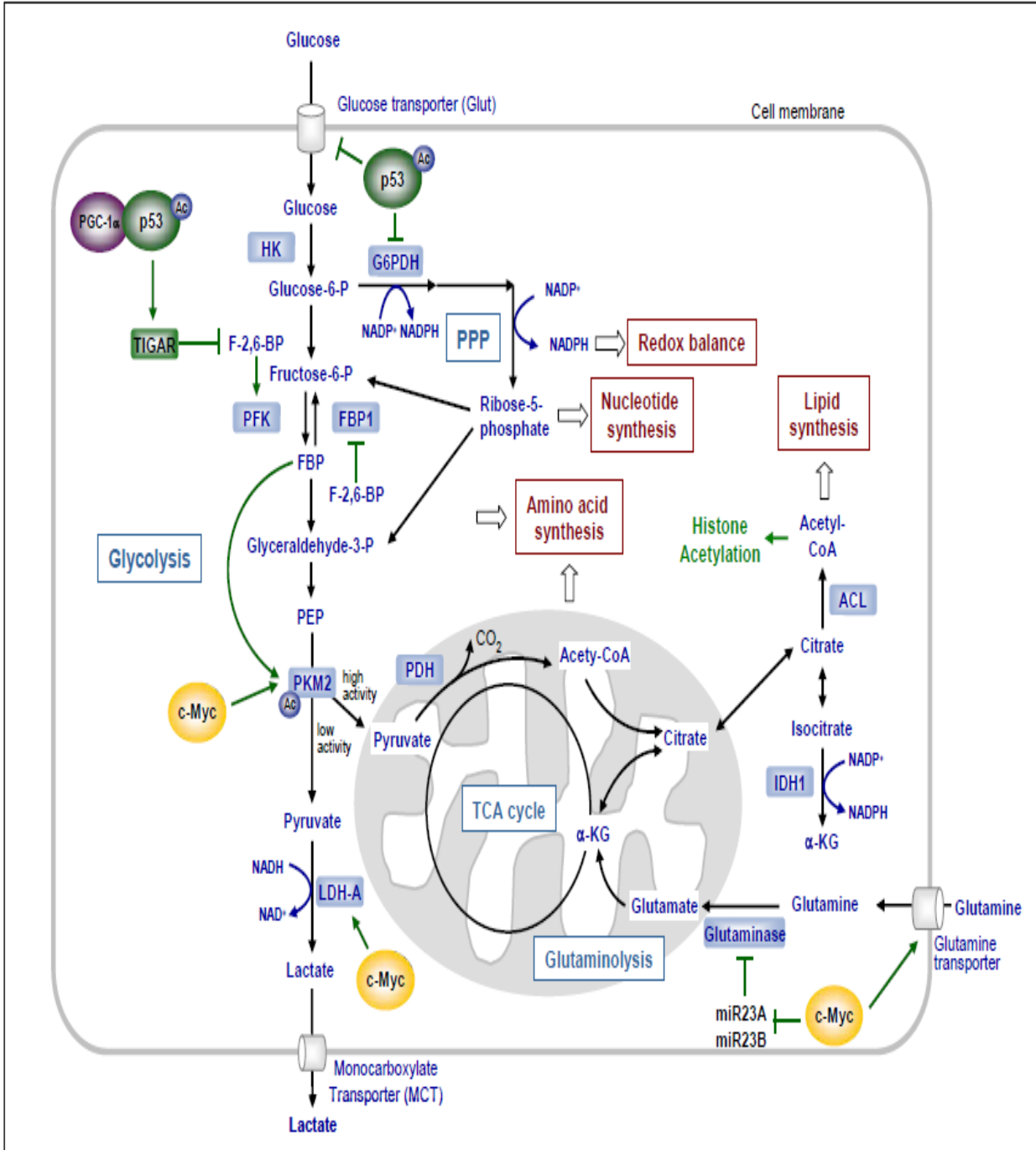


Figure 3. Interconnection of glycolysis, oxidative phosphorylation via the tricarboxylic (TCA) cycle, the pentose phosphate pathway (PPP) and glutaminolysis in proliferating cancer cells

Sources: (Ciocce and Blandino, 2011).

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2.3 Epigenetic Regulation

The term “epigenetics” refers to modifications in gene expression caused by heritable, but potentially reversible, alterations in chromatin structure and/or DNA methylation without changes in the DNA sequence. Epigenetic mechanisms play an important role for diverse cellular processes, for example during development, tissue specific gene expression and memory formation (Stilling and Fischer, 2011). However, epigenetic mechanisms are also involved in the development of age- and lifestyle-related diseases such as metabolic syndrome, cancer and Alzheimer’s disease (Bruce and, Cagampang, 2011). Best investigated epigenetic modifications comprise of DNA methylation, posttranslational histone modifications including acetylation, methylation, phosphorylation, ubiquitination and sumoylation, and regulation of gene expression by noncoding (nc) RNA including microRNA (Jaenisch and Bird, 2003). These epigenetic modifications can be inherited to daughter cells. Thus epigenetic modifications have the potential to correct altered gene expression patterns that have been established as a consequence of environmental stimuli (e.g. nutrition, chemical exposure, radiation etc.) or as a result of signals in a cells microenvironment and therefore could act as a ‘memory’ for gene expression patterns (Herceg *et al.*, 2011).

3.0 Cancer chemotherapy

3.1 History of cancer chemotherapy

The first practical anticancer drugs were discovered accidentally. One such discovery was an outcome of war, stemming from the finding that sulfur mustard gas, used as a toxic vesicant in the First World War, caused myelosuppression. Although gas warfare was not employed in the Second World War, a considerable stock of mustard

gas canisters was maintained in the Mediterranean area. An accident in the Italian port of Bari, involving leakage of one of these canisters, rekindled interest in the myelosuppressive effect of nitrogen mustard, leading to clinical trials in lymphoma patients (Kohn, 1996).

The identification of vitamins as small low-molecular weight enzyme cofactors was an important biochemical achievement in the early part of the 20th century. The structural elucidation and crystallization of folic acid in 1946 led, as with other isolated vitamins, to studies on its effect on the course of a number of diseases. Unexpectedly, administration to leukemia patients of folic acid and its glutamylated derivatives resulted in an increase in tumor growth. While the use of low-folate diets in the management of leukemia was investigated, the development of the folic acid analogue aminopterin provided a significant advance in the management of childhood acute leukemia (Bertino, 1979).

The link between these two disparate types of drugs and their biological activity was found to be related to their damaging effect on DNA. Although Friedrich Miescher had characterized DNA as a substance in 1862, the informational complexity and significance to life of DNA was not appreciated until the 1940s. The elucidation in 1953 by James Watson and Francis Crick of the double-helical structure of DNA had a singular impact on strategies of anticancer drug development. The cancer chemotherapeutic agent nitrogen mustard was found to react chemically with DNA (Kohn *et al.*, 1966). Studies on aminopterin indicated that it interrupted

DNA biosynthesis and in so doing caused DNA damage. The next two decades brought a massive development of new drugs that affected the integrity of the cell’s genetic material, with approximately one new drug entering widespread clinical use every 2 years. Many of these drugs, which revolutionized the treatment of many types of cancer, are shown in Figure 4.

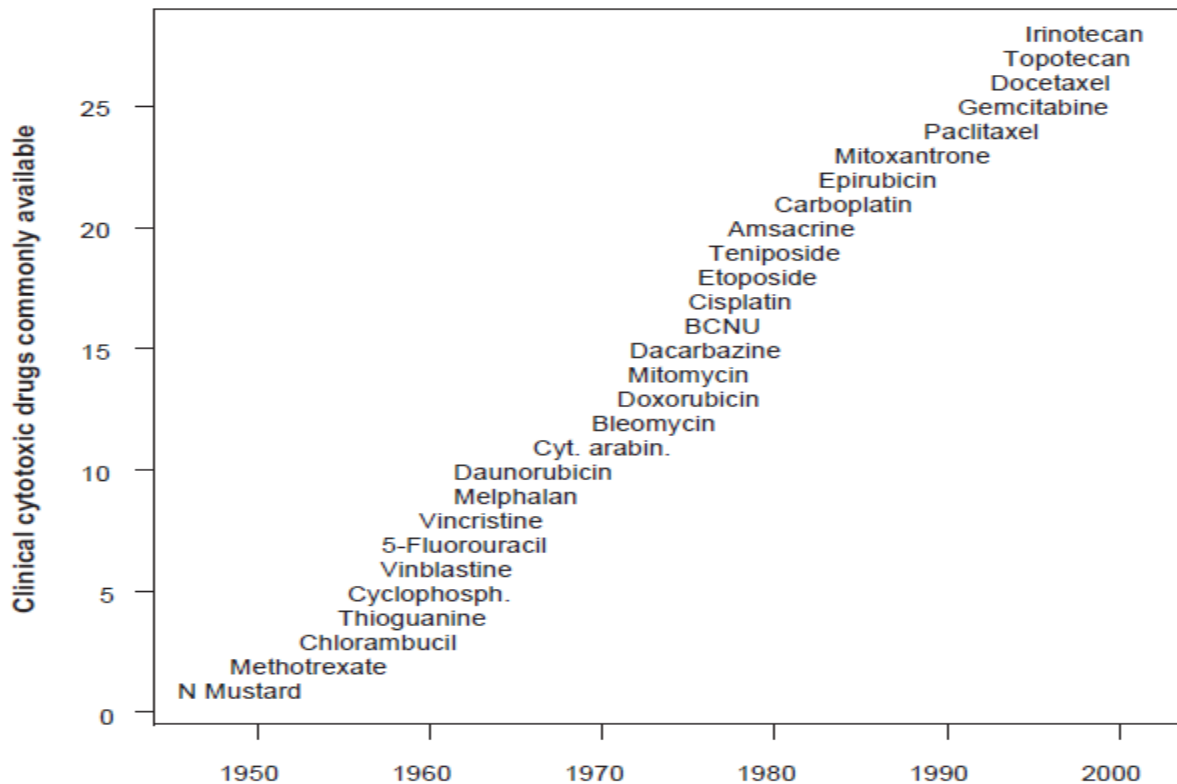


Figure 4. Chronology for the development of some of the anticancer drugs currently in use today. The abbreviations are N mustard (nitrogen mustard), cyt. arabin. (cytosine arabinoside), and BCNU (bischloroethylnitrosourea).

3.2 Classification of Chemotherapy Drugs

Chemotherapy drugs can be divided into several groups based on factors such as their mechanism of action, their chemical structure, and their relationship to another drug. Some drugs act in more than one way, and may belong to more than one group. Knowing how the drug works is important in predicting side effects (Missailidis, 2008).

3.2.1 Alkylating agents

Alkylating agents directly bind to DNA, thereby inhibiting DNA replication and initiating cell death. These drugs work in all phases of the cell cycle and are used to treat many different cancers, including leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma, as well as cancers of the lung, breast, and ovary (Pereg *et al.*, 2008). Because these drugs damage DNA, they can cause long-term damage to the bone marrow. In rare cases, this can lead to acute leukemia. The risk of leukemia from alkylating agents is

“dose-dependent,” meaning that the risk is small with lower doses, but goes up as the total amount of the drug used gets higher. The risk of leukemia after getting alkylating agents is highest about 5 to 10 years after treatment. Alkylating agents are divided into different classes, including: Nitrogen mustards: such as mechlorethamine (nitrogen mustard), chlorambucil, cyclophosphamide (Cytoxan®), ifosfamide, and melphalan, Nitrosoureas such as streptozocin, carmustine (BCNU), and lomustine, Alkyl sulfonates such as busulfan, Triazines such as dacarbazine (DTIC) and temozolomide (Temodar), Ethylenimines such as thiotepa and altretamine (hexamethylmelamine) (Pereg *et al.*, 2008)

3.2.2 Platinum compounds

Platinum compounds form DNA adducts that result in DNA crosslinking. DNA crosslinks inhibit replication, transcription, and other nuclear functions. The combination of these events arrests cell proliferation and ultimately tumour growth. Cisplatin and carboplatin are among the most commonly used platinum compounds (Koren *et al.*, 2005).

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3.2.3 Antimetabolites

Antimetabolites are small compounds that act as false substrates during DNA or RNA synthesis. They interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA. These agents damage cells during the S phase, when the cell's chromosomes are being copied. They are commonly used to treat leukemias, cancers of the breast, ovary, and the intestinal tract, as well as other types of cancer. 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), Capecitabine, Cytarabine, Floxuridine, Fludarabine, Gemcitabine, hydroxyurea, Methotrexate and Pemetrexed are among those commonly used antimetabolites (Azim and Peccatori, 2011).

3.2.4 Anti-tumor antibiotics

Microorganisms produce these cytotoxic agents that interact directly with DNA resulting in anti-cancer activity. The manner in which antibiotics interact with DNA differs considerably between agents. These drugs are not like the antibiotics used to treat infections. They work by altering the DNA inside cancer cells to keep them from growing and multiplying (Cardonick *et al.*, 2010).

Anthracyclines

Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in DNA replication. These drugs work in all phases of the cell cycle. They are widely used for a variety of cancers. Examples of anthracyclines include: Daunorubicin, Doxorubicin, Epirubicin and Idarubicin. A major concern when giving these drugs is that they can permanently damage the heart if given in high doses. For this reason, lifetime dose limits are often placed on these drugs. Other anti-tumor antibiotics that are not anthracyclines include: Actinomycin-D, Bleomycin, Mitomycin-C and Mitoxantrone (also acts as a *topoisomerase II inhibitor*) (Van Calsteren *et al.*, 2010).

3.2.5 Topoisomerase inhibitors

These drugs interfere with enzymes called topoisomerases, which help separate the strands of DNA so they can be copied during the S phase. Topoisomerase inhibitors are used to treat certain leukemias, as well as lung, ovarian, gastrointestinal, and other cancers. Topoisomerase inhibitors are grouped according to which type of enzyme they affect: *Topoisomerase I inhibitors* include: Topotecan and Irinotecan (CPT-11). While *Topoisomerase II inhibitors* include: Etoposide (VP-16), Teniposide and Mitoxantrone (also acts as an *anti-tumor antibiotic*). Topoisomerase II

inhibitors can increase the risk of a second cancer – acute myelogenous leukemia (AML) – as early as 2 to 3 years after the drug is given (Missailidis, 2008).

3.2.6 Mitotic inhibitors

Mitotic inhibitors are often plant alkaloids and other compounds derived from natural products. They work by stopping mitosis in the M phase of the cell cycle but can damage cells in all phases by keeping enzymes from making proteins needed for cell reproduction. Examples of mitotic inhibitors include: Estramustine, Taxanes such as paclitaxel and docetaxel, Epothilones such as ixabepilone, Vinca alkaloids such as vinblastine, vincristine, and vinorelbine. They are used to treat many different types of cancer including breast, lung, myelomas, lymphomas, and leukemias. These drugs may cause nerve damage, which can limit the amount that can be given (Pereg *et al.*, 2008).

3.2.7 Corticosteroid

Corticosteroids, often simply called steroids, are natural hormones and hormone-like drugs that are useful in the treatment of many types of cancer, as well as other illnesses. When these drugs are used as part of cancer treatment, they are considered chemotherapy drugs. Examples of corticosteroids include: Prednisone, Methylprednisolone and Dexamethasone. Steroids are also commonly used to help prevent nausea and vomiting caused by chemotherapy. They are used before chemotherapy to help prevent severe allergic reactions, too (Koren *et al.*, 2005).

3.2.8 Other chemotherapy drugs

Some chemotherapy drugs act in slightly different ways and do not fit well into any of the other categories. Examples include drugs like L-asparaginase, which is an enzyme, and the proteasome inhibitor bortezomib.

3.3 Effects of Vitamins On Chemotherapy

Many people want to take an active role in improving their overall health. They want to help their body's natural defenses fight the cancer and speed up their recovery from chemo. Because most people think of vitamins as a safe way to improve health, it's not surprising that many people with cancer take high doses of one or more vitamins. But few know that some vitamins might make their chemo less effective (Azim and Peccatori, 2011). Certain vitamins, such as A, E, and C act as antioxidants. This means that they can prevent formation of ions (free radicals) that damage DNA. This damage is thought to have an important role in causing cancer. But some chemotherapy drugs (as well as radiation

treatments) work by producing these same types of free radical ions. These ions severely damage the DNA of cancer cells so the cells are unable to grow and reproduce. Some scientists believe that taking high doses of antioxidants during treatment may make chemo or radiation less effective (Cardonick *et al.*, 2010; Van Calsteren *et al.*, 2010).

3.4 Methods of Chemotherapy Administration

In most cases, chemo drugs are put right into the bloodstream or taken as pills. They then travel throughout the body to kill cancer cells. Sometimes there's a need to get high doses of chemo to a specific area of the body. Regional chemotherapy directs the anti-cancer drugs into the part of the body where the cancer is. The purpose is to get more of the drug to the cancer, while trying to limit effects on the whole body. Side effects will often still happen because the drugs can be partly absorbed into the bloodstream and travel throughout the body (Cardonick *et al.*, 2010). Examples of regional chemo include drugs given into these parts of the body

3.4.1 Intra-arterial chemo

An intra-arterial infusion allows a chemo drug to be given right to the tumor through a small, flexible tube (catheter) that's put in the main artery that supplies blood to the tumor. This method is used to treat disease in an organ such as the liver (this is called isolated hepatic perfusion), or to treat an extremity such as the leg (called isolated limb perfusion).

The goal is to concentrate the drug in the area of the tumor and decrease systemic side effects. The catheter is attached to an implanted or portable pump. Although this approach sounds like a good idea, most studies have not found it to be as useful as expected. This approach is being studied for many types of cancer in clinical trials. Except for clinical trials, it's rarely available outside of specialized cancer centers (Missailidis, 2008).

3.4.2 Intracavitary chemo

Intracavitary is a broad term used to describe chemo given right into a body cavity. The chemo drug is given through a catheter that's put into one of the areas as described below.

3.4.2.1 Intravesical chemotherapy is often used for early stage bladder cancer. The chemo is usually given weekly for 4 to 12 weeks. For each treatment, a soft, flexible tube (called a urinary catheter) is put into the bladder to give the

drug. The drug is kept in the bladder for about 2 hours and then drained. The catheter is taken out after each treatment (Van Calsteren *et al.*, 2010).

3.4.2.2 Intrapleural chemotherapy is not used very often but may be helpful for some people with mesothelioma (cancer that develops in the lining of the lung), and those with lung or breast cancers that have spread to the pleura (the membrane around the lungs and lining the chest cavity). Intrapleural chemotherapy is given through soft, flexible tubes called chest catheters. These catheters can be used to give drugs and to drain fluid that can build up in the pleural space when cancer has spread to that area (NCI, 2015).

3.4.2.3 Intraperitoneal chemotherapy has become one of the standard treatments for certain stages of ovarian cancer. It may also be used to treat some colon cancers that come back after treatment, as well as mesotheliomas and cancers of the appendix, liver, or stomach that have spread throughout the belly (abdomen). Intraperitoneal chemo is given through a Tenckhoff catheter (a soft tube specially designed for removing or adding large amounts of fluid from or into the abdominal cavity) or through an implanted port (a small drum-like device) attached to a catheter. Chemo injected into the port travels through the catheter into the abdominal cavity where it's absorbed into the affected area before entering the bloodstream. This approach can work very well, but it can also have more severe side effects than chemo put into the bloodstream (IV chemo). The higher doses that are used, along with more gradual absorption of the drug into the body, may be part of why the side effects may be worse (NCI, 2015).

3.4.2.4 Intrathecal chemotherapy is given right into the fluid surrounding and cushioning the brain and spinal cord (called the cerebrospinal fluid or CSF) to reach cancer cells in the fluid and the central nervous system (brain and spinal cord). Most chemo drugs that are put into the bloodstream are unable to cross the barrier between the bloodstream and the central nervous system, called the *blood-brain barrier*. Intrathecal chemotherapy gets the drug directly to the central nervous system. Intrathecal chemotherapy is given in 1 of 2 ways:

The chemo can be given by a *lumbar puncture* (spinal tap) done daily or weekly. This is when a thin needle is placed between the bones of the lower spine and into the space through which the CSF flows around the spinal cord (NCI, 2015).

A special device called an *Ommaya reservoir* can be used. It's a small, drum-like port that's placed under the skin of the skull. An attached catheter goes through the skull into a ventricle (a space inside the brain filled with CSF). A special needle is put through the skin and into the port to give the chemo (Van Calsteren *et al.*, 2010).

Chemo is given this way when it's needed to treat cancer cells that have entered the central nervous system. This is seen most commonly in leukemias, but also may happen with some lymphomas and advanced solid tumors like breast and lung cancers. Intrathecal chemotherapy does not help when tumors have already started growing in the brain or spinal cord (Cardonick *et al.*, 2010).

3.4.3 Intralesional chemo

Intralesional chemo refers to the drug being injected directly into the cancerous tumor. It may be used for tumors that are in or under the skin, and rarely for tumors that are on an organ inside the body. It's only possible when the tumor can be safely reached by a needle, and is most often used when surgery isn't an option.

3.4.4 Topical chemo

In this use, chemo is put on the skin in the form of a cream or lotion. Most often, it's used to treat basal cell or squamous cell skin cancers. It's also used to treat pre-cancerous growths on the skin. The patient or a family member usually puts on the chemo cream. It's important to understand the schedule, know exactly how to use these potent drugs, and know what kinds of precautions to use (NCI, 2015).

3.5 Cancer and Pregnancy

The diagnosis of cancer during pregnancy poses difficult dilemmas for the pregnant patient, her family, and the medical team. Cancer in pregnancy is rare, complicating up to 0.02% to 0.1% of pregnancies annually (NCI, 2015). The cancers most commonly diagnosed in pregnancy are breast cancer, cervical cancer, thyroid cancer, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The main challenge in managing cancer during pregnancy is treating the patient with the optimal anti-cancer regimen without harming the developing fetus. Critically, for the best chance at survival for the mother, chemotherapy cannot always be postponed until the end of the pregnancy, and no current regimen has been confirmed (by studies with sufficient statistical power) safe for use during gestation. Because of their relatively low molecular weight, most cytotoxic agents

cross the placenta and reach the fetus (Cardonick and Iacobucci, 2004).

The pharmacology of various anti-cancer drugs may be altered by the normal physiological changes that occur during pregnancy, such as increased plasma volume, enhanced renal and hepatic elimination, and decreased albumin concentration. Dosing similar to that of nonpregnant women of the same weight may lead to undertreatment of pregnant women with cancer. However, it is still not clear whether pregnant women should be treated with different doses of chemotherapy, and no studies have addressed the effectiveness of treatment regimens in pregnancy (Van Calsteren *et al.*, 2010).

Chemotherapy during the first trimester may increase the risk of spontaneous abortions, fetal death, and major congenital malformations. The teratogenic effects depend on the dosage, time of administration, and cumulative exposure to the chemotherapeutic agent. Fetal malformations reflect the gestational age at exposure, and the most vulnerable period is during weeks 2 to 8, when organogenesis occurs. The eyes, ears, teeth-palate, genitalia, hematopoietic system, and CNS remain vulnerable to chemotherapy beyond organogenesis (Cardonick and Iacobucci, 2004)

The administration of chemotherapy during the second and third trimesters has not been associated with major congenital malformations but may increase the risk for intrauterine growth restriction (IUGR), low birth weight, and stillbirth. A review of 376 cases of fetuses exposed to chemotherapy in utero, most after organogenesis, demonstrated 5% fetal death rate and 1% neonatal death rate. Other complications included preterm delivery (5%), IUGR (7%), and transient myelosuppression (4%) (Van Calsteren *et al.*, 2010).

4.0 Problems of Chemotherapy: Side-Effects

Chemotherapeutic drugs are designed on the basis of their killing ability of cells that grow faster, the main characteristic feature of cancer cells. However, chemotherapeutic drugs also kill normal cells that divide; e.g. bone marrow cells, gut cells, etc. For this reason, the range and effectiveness of chemotherapy becomes restricted.

The growing capability of cancer cells to resist the chemotherapeutic drug is one of the main drawbacks of conventional chemotherapy. In drug-resistant cancer cells, expression of surface small pump like p- glycoprotein and

intercellular antioxidant efflux prevent the chemotherapeutic agents from entering into the cells (Johnstone *et al.*, 2000). Many critical molecular types of machinery are involved in chemotherapeutic drugs and tumor cell interactions. Genotoxic drugs used in chemotherapy may induce alteration of gene expressions causing aggravation of DNA damage, resulting in cell death. But sometimes, structural changes in protein induced by genetic mutation prevent binding of drug with target protein, which in turn can resist the chemotherapeutic effect (Luqmani, 2005). Acquired capabilities of cancer cells to produce gene amplification and alteration of gene expressions by mutation on coding genes for apoptosis-inducing proteins play an important role in generating resistance against chemotherapeutic drugs. Defect in apoptotic pathway by genetic alteration of normal cells that involve in tumor genesis can also resist the chemotherapeutic drugs which kill the cancer cells by apoptosis. Thus, mutation in genes involving development of cancer cell can prevent apoptosis and also play important role in drug resistance.

Over-dosage in chemotherapy can produce much harmful effects in the patients. Therefore, much care has to be taken to determine the effective dosage. Several factors like body surface area (BSA) formula, mathematical calculation on the basis of the patients' weight and height had been approved in early 1950s for calculating individual chemotherapeutic dosage. The effectiveness of chemotherapeutic drug varies with concentration of the drug in the patient's bloodstream which is subjected by multiple factors, including metabolism, cancer state, drug-target interactions, and patients' physiological and genetically state (Kaestner and Sewell, 2007). Now-a-days researchers are trying to establish a formula by which individual patient can achieve optimal systemic drug exposure which can maximize the drug efficacy and minimize cytotoxic effects.

Determination of cancer type and cancer stage is a very important phenomenon for success of chemotherapy. In certain cancer type where drug delivers through circulatory system, chemotherapy fails because of improper blood vessel in tumor cells (Minchinton and Tannock, 2006). Patients with late stage cancer may not fully cure and face greater risk of early death because they may not tolerate chemotherapeutic side-effects. Thus, side-effects are one of the major and leading problems of chemotherapy and often limit its use (Kovacic, 2007).

Side-effects occur mostly when the chemotherapy damages the healthy cells that maintain the body's function and

appearance. Different side-effects arise depending on the nature of the drug. As for example, the Alkalyting agents and anti-metabolites directly damage DNA to prevent the cancer cells from reproducing; thus they can cause long-term damage to the bone marrow, which can eventually lead to acute leukemia. Similarly, Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in DNA replication. These drugs work in all phases of the cell cycle. A major consideration when giving these drugs is that they can permanently damage the heart if given in high doses for a long time. For this reason, lifetime dose limits are often put on place on these drugs. In the same way, some plant alkaloids and other compounds derived from natural products are often known to be mitotic inhibitors. They can stop mitosis or inhibit enzymes from making proteins needed for normal cell reproduction. These drugs are known for their potential to cause peripheral nerve damage, which can be a dose-limiting side effect. Likewise, topoisomerase inhibitors that cause DNA damage to cancer cells produce harmful side effects like symptoms of allergic reaction including fast heartbeat, itching or hives, swelling in the face or hands, swelling or tingling in the mouth or throat, chest tightness, and wheezing. Cytotoxic medicines are generally very powerful but often cause many unwanted side-effects. Since cytotoxic medicines mainly work by killing cells in their divisional stages, irrespective of whether they are normal or cancer cells, protection to normal cells is of prime importance while a patient is undergoing cancer therapy.

Immune-suppression during chemotherapy causes various side-effects also. Bone marrow suppression decreases the production of blood cells leading to anemia and thrombocytopenia. Another serious problem of immune compromised patients, caecitis-infection of the gut-includes diarrhea, nausea, vomiting, fever and distended abdomen etc (Keidan *et al.*, 2009). Prolonged autoinfection manifests as systemic disease conditions like sepsis (Boggio *et al.*, 2000).

In early stage of chemotherapy mucositis, a painful inflammation and ulceration of mouth begins by damaging of normal cells lining the mouth (Sonis, 2004). Chemotherapeutic drugs target rapidly dividing cells like gastrointestinal cells resulting in nausea, vomiting, anorexia, diarrhea, abdominal cramps, and constipation etc. Gastrointestinal damage causes gastro paresis, decreased gut motility or delayed emptying of the stomach and small intestines leading to malnutrition and dehydration. Fatigue, one of the most frequent and long lasting side-effects of chemotherapy, is a very problematic issue and it imposes limitations on normal daily activities of about 70% patients

(Berger *et al.*, 2010). Every chemotherapeutic agent targets and damages fast dividing hair follicles resulting in vigorous hair loss leading to certain type of alopecia like alopecia totalis, telogen effluvium, or less often alopecia areata (Chadha and Shenoi, 2003). Some Alkylating chemotherapeutic agent constructs secondary neoplasia like acute myeloid leukemia which increases in frequency (Rüther *et al.*, 2000). It has been observed that many chemotherapeutic patients lack their interest in sex (Stead, 2004).

Infertility arises in both female and male patients by some gonadotoxic chemotherapeutic agents (Brydøy *et al.*, 2001). During pregnancy chemotherapy makes congenital abnormalities including growth retardation, delayed mental development or other congenital disorders (Arnon *et al.*, 2001). Patients may suffer from peripheral neuropathy, a damage or disease affecting nerves which produces symptoms like numbness, abnormalities in brain and spinal cord, tremor, and gait abnormality (del Pino, 2010). Many chemotherapeutic agents cause non-specific neuro-cognitive problems in which patients suffer from inability to concentrate. Some chemotherapeutic drugs rapidly break down and cancer cells in turn release chemicals from inside the cells producing high levels of uric acid, potassium, phosphate and calcium in the blood. One of the decisive problems during chemotherapy is damages inflicted on normal organs. Organ-specific toxicities arise by specific chemotherapeutic agents. Most chemotherapeutic drugs generate many free radicals producing Cytotoxicity, which in turn causes DNA damage in the cells leading finally to apoptosis. Cardio toxicity, hepatotoxicity, nephrotoxicity and ototoxicity, are some of the leading problems generating from the non-specific cytotoxic nature of these chemotherapeutic drugs (Shaikh, 2012). Chemotherapeutic drugs may also produce many other side-effects like dry skin and mouth, water retention, dental problem, digestive problem, emotional difficulties etc.

4.2 The Future of Primary Chemotherapy (pCR)

The increase in pCR rate seen in the docetaxel-containing arm of NSABP B-27 is an encouraging result. However, we do not know to what degree the improved pCR rate brought about by the addition of docetaxel will translate into an improvement in overall survival. But we do know that this systemic chemotherapy still fails to induce a pCR in three-fourths of treated patients. This suggests that we have a long way to go, therapeutically. What are reasonable future directions for primary therapy trials? Some directions will necessarily involve chemotherapeutic approaches.

The recent presentation of C9741, an intergroup trial testing the dose-density hypothesis, suggests that the use of granulocyte-colony-stimulating factor to narrow the interval between treatments may result in improved relapse-free and overall survival in the adjuvant setting. This approach certainly might be used in a primary chemotherapy setting, shortening the time before definitive surgery and perhaps increasing operability. Pilot dose-dense trials have been performed in the preoperative setting. Another approach would be to utilize docetaxel as a platform on to which other chemotherapeutic agents might be added. The obvious agent to consider in this context is capecitabine. In the setting of metastatic disease, the addition of capecitabine to docetaxel has been shown to improve overall survival; it is reasonable to expect that its addition in the adjuvant setting might improve the cure rate of patients with early disease. There is certain poignancy to this approach. In the United States during the 1990s, fluorouracil was widely dropped from adjuvant regimens in cooperative group trials, based on convenience factors rather than any data suggesting inactivity in the adjuvant setting. Now we may see the return of the fluoropyrimidines in another guise.

The primary chemotherapy setting also offers nonchemotherapeutic possibilities. Preoperative trastuzumab-based regimens (in combination with chemotherapy) have already been piloted in the primary chemotherapy setting in patients with HER-2 positive disease, and are certainly worthy of consideration for confirmatory randomized trials. And while the vast majority of the preoperative therapy literature has examined the use of systemic chemotherapy, more recent trials have suggested a place for preoperative hormonal therapy for estrogen receptor-positive breast cancer (Miller *et al.*, 2009). While we have no direct comparisons of preoperative hormonal therapy to preoperative chemotherapy, data from the adjuvant setting certainly suggests that this would be a reasonable approach for some patients (Burstein *et al.*, 2001).

Finally, the preoperative therapy setting offers us some useful possibilities with regard to therapeutic targeting and treatment individualization. The preoperative setting represents a potentially useful clinical laboratory for exploring surrogate markers of response. When one can obtain tissue before therapy, treat a patient, and then obtain residual tissue at the time of definitive surgery, the possibility exists for analysis of this tissue to evaluate molecular markers of response and resistance. As in every other aspect of oncology, novel technologies such as cDNA microarrays (“gene chips”) have the potential to

revolutionize our understanding of response and resistance. A cDNA microarray analysis of tumor samples obtained before primary chemotherapy has recently been presented, and suggests that this technology may soon be able to predict who will benefit from such therapy. NSABP B-27 has several important correlative trials that will be reported in coming years. There is no doubt that this important trial will continue to teach us new lessons about the biology and treatment of breast cancer (O'Shaughnessy et al., 2002)

4.3 Conclusion

Cancer, a dreadful disease, is one of the burning issues that need collective efforts to successfully combat and cure. Cancer is an uncontrolled growth of abnormal cells in the body. This uncontrolled growth of cells can be attributed to mutations in the signals that regulate the cell cycle of growth and division. In normal cells, tumor suppressor genes act as braking signals during the cell cycle. DNA repair genes are active throughout the cell cycle. Cancer cells overcome the normal cell signalling process and become immortal. Chemotherapy is one among many options like surgery, radiation therapy, targeted molecular therapy, etc., which is widely used to successfully treat certain types of cancer, but its use is restricted for the adverse side-effects of most of the chemotherapeutic drugs. The toxic by-products of some chemotherapeutic drugs are deposited mainly in the liver producing hepatotoxicity, leading to many side-effects like loss of appetite, nausea, vomiting, diarrhea, abdominal cramps and constipation, anemia, fatigue, hyperthermia, loss of hair, etc.

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