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Chemotherapy

K. Malleswari associate professor, D.Rama Brahma Reddy[1]principal , V. Jhansi[1] student, M.E. Himabindu[1] student , M. Praveen Chand[1] stuudent.
Nalanda Institute of Pharmaceutical Sciences, Kantepudi (v), Sattenapalli (m), Guntur(dt).

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ABSTRACT
[1] Chemotherapeutics are chemical entities used to treat or cure cancers. These agents target critical processes for cell division in rapidly growing cancer cells. Most cancer drugs are derived from natural sources such as plants and bacteria, other are derived from synthetic or semisynthetic processes. Cancers can arise in virtually all tissues of the body, but the frequency of incidences varies depending on genetic influence, diet, lifestyle and environmental exposures. The most common cancers worldwide are lung, breast and prostate cancers which have had increased survival due to improvements in diagnoses and treatment options. Naturally derived agents have been the mainstay of cancer therapy and the potential to uncover endemic compounds that may exhibit potent anticancer properties has driven research for novel anticancer agents. A number of active agents or extracts from plants extracts have been studied for their anti-cancer properties, some of these will be discussed herein.

KEY WORDS: Chemotherapy,Alkylating agents, Apatosis, Cytotoxixity.

I. INTRODUCTION

[2,3] Chemotherapy (often abbreviated to chemo and sometimes CTX or CTx) is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. Chemotherapy may be given with a curative intent (which almost always involves combinations of drugs), or it may aim to prolong life or to reduce symptoms (palliative chemotherapy). Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called medical oncology.

[4] The term chemotherapy has come to connote non-specific usage of intracellular poisons to inhibit mitosis (cell division) or induce DNA damage, which is why inhibition of DNA repair can augment chemotherapy.[4] The connotation of the word chemotherapy excludes more selective agents that block extracellular signals (signal transduction). The development of therapies with specific molecular or genetic targets, which inhibit growth-promoting signals from classic endocrine hormones (primarily estrogens for breast cancer and androgens for prostate cancer) are now called hormonal therapies. By contrast, other inhibitions of growth-signals like those associated with receptor tyrosine kinases are referred to as targeted therapy.

Importantly, the use of drugs (whether chemotherapy, hormonal therapy or targeted therapy) constitutes systemic therapy for cancer in that they are introduced into the blood stream and are therefore in principle able to address cancer at any anatomic location in the body. 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, surgery or hyperthermia therapy.

Traditional chemotherapeutic agents are cytotoxic by means of interfering with cell division (mitosis) but cancer cells vary widely in their susceptibility to these agents. To a large extent, chemotherapy can be thought of as a way to damage or stress cells, which may then lead to cell death if apoptosis is initiated. 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. This results in the most common side-effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss). Because of the effect on immune cells (especially lymphocytes), chemotherapy drugs often find use in a host of diseases that result from harmful overactivity of the immune system against self (so-called autoimmunity). These include

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rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, vasculitis and many others.

II. TYPES OF CHEMOTHERAPY

Alkylating agent:

[5] Alkylating agents are a class of antineoplastic or anticancer drugs which act by inhibiting the transcription of DNA into RNA and thereby stopping the protein synthesis. Alkylating agents substitute alkyl groups for hydrogen atoms on DNA, resulting in the formation of cross links within the DNA chain and thereby resulting in cytotoxic, mutagenic, and carcinogenic effects. This action occurs in all cells, but alkylating agents have their primary effect on rapidly dividing cells which do not have time for DNA repair. Cancer cells are among the most affected because they are among the most rapidly dividing cells. However, hematopoetic, reproductive, and endothelial cells also divide rapidly which accounts for the common side effects of the alkylating agents: anemia, pancytopenia, amenorrhea, impaired spermatogenesis, intestinal mucosal damage, alopecia, and increased risk of malignancy. The end result of the alkylation process results in the misreading of the DNA code and the inhibition of DNA, RNA, and protein synthesis and the triggering of programmed cell death (apoptosis) in rapidly proliferating tumor cells. The alkylating agents are generally separated into six classes:

(1) The nitrogen mustards [mechlorethamine, cyclophosphamide, ifosfamide, melphalan andchlorambucil]
(2) Ethylenamine and methylenamine derivatives [altretamine, thiotepa]
(3) Alkyl sulfonates [busulfan]
(4) Nitrosoureas [carmustine, lomustine]
(5) Triazenes [dacarbazine, procarbazine, temozolomide]
(6) The platinum-containing antineoplastic agents [cisplatin, carboplatin, oxaliplatin], which
are referred to as platinum coordination complexes. These antineoplastic drugs are
usually classified as alkylating agents, although they do not alkylate DNA, but cause
covalent DNA adducts by a different means.

The alkylating agents all have major toxicities, but the predominant toxicities are to the bone marrow and gastrointestinal tract. Most agents have been shown to cause transient serum aminotransferase elevations in a proportion of patients. Several alkylating agents have also been implicated in causing rare cases of idiosyncratic, clinically apparent acute liver injury which is typically cholestatic and best described for temozolomide, cyclophosphamide and chlorambucil, perhaps because these agents are most frequently used and can be given orally over a prolonged period. Importantly, the alkylating agents can also cause sinusoidal obstruction syndrome (veno-occlusive disease) when given in high doses, and nodular regenerative hyperplasia when given for prolonged periods. These latter two hepatic effects are typically dose related and may be due to direct toxicity.

ANTIMETABOLITES

[6] An antimetabolite is a chemical that inhibits the use of a metabolite, which is another chemical that is part of normal metabolism.[7]Such substances are often similar in structure to the metabolite that they interfere with, such as the antifolates that interfere with the use of folic acid; thus, competitive inhibition can occur, and the presence of antimetabolites can have toxic effects on cells, such as halting cell growth and cell division, so these compounds are used as chemotherapy for cancer.

[8] Antimetabolites can be used in cancer treatment, [9]as they interfere with DNA production and therefore cell division and tumor growth. Because cancer cells spend more time dividing than other cells, inhibiting cell division harms tumor cells more than other cells. Antimetabolite drugs are commonly used to treat leukemia, cancers of the breast, ovary, and the gastrointestinal tract, as well as other types of cancers. [10] In the Anatomical Therapeutic Chemical Classification System antimetabolite cancer drugs are classified under L01B.

TROPOISOMERASE

Topoisomerase I and II are normal host enzymes that are found in the nucleus of mammalian cells and are required for normal DNA replication and cellular division. The enzymes create and then repair single stranded nicks in cellular DNA. The nicks allow for the untangling and relaxation of supercoiled double stranded DNA, so that replication can proceed. Once the DNA torsional strain has been relieved, the topoisomerase reseals the relaxed double helix. Topoisomerase activity is particularly increased in rapidly dividing and in cancer cells. It represents an appropriate, but nonselective target for anticancer therapy.

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Topoisomerase inhibitors in current use in the United States include irinotecan and topotecan, inhibitors of topoisomerase I, and etoposide and teniposide, inhibitors of topoisomerase II. All four agents are semisynthetic analogues of natural toxins that were initially identified in plants. All four are given parenterally, typically in combination with other antineoplastic agents in cycles of every 3 to 4 weeks. The major dose limiting toxicities of topoisomerase inhibitors are largely hematologic (neutropenia, anemia, thrombocytopenia) and gastrointestinal (diarrhea, nausea). While serum enzyme elevations are not uncommon with chemotherapeutic regimens that include topoisomerase inhibitors, clinically apparent liver injury is uncommon.

Irinotecan and topotecan are derived from camptothecins, cytotoxic compounds which were initially isolated from the bark of the Chinese tree, Camptotheca acuminata. These agents bind to the DNA-topoisomerase I complex and prevent resealing of the DNA. Accumulation of DNA breaks results in inhibition of DNA replication and cell death. Once the mechanism of toxicity of camptothecins was elucidated, more soluble and less toxic analogues were produced. Irinotecan and topotecan are two camptothecin derivatives currently in use in the United States and are used as adjunctive therapies for advanced colorectal, ovarian and small cell lung cancer.

Etoposide and teniposide are semisynthetic derivatives of extracts of the American mandrake plant or Mayapple (Podophyllum peltatum) and bind to topoisomerase II and DNA, preventing the resealing of DNA breaks and thus causing inhibition of DNA replication and cell death. These agents are in current use as adjunctive therapies for advanced testicular and small cell lung cancer (etoposide, originally called VP-16), and for acute leukemia in children and malignant brain tumors (teniposide, VP-26).

CYTOTOXIC ANTIBIOTICS

5] Several naturally occurring compounds with antibiotic activity also have potent antitumor activity and were developed as anticancer agents. These cytotoxic antibiotics are often grouped together, even though they have diverse mechanisms of action, widely different indications, a range of efficacies and distinctive toxicities. The cytotoxic antibiotics in current use in the United States include (with trade name and year of approval): bleomycin (Blenoxane, 1973), dactinomycin (Cosmegen, 1964), daunorubicin (Cerubidine, 1979), doxorubicin (Adriamycin, 1974), epirubicin (Ellence, 1999), idarubicin (Idamycin, 1990), plicamycin (previously known as mithramycin, still experimental), mitomycin (Mutamycin, 2002) and mitoxantrone (Novantrone, 1987). A discussion of the mechanism of action, current use and hepatotoxicity, along with structural information and references of these drugs, are provided for each agent individually. The anthracycline antibiotics include daunorubicin, doxorubicin, epirubicin and idarubicin (which are discussed together) and mitoxantrone, which is an anthracycline analog and discussed separately.

Most of the cytotoxic antibiotics used in cancer chemotherapy have been implicated in cases of drug induced liver injury, generally associated with the use of high doses and with either direct hepatocellular injury or sinusoidal obstruction syndrome (from direct sinusoid cell injury). Because they are typically used in combination with other antineoplastic agents, it is often difficult to identify which is responsible for the liver injury.

FUNCTIONS OF CHEMOTHERAPY

The goal of chemotherapy is to inhibit cell proliferation and tumor multiplication, thus avoiding invasion and metastasis. But this results in toxic effects of chemotherapy due to effect or normal cells as well. Inhibition of tumor growth can take place at several levels within the cell and its environment.

Traditional chemotherapy agents primarily affect either macromolecular synthesis and function of neoplastic cells by interfering DNA, RNA, or proteins synthesis or affecting the appropriate functioning of the preformed molecule. When interference in macromolecular synthesis or function is sufficient, it leads to cell death either due to the chemotherapeutic agent's direct effect or by triggering apoptosis. With traditional agents, cell death may be delayed as a proportion of the cells die as a result of a given treatment. So, the treatment may require repeating to achieve a response. The toxicity of cytotoxic drugs is greatest during the S phase, as it is the DNA synthetic phase of the cell cycle. Vinca alkaloids and Taxanes act in the M phase and block mitotic spindle formation.

Combination chemotherapy is a common choice to produce effective responses as well. They appear to prevent the development of resistant clones by promoting cytotoxicity in resting and dividing cells. [12]Cellular mechanisms that promote or suppress cell proliferation and cell

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differentiation are intricate, involving several genes, receptors, and signal transduction. Investigations in cancer cell biology have led to significant insight into mechanisms of apoptosis, angiogenesis, metastasis, cell signal transduction, differentiation, and growth factor modulation.[13] Researchers are designing molecular targeted therapy on these pathways, selectively inhibiting growth, e.g., targeting cell signaling or angiogenesis, blocking protein degradation, etc.

ENHANCING TEAM OUT COME IF CHEMOTHERAPY

Since the administration of most chemotherapy agents occurs at infusion centers, nursing and allied health professionals play a significant role in taking care of patients on such drugs. They are usually the first point of contact for the patients. All the health professionals need to understand the type of drug in use and its associated side effects for the patient. Close monitoring and early recognition of side effects can help prevent significant morbidity and mortality. For example, patients with a history of anemia, thrombocytopenia should avoid the use of NSAIDs. Intra-muscular injections and rectal suppositories should be avoided in such patients.

Thorough buccal cavity assessments and avoidance of commercial mouthwashes in patients with mucositis can help decrease patient discomfort. Many chemotherapeutic agents have specific known side effects that are minimizable prophylactically. For instance, following folate inhibitors such as methotrexate with folate analogs such as leucovorin help reduce bone marrow suppression severity.[14] This concept applies to general chemotherapy side effects. For example, oral mucositis is a common chemotherapy side effect, which can be minimized by administering Palifermin, a keratinocyte growth factor that helps reduce mucosal endothelial cell damage.

[15] Patients undergoing chemotherapy usually need strong emotional support, and they are going through anxiety, depression, and anticipatory grief from the expected side effects of the drugs. Multidisciplinary and interprofessional interventions at various stages of their treatment regimen can promote mental health.

Patients undergoing chemotherapy require a team-based approach for monitoring any adverse events. The role of nursing and allied health professionals includes providing supportive care, preventing infections, monitoring for adequate nutrition and hydration, and monitoring patient safety: handwashing and infection precautions like isolation protocols require strict adherence. Since patients require frequent laboratory monitoring, it is important to understand and equip themselves with the infusion protocols parameters and alert the treating clinicians if they notice any abnormal parameters. Early nursing interventions can revert worse outcomes in patients.

It is crucial to recognize the common causes and the magnitude of the impact of errors involving cancer chemotherapy. Improving communication, standardizing protocols, utilizing read back and verifying dosages, working with pharmacists are all interventions that can help reduce medical errors in a multidisciplinary setup.

DELIVERY

Most chemotherapy is delivered intravenously, although a number of agents can be administered orally (e.g., melphalan, busulfan, capecitabine). According to a recent (2016) systematic review, oral therapies present additional challenges for patients and care teams to maintain and support adherence to treatment plans.

[16] There are many intravenous methods of drug delivery, known as vascular access devices. These include the winged infusion device, peripheral venous catheter, midline catheter, peripherally inserted central catheter (PICC), central venous catheter and implantable port. The devices have different applications regarding duration of chemotherapy treatment, method of delivery and types of chemotherapeutic agent.

[17] Depending on the person, the cancer, the stage of cancer, the type of chemotherapy, and the dosage, intravenous chemotherapy may be given on either an inpatient or an outpatient basis. For continuous, frequent or prolonged intravenous chemotherapy administration, various systems may be surgically inserted into the vasculature to maintain access.[18] Commonly used systems are the Hickman line, the Port-a-Cath, and the PICC line. These have a lower infection risk, are much less prone to phlebitis or extravasation, and eliminate the need for repeated insertion of peripheral cannulae.[citation needed]Isolated limb perfusion (often used in melanoma),or isolated infusion of chemotherapy into the liver or [19] the lung have been used to treat some tumors. The main purpose of these approaches is to deliver a very high dose of chemotherapy to tumor sites without causing overwhelming systemic damage.[20] These approaches can help control solitary or limited metastases, but they are by

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definition not systemic, and, therefore, do not treat distributed metastases or micrometastases.

Topical chemotherapies, such as 5-fluorouracil, are used to treat some cases of non-melanoma skin cancer.[21] If the cancer has central nervous system involvement, or with meningeal disease, intrathecal chemotherapy may be administered.

STRATAGIES FOR CANCER THERAPY

Treatment strategies

Now a day, many strategies have been adapted to administered chemotherapeutic drugs. Chemotherapeutic drugs may be used with a curative purpose or it may be aimed to prong life.

a) Combined chemotherapy is the one kinds of treatment strategy where more one type of therapy can be adopted at a time to treat cancer, such as radiation therapy, surgery and/ or hypertheremia. However, induction chemotherapy is used for the first time treatment of cancer with anticancer drug.

b) [22] Consolidation chemotherapy is generally given after remission in order to prolong the overall disease-free time and improve overall survival .

c) [23] Intensification chemotherapy is identical to consolidation therapy but a different drug than induction therapy is used.

d) In combined chemotherapy, different dugs are having different kinds of mechanism of action and their side effects. The most advantage of combined chemotherapy is to minimize the chances of development of resistance to any one the drug. Also the drugs can be administered at lower dose with minimal side effects and toxicity

e) .Neoadjuvant chemotherapy is used prior to a local treatment such as surgery, and is meant to shrink the primary tumor .[24] It is also used to a condition where a high risk of micrometastatic disease observes.

f) This therapy (Neoadjuvant chemotherapy) can be used where there is a little a chance or evidence of cancer present and also there is risk of recurrence. It is also beneficial to kill the cancerous cells that have proliferated to other part of the body.

g)[25] Maintenance chemotherapy is one where a repeated low-dose is used to treat for prolong remission.

h) Salvage chemotherapy is useful to simply decrease tumor load and increase life expectancy.

CHEMOTHERAPY TREATMENT STRATAGY USING HYPERTHERMIA

[26] Chemotherapy Treatment Strategy Using Hyperthermia. In traditional chemotherapy, there is a major drawback of the lack of selectivity, leads to various side- effects, such as alopecia (hair loss), blood disorder, fatigue, nausea and vomiting. So, there is a need to explore other treatment strategy where application of heat (Hyperthermia) is accompanied together with other chemotherapies in order to improve treatment selectivity, reduce recurrence and improve the quality of life of patients. It has been observed that surgical removal of solid tumor generally fails in total remission and therefore a combination therapy must be accompanied by anticancer drugs with radiotherapy or hyperthermia or targeted therapy etc. One new approach, which may achieve these goals, is to the use of hyperthermia technique along with other mode of chemotherapy. In the hyperthermia process a fractionated or continued dose is delivered at the target site that can increase the sensitivity of tumor to chemotherapy, radiotherapy, immunotherapy and immune-based strategies .[27] However, this kind of new approach where the successful application of hyperthermia (where heat is applied only at the tumor site) together with other chemotherapeutics has led to renewed interest in the field of modern chemotherapy. The major objective of hyperthermia is to make tumor cells more sensitive towards the therapeutic agents and facilitate drug release from thermo responsive nano carriers (usually below 43°C, referred to as mild hyperthermia) or, at higher temperatures, directly inducing necrosis (above 43°C, referred to as thermal ablation) .[28] Furthermore, cancer cells are more sensitive towards thermal environment than normal tissues between 42-45°C with a directly proportional relationship between tissue death and the temperature or exposure time. The mechanism of action of hyperthermia is accompanied by various way where the cells or tissues leading to an enhanced antitumor response. In general, hyperthermia inhibits cell functions, increase permeability and modify fluidity, disrupt stability and shape of cell membrane, impending trans membrane transport proteins and cell surface receptors.[29] Transfer of heat, away from tumor cells is directly proportional to the rate and volume of tumor perfusion,[30] and assuming that the process is more efficient in malignant tissue compared to healthy tissue ,[31,32] enforcing selectivity of hyperthermia. However, the significant effects of hyperthermia are supposed to be on protein as they undergo denaturation and precipitation at temperature > 40°C. Although the effects on lipids are mostly reversible, but the effect on DNA where, double strand break and effect produced is substantial and non-reversible.

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This basically inhibits many cellular processes such as cell cycle arrest, replication and synthesis of DNA and alters protein synthesis, leading to inhibition of cell proliferation and death .[33] There are a number of other strategies that oncologists can use to regulate chemotherapy.

Targeted Therapy

Targeted therapies specifically target a protein or other molecules and have the benefit of reducing chemo side effects.

Hormone Therapy

Activated hormone receptors change the way that a gene is expressed. That means these receptors change the way that the gene behaves, often stimulating cell growth. Hormone-sensitive cancer cells have extra hormone receptors.

Dose-Dense Chemotherapy

[34] Dose-dense chemotherapy treatment refers to treatments that are timed to occur close together. If conventionally scheduled chemotherapy treatments are once every three weeks, the dosedense schedule might be once every two weeks. This strategy is used for more advanced cancers that are starting to spread .

Combined Modality Chemotherapy

[35] Combined modality simply means using more than one type of therapy to treat the cancer. If the cancer is aggressive and at stage 3, the treatment includes surgery, chemotherapy, radiation, and then a year of Herceptin.

Palliative Chemotherapy

Palliative therapy is treatment that is given to improve quality of life. The purpose of palliative care is to ease pain and reduce the tumor size to improve organ function, rather than to eliminate the cancer altogether. While it is often thought of as a long-term end-of-life strategy to provide comfort, palliative care can also be a temporary addition to the treatment strategy at any point in the process to address a quality-of-life issue.

Photodynamic therapy (PDT)

[36] It is a ternary treatment for cancer involving a photo sensitizer, tissue oxygen, and light (often using lasers. Photodynamic therapy can be used as treatment for basal cell carcinoma (BCC) or lung cancer; PDT can also be useful in removing traces of malignant tissue after surgical removal of large tumors .

Cancer immunotherapy

[37]Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesical BCG immunotherapy for superficial bladder cancer, and use of interferon and other cytokines to induce an immune response in renal cell carcinoma and melanoma patients.

III. CONCLUSION

There are so many types of treatments that this is not an exhaustive listing of all the chemotherapy strategies available to oncologists. Research continues to develop new treatments and more strategies for using existing treatments. Further improvements of this treatment strategy will undoubtedly involve the development of more efficient anticancer drugs. The strategy reported herein, i.e. based on modifying clinically approved drugs certainly holds promise. However, further validation of all this approaches are still needed as authentic strategy also display relevant therapeutic properties under normal conditions and to determine whether it has advantages the well-established use of chemotherapeutics, some of which are progressing through clinical trials.

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