WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 14, 369-377. Review Article ISSN 2277– 7105

AN OVERVIEW ON ANTICANCER DRUGS

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Article Received on
10 October 2021,

Revised on 30 October 2021,
Accepted on 20 Nov. 2021

DOI: 10.20959/wjpr202114-22265

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ABSTRACT

Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant or cancerous disease. Cancer is second leading cause for death in the world. Cancer patients who are crippled with this disease and are suffering from harmful side- effects from chemotherapeutic drugs are turning down to natural remedies hoping for better cure. There are several major classes of anticancer drugs; these include alkylating agents, antimetabolites, natural products, and hormones in modern system of medicine. The drugs which acts as gulmahara, shothahara, vishahara, arbudaghna, vidradihara can be taken for Ayurvedic anticancer drugs. There are abundance of anticancer drugs in Ayurveda. Each herb contains multiple active principles that often operate synergistically producing therapeutic benefits and lowering the risks of adverse effects, and avoid the need for supplemental therapy to manage cachexia. The detailed pharmocolgy of certain anticancer drugs has been explained in this article, and an effort is made to raise awareness and encourage implementation of Ayurvedic therapies for combacting cancer and suggest an integrated approach in tumor management and treatment.

KEYWORDS:- Anticancer, DNA, Herbs, RNA.

INTRODUCTION

The term chemotherapy frequently is equated with the use of anticancer drugs, although it more accurately refers to the use of chemical compounds to treat disease generally. One of the first drugs that was used clinically in modern medicine for the treatment of cancer was the

alkylating agent Mechlorethamine,[1] a nitrogen mustard that in the 1940s was found to be effective in treating lymphomas. In 1956 the antimetabolite methotrexate became the first drug to cure a solid tumour, and the following year, 5-fluorouracil was introduced as the first of a new class of tumour-fighting compounds known as pyrimidine analogs. Since then many anticancer drugs have been developed and used with much success. The decision to use a certain anticancer drug depends on many factors, including the type and location of the cancer, its severity, whether surgery or radiation therapy can or should be used, and the side effects associated with the drug. Most anticancer drugs are administered intravenously; however, some can be taken orally, and others can be injected intramuscularly or intrathecally (within the spinal cord). The treatment of cancer is complicated in that the drugs used target human cells, that have undergone genetic changes and are dividing at a fast and uncontrolled rate. However, certain anticancer drugs can differentiate to some degree between normal tissue cells and cancer cells, and the rate at which cancer cells proliferate may in fact play a role in the apparent selectivity of agents. For instance, alkylating agents, which act on cells at all stages of the cell cycle, appear to be most toxic to cells in the synthesis, or S, stage, when DNA is in the process of replicating and unpaired nucleotides (the nitrogen-containing units of DNA and RNA.

Specificity of anticancer drugs: Specificity of anticancer drugs plays an important role in reducing the severity of side effects. Indeed, because cancer cells are similar to normal human cells, anticancer agents are generally toxic to normal cells and can cause numerous side effects, some of which are life-threatening. Such side effects include hair loss, sores in the mouth and on other mucous membranes, cardiac anomalies, bone marrow toxicity, and severe nausea and vomiting. The bone marrow toxicities result in anemia. Permanent infertility can also result. Those adverse effects may require that the drug dosage be reduced or the drug regimen be changed to make the drug tolerable to the patient. In rare instances prolonged use of anticancer drugs can lead to the development of secondary cancers. Egs- secondary cancers associated with anticancer drug therapy are myelodysplastic syndrome and acute leukemias, risk of which is increased particularly with the use of alkylating agents and topoisomerase inhibitors (e.g., etoposide).

Rationality of using multi drug therapy- The side effects associated with anticancer drugs can be reduced through the use of multiple agents, which often enables the administration of lower dosages of each drug. The use of multiple agents may also reduce the incidence of

cellular resistance, a phenomenon that allows tumours to escape treatment and to continue to grow after a period of remission. Multidrug therapy is based on different types of anticancer drugs exert their effects in a certain part of the cell cycle (e.g., cell growth phase, cell division phase, resting phase). Thus, one drug may be used to stop the growth of cancer cells in a certain phase, while another agent may work at a different phase. In addition to using complex regimens that employ several drugs. Cancer chemotherapy is often combined with surgery to reduce the number of cancer cells and with radiation treatment to destroy more cells.

Classification of anti neoplastic drugs- The antineoplastic agents or anticancer drugs represent a large and diverse class of medications. They generally have limited but important uses. The antineoplastic agents are not easily classified. Historically, they are categorized as (1) alkylating agents, (2) antimetabolites, (3) natural products, (4) hormones and antagonists, and (5) miscellaneous. In recent years, however, the miscellaneous group has come to include some of the most important agents. Anticancer agents can also be classified by indication (lymphoma, leukemia, melanoma, solid tumor), mechanism of action (such as alkylating agents, antibiotics, biological response modifiers, antiandrogens, topoisomerase inhibitors or protein kinase inhibitors), chemical structure (folic acid analog, platinum coordination complex, purine or pyrimidine analog, monoclonal antibody) or as cytotoxic or non cytotoxic. A recent trend in classification of the antineoplastic agents with listing of individual agents is given below.

Antineoplastic agents[2]

1) Alkylating Agents - Busulfan, Cyclophosphomide, Mechlorethamine etc.
2) Platinum Coordination Complexes- Carboplatin, Cisplatin, Oxaliplatin
3) Antibiotics - Bleomycin, Doxorubicin, Mitomycin etc
4) Antimetabolites-

A) Antifolates: Methotrexate, Pemetrexed, Pralatrexate
B) Purine Analogues: Azathioprine, Mercaptopurine
C) Pyrimidine Analogues: Azacitidine, Fluorouracil, Gemcitabine,

5) Hormonal Agents

A) Antiandrogen- Abiraterone, Apalutamide, Bicalutamide, Flutamide
B) Antiestrogens -Anastrozole, Exemestane, Fulvestrant, Letrozole
C) Peptide Hormone- Lanreotide, Octreotide, Pasireotide

6) Monoclonal Antibodies - Avelumab, Bevacizumab, Blinatumomab, Brentuximab
7) Taxanes- Cabazitaxel, Docetaxel, Paclitaxel
8) Topoisomerase Inhibitors- Etoposide, Irinotecan, Teniposide, Topotecan
9) Vinca Alkaloids - Vinblastine, Vincristine, Vinorelbine
10) Miscellaneous- Asparaginase (Pegaspargase), Omacetaxine, Thalidomide.

Pharmocology of some important drugs[7]

1) **Cyclophosphamide-** Cyclophosphamide is an alkylating agent used in the treatment of several forms of cancer including leukemias, lymphomas and breast cancer. Cyclophosphamide (sye" kloe fos' fa mide) is a synthetic, nitrogen mustard-like alkylating agent that is widely used in the therapy of cancer and in severe forms of autoimmune disease. It requires activation in the liver to form its active intermediaries which act by modifying and cross linking purine bases in DNA, thus inhibiting DNA, RNA and protein synthesis and causing cell death in rapidly dividing cells. Indications- treatment of breast, head, neck, lung, cervix, testis and ovarian cancer, acute and chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, malignant histiocytosis, multiple myeloma, soft tissue sarcoma, mycosis fungoid, neuroblastoma, and retinoblastoma. Cyclophosphamide is also used in severe autoimmune disorders including minimal change nephrotic syndrome not responsive to conventional therapy. Cyclophosphamide is also occasionally used in the prevention of rejection after organ transplantation. Dose- Cyclophosphamide is available as tablets or capsules of 25 and 50 mg and as a powder or in liquid solution for intravenous use in generic forms and under the trade name Cytoxan. The recommended dosage varies from 1 to 5 mg/kg per day with the patient age, body weight, mode of administration and disease entity. Sideeffects- alopecia, nausea, vomiting, diarrhea, gastrointestinal upset, cystitis, oral ulcers and bone marrow suppression. Rare, but potentially severe adverse events include severe neutropenia, sepsis, cardiotoxicity, hemorrhagic cystitis, embryo-fetal toxicity and secondary malignancies.

2) **Carboplatin-** Carboplatin is an platinum coordination complex and alkylating agent which is used as a chemotherapeutic agent. Carboplatin (kar" boe pla' tin) is a cisplatin analog, it more stable and perhaps less toxic than cisplatin. Carboplatin and cisplatin act as alkylating agents causing cross linking between and within DNA strands, leading to inhibition of DNA, RNA and protein synthesis and the triggering of programmed cell

death, mostly in rapidly dividing cells. Indication- treatment of various cancers, mainly ovarian, head and neck and lung cancers .It is currently indicated for advanced ovarian carcinoma, but is also used in other solid tumors including lung and head and neck cancer. Dose- Carboplatin is available in a powder or aqueous solution for injection in 50, 150 and 450 mg. Side-Effects- nausea and vomiting, diarrhea, bone marrow suppression, as well as neuro-, oto- and nephrotoxicity. They are also mutagenic, teratogenic and carcinogenic. Carboplatin is somewhat better tolerated than cisplatin.

3) **Cisplatin-** Cisplatin is the prototype platinum coordination complex classified as an alkylating agent. Cisplatin (sis pla' tin) was the first chemotherapeutic agent of its subclass to be discovered. It is an inorganic, water soluble complex containing a central platinum atom surrounded by 2 chlorine atoms and ammonia moieties in the cis position in the horizontal plane. Cisplatin forms irreversible covalent links with DNA, causing cross linking of DNA chains as well as breaks in the DNA chain and missense mutations. The DNA injury triggers cell death and inhibits RNA and protein synthesis, particularly in rapidly dividing cells. Indications- testicular, ovarian and bladder cancer. It is also used in combination with other agents in head and neck, breast, lung and colon cancer. Dosage- Cisplatin is administered parenterally and is available in 50 and 100 mg vials. The recommended dose varies by indication, tumor type, patient age and body weight. Sideeffects- Common side effects include nausea, vomiting, bone marrow suppression, electrolyte imbalance, neuropathy, ototoxicity and nephrotoxicity. Cisplatin is mutagenic, teratogenic and carcinogenic and its use has been show to increase the risk of secondary malignancies, particularly leukemia.

4) **Mechlorethamine-** Mechlorethamine is a nitrogen mustard and antineoplastic agent that has been in clinical use for more than 60 years. Mechlorethamine (mek" lor eth' a meen), also known as chlormethine and mustine, is a nitrogen mustard and was the first alkylating agent developed for use as an antineoplastic agent in man. It remains the most reactive in this class of agents. Because it is irritating to local tissues and causes gastrointestinal intolerance, mechlorethamine is administered intravenously. The alkylating agents act by causing modification and cross linking of DNA, thus triggering programmed cell death (apoptosis) and inhibiting DNA, RNA and protein synthesis in rapidly dividing cells. Indications- Hodgkin's disease, lymphosarcoma, chronic leukemias, polycythemia vera, mycosis fungoides and lung cancer. Dose-

Mechlorethamine was previously available in 10 mg vials generically and under the brand name Mustargen. Side effects- nausea, vomiting diarrhea, alopecia, pruritus, bone marrow suppression and rash.

5) **Methotrexate-** Methotrexate is an antineoplastic and immunosuppressive agent. Methotrexate (meth" oh trex' ate) is an antifolate and antimetabolite. Methotrexate acts by inhibition of folate metabolism, blocking dihydrofolic acid reductase, there by inhibiting synthesis of purines and pyrimidines and decreasing DNA and RNA synthesis. Recent results suggest that methotrexate also leads to increase and release of adenosine, which may mediate its immunosuppressive activity. Methotrexate was approved for use in cancer in the United States in 1955, for psoriasis in 1972 and R arthritis in 1988 and is still widely used for these indications. Indications- It is used extensively in the therapy of leukemia, lymphoma and several solid organ tumors. It also has potent immunomodulatory activity against psoriasis, inflammatory bowel disease and the inflammatory arthritidies. Methotrexate is considered a disease modifying antirheumatic drug (DMARD) and used widely in rheumatoid arthritis and other autoimmune diseases. Dose- tablets of 2.5, 5, 7.5, 10 and 15 mg, and in both powdered and liquid-for-injection forms in vials of various strengths for intravenous, intramuscular or intrathecal injection. The typical maintenance dose used to treat psoriasis and rheumatoid arthritis is 7.5 to 25 mg once weekly either orally or by injection. Side effects- stomatitis, oral ulcers, hair loss, fatigue, headache, gastrointestinal upset, nausea, diarrhea and bone marrow suppression. Severe adverse events include bone marrow suppression, severe infections, severe liver and lung disease, lymphomas, severe skin reactions, tumor lysis syndrome, fetal death and congenital abnormalities.

6) **Taxanes-** The taxanes or taxoids are a closely related group of antineoplastic agents that have a unique mechanism of action as inhibitors of mitosis. Three taxanes are in clinical use, paclitaxel, docetaxel and cabazitaxel. Paclitaxel was the first compound in this chemical group to be introduced into clinical use and was initially isolated from the bark of the Western yew tree. Docetaxel is a semisynthetic analogue of paclitaxel and a derivative of extracts from needles of the European Yew (Taxus baccata). The taxanes are similar to the vinca alkaloids in that they bind to tubulin and cause inhibition of mitosis. However, the taxanes bind at a different site than the vinca alkaloids and cause inhibition of mitosis by prevention of degradation of microtubules, rather than prevention of their

assembly. 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. Dosage- The three taxanes are all given intravenously, usually every 1 to 3 weeks. Indications- widely used in the therapy of ovarian, breast, lung, esophageal, prostate, bladder and head and neck cancers. Side- Effects- The hepatic injury varies in severity but can be severe and lead to acute liver failure and death.

7) **Topoisomerase inhibitors-** 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 helps for the untangling and relaxation of supercoiled double stranded DNA, so that replication can proceed. Once the DNA torsional strain has been relieved. Topoisomerase activity is particularly increased in rapidly dividing and in cancer cells hence the inhibitors acts on them. It represents an appropriate, but nonselective target for anticancer therapy. 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. Dose- given parenterally, typically in combination with other antineoplastic agents in cycles of every 3 to 4 weeks. Side Effects- hematologic (neutropenia, anemia, thrombocytopenia) and gastrointestinal (diarrhea, nausea). Indications- advanced colorectal, ovarian and small cell lung cancer, testicular and small cell lung cancer and for acute leukemia in children and malignant brain tumors.

8) **Vinblastine, Vincristine, Vinorelbine-** The vinca alkaloids include vincristine, vinblastine and vinorelbine which are important antineoplastic agents used in many chemotherapeutic regimens for a wide variety of cancers. The vinca alkaloids are antineoplastic agents that act by binding to intracellular tubulin, the basic protein subunit of microtubules which are important in many intracellular processes including mitosis and cell division. The vinca alkaloids inhibit cell division by blocking mitosis; they also inhibit purine and RNA synthesis causing death of rapidly dividing cells. Vincristine and vinblastine were initially isolated from periwinkle (vinca rosea), extracts of which were found to have antitumor activity. Indications - acute leukemia, Hodgkin disease and other lymphomas, various sarcomas, Wilms tumor, neuroblastoma, and breast and lung cancer.

Dosage- The vinca alkaloids are given intravenously, typically at one or two week intervals in cycles with other agents. if given intrathecally, they cause a progressive neurological syndrome, ascending paralysis and death. Side effects- Nausea, vomiting, fatigue, headache, dizziness, peripheral neuropathy, hoarseness, ataxia, dysphagia, urinary retention, constipation, diarrhea, bone marrow suppression, alopecia and phlebitis at the infusion site. Uncommon but potential severe adverse events include severe neutropenia, bleeding, peripheral neuropathy, pulmonary toxicity, hypersensitivity reactions and embryo-fetal toxicity.

DISCUSSION

Ayurveda, a healing science has a wide range of therapies and herbs to purify & support body tissues for natural recovery. Ayurveda mainly deals with balancing tridoshas, saptadhatus and trigunas., which are abruptly disturbed in general cancer. Chemotherapy and radiotherapy puts the patients under lot of strain and stress and further destroying of normal healthy cells. Antineoplastic drugs are considered as first line of treatment, undoubtedly gain is found along with pain where with certain relief of symptoms, there is counteraction of various side effects. Even though pharmacology of anti neoplastic drugs is well versed & explained in detail by modern pharmacologists, they fail to combact these sideeffects, which are worse then the actual disease, hence patient will be rejected by oncologists for further continuation of chemotherapy or they drop themselves from ongoing treatment due to intolerable sideeffects. Ayurveda plays an key role in initial as well in advanced stage of disease, by its abundance of herbs and treatment strategies. The treatments also plays an vitol role in reducing side effects of radiotherapy and chemotherapy, so there is lot of scope and focus on alternative treatment against cancer. But many of Ayurvedic formulation lack in data regarding their mechanism and detailed pharmacology& this gives neo researchers to pave a way towards giving Ayurveda, a scientific as well evident based pharmacological approach. Among the chemotherapy drugs many are plant derived drugs. Many experimental as well pharmacological study has been done on action of herbs, the first discovered chemotherapy drug is derived from nitrogen mustard gas. The sesame seeds (Brassica nigra) has antitumor effect by arresting the G2 / M cell cycle in lung carcinoma. Brassica nigrum seeds extract affect the proliferation, migration of cancer cells. It also reduces the normal DNA damage in cancer by its anti oxidant property. The allyl isothiocyanate is active ingredient against lung cancer in sesame seeds. so basically sesame seeds arrest the cell cycle, apoptosis induction, and antiproliferative effect. Studies shows that Sesame seeds resembles topo isomerase

enzyme inhibitors. Vinca alkaloids are derived from plant Catharanthus roseus. Vinca alkaloids are antimitotic, antimicrotubule alkaloid agents, sadapushpa inhibits microtubules formation inhibiting metaphase arrest. The epipodophyllotoxins (etoposide & teniposide) are derived from common mayapple (Podophyllum peltatum) which are abruptly used in treatment of testicular as well small cell lung carcinoma.[4] National cancer institute has screened approximately 35000plant species for potential anticancer effect among them some examples are Bhunimba (Andrographis paniculata) in epidermoid cancer, P388 lymphocytic cells, MCF – 7 breast cancer cells, mandukaparni (Centella asiatica) in Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells, Bhumiamalaki (Phyllantus amarus) in ascites tumor. Shatavari (Asparagus racemosa) in epidermoid carcinoma, Shallaki (Boswellia serrata)[4] in human epidermal carcinoma of nasopharynx, Katuki (Picrorrhiza kurroa) in hepatic cancer, Ashwaganda (Withania somnifera) in various tumors. Piperine present in pippali and maricha has activity against prostate, breast, lung, colon cancer, lymphoma, leukaemia. So a further detail classification of antineoplastic drugs in Ayurveda is required and present review aimed to collaborate all the pharmacological knowledge of antineoplastic drugs.

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