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A review on Recent Advances in Cancer Chemotherapy

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ABSTRACT

Cancer is an abnormal growth of normal cells and the term is also known as malignancy. There are more than 100 different types of cancers that affects human body. Different type of cancer includes Lymphoma, Sarcoma, Lungs cancer, breast cancer, bladder cancer, cervical cancer, ovarian cancer, colorectal cancer etc. Cancer is not a single disease it is a collection of various diseases which causes almost in any tissue in the body. There are various symptoms vary depending on the types of cancer including- a new lump, abnormal bleeding, a prolonged cough, weight loss, change in appetite, change in bowel movements. Cancer effects mental, physical and social activity of person. The treatment of cancer may possible by different treatments like chemotherapy, surgeries, targeted therapies, radiation therapies.

KEY WORDS: Lymphoma, Sarcoma, cancer cells treatment

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INTRODUCTION:

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. There are various symptoms vary depending on the types of cancer including- a new lump, abnormal bleeding, a prolonged cough, weight loss, change in appetite, change in bowel movements[1].There are various causes of cancer like excessive drinking alcohol, poor diet, obesity, chewing tobacco, excessive smoking cigarette due to which about 25% cancer death. Other factors includes like infections, exposure of harmful radiations, environmental pollutants.[2,3]Approximately 10–15% of cancers are due to inherited genetic defects from a person's parents to children. Cancer can be detected by certain signs and symptoms or screening tests. It is typically further investigated by medical imaging and confirmed by biopsy.

cancers can be prevented by drinking plenty of purified water, healthy and nutritional food, not smoking, maintaining a healthy weight, not drinking too much alcohol, eating plenty of vegetables, fruits and whole grains, vaccination against infectious diseases, avoid eating too much processed and red meat, and avoiding too much sunlight exposure. Early detection through screening is useful for cancers like cervical and colorectal cancer.[4] The benefits of screening in breast cancer are controversial. Cancer treatments with some combination of radiation therapy, surgery, chemotherapies, and targeted therapies. “Carcinos means crab” Over 100 different type of cancer & each is classified by the type of cell that is initially affected.[5]Second leading cause of death worldwide expected to increase five fold in the next 26 years.

SIGN AND SYMPTOMS:

When cancer begins, it produces no symptoms. Signs and symptoms appear slowly the mass grows or ulcerates.[6]Few symptoms are specific but not in each types of cancers. Many frequently occur in individuals who have other conditions. Thus, it is common for people diagnosed with cancer to have been treated for other diseases, which were hypothesized to be causing their symptoms. People may become anxious or depressed post-diagnosis. Now a day risk of suicide in people with cancer is approximately double.

(a) Systemic symptoms

Common symptoms occur due to effects that indirect or metastatic spread. These may include: weight loss, fever, excessive fatigue and changes to the skin. Hodgkin disease, leukemia’s and cancers in liver or kidney can cause a persistent fever. Some cancers may cause specific groups of systemic symptoms, termed Para neoplastic.

(b) Local symptoms

Local symptoms may occur due to the mass of the tumor,esophageal cancer can cause narrowing of the esophagus, making it difficult or painful to swallow; and colorectal cancer may lead to narrowing or blockages in the bowel, affecting bowel habits. Masses in breasts or testicles may produce lumps, Ulceration can cause bleeding. Although localized pain may occur in advanced cancer, the initial swelling is usually painless. Some cancers can cause retention of fluid within the chest or abdomen.

(c) Metastasis

Cancer can spread from its original site by local spread, lymphatic spread to regional lymph nodes or by hematogenous spread via the blood to distant sites, known as metastasis. The symptoms of etastatic cancers depend on the location of tumor and can include enlarged lymph nodes (which can be felt or sometimes seen under the skin and are typically hard), enlarged liver or enlarged spleen, which can be felt in the abdomen, pain or fracture of affected bones and neurological symptoms.

CAUSES OF CANCER:

Cancer are related to multiple factors, including sex, age, race, genetic predisposition, and exposure to environmental carcinogens. Other factors are environmental exposure; Chemical carcinogens (particularly those in tobacco smoke) as well as azo dyes, aflatoxins, asbestos, and benzene have been clearly implicated in cancer induction in humans and animals.[7]Identification of potential carcinogens in the environment has been greatly simplified by the widespread use of the Ames test for mutagenic agents. Ninety percent of carcinogens can be shown to be mutagenic with this assay. Ultimate identification of potential human carcinogens, however, requires testing in at least two animal species.

Certain herpes and papilloma group DNA viruses and type C RNA viruses have also been implicated as causative agents in animal cancers and are responsible for some human cancers as well. Oncogenic RNA viruses all appear to contain a reverse transcriptase enzyme that permits translation of the RNA message of the tumor virus into the DNA code of the infected cell.

Thus, the information governing transformation can become a stable part of the genome of the host cell. Expression of virus-induced neoplasia probably also depends on additional host and environmental factors that modulate the transformation process. A specific human retrovirus (HTLV-I) has been identified as being the causative agent for a specific type of human T cell leukemia. The virus that causes AIDS (HIV-1) is closely related.[8]

CLASSIFICATION OF ANTI CANCER DRUGS:

ALKYLATING AGENTS[9]

A. Nitrogen mustard

B. Alkyl sulfonates

C. Nitrosoureas

D.Other alkylating agents

PLATINUM COMPOUNDS

ANTI METABOLITIES

A. Antifolates

B. Purines analogue

C. Pyrimidines analogue

MITOTIC SPINDLE INHIBITORS

A. Vinca alkaloids

B. Taxanes

C.Epothiolone

TOPOISOMERASE INHIBITORS

A. Camtothecins

B. Antitumor antibody

ALKYLATING AGENT:

Mechanism of action:

- Alkylate nucleophilic group of DNA bases (N7 Guanine)
- Abnormal base pairing, cross linking of bases & DNA strand breakage
- Cell cycle non-specific[10]

Common Adverse Effect:

- Gastrointestinal distress
- Bone marrow suppression
- Alopecia
- Secondary Leukemia's
- Veno-occlusive disease of liver (increase dose)

Mechanism of Resistance Development:

- Decrease permeation of activity transported drug (mechloethamine, melphalan)
- Increase contraction of nucleophilic substances

- Increase activity of DNA repair pathways
- Increase of metabolism of the activated forms of cyclophosphamide and ifosfamide.

Newer agents:

Trofosfamide:

- Prodrug of ifosfamide
- Orally active
- Metastatic soft tissue sarcomas

Prdnimustine:

- Ester of prednisolone and chlorambusil
- Better drug delivery
- Side effect: myelosuppression, fluid retention

Uramustin:

- Derivative of nitrogen mustard and uracil
- Non-Hodgkin's lymphoma

Bendamustin:

- Inhibit mitotic checkpoint & include mitosis
- Hodgkin's lymphoma NHL, Multiple myeloma, breast Cancer
- Side effect : myelosuppression, nausea, vomiting, hypersensitivity reaction

B) Alkylsulfonates:

Currently used:

- Busulfan – Chronic myelogenous leukemia (CML)
- Side effect : Pulmonary fibrosis, hyperpigmentation, adrenal insufficiency

Newer drugs:

Mannosulfan:

- Tried for polycythemiarubravera
- Lesser Side effect
- Phase 2 trials

Treosulfan:

- Evaluated for ovaries
- Lesser Side effect compared to busulfan

(C) Nitrosoureas:

- Highly lipid soluble
- Cross blood brain barrier

Currently used agents:

- Carmustine, Lomustine, Semustine – Brain tumours like gliomas
- Streptozocin – Pancreatic islet cell carcinoma, malignant carcinoid tumors
- Adverse effect : Delayed myelosuppression, renal failure

Newer agents:

Fotemustine:

- Approved for metastasizing melanoma

Nimustin:

- Oligodendroglioma, Glioblastoma Multiforme
- Used with cytarabine

Ranimustine:

- Approved in Japan
- CML and polycythemia vera

(D) Other Alkylating Agent:

Currently used:

- **Procarbazine –** Hodgkin's lymphoma, brain tumors
- **Dacarbazine –** Malignant melanoma, Hodgkin's lymphoma

PLATINUM COMPOUNDS:

Mechanism of action:

- Use platinum to form dimers of DNA[10,11]
- Intrastrand / Interstrand crosslinks

Currently used agents:

• Cisplatin	First generation	Highly nephrotoxic
• Carboplatin	Second generation	Less nephrotoxic
• Oxaliplatin	Third generation	Cisplatin /Carboplatin resistant

Newer drugs:

Nedaplatin:

- Second generation analogue of cisplatin
- Increase sensitivity gynecological tumors : Ovarian , Cervical Endometrial cancer
- Decrease renal toxicity , nausea and vomiting

Triplatintetranitrate:

- Chloride prevents hydrolysis outside the cell
- Decrease diarrhea , vomiting
- Cancer with cisplatin resistant
- Phase 2 trials : Ovarian cancer, small cell lung cancer & Gastro- oesophageal adenocarcinomas

Picoplatin:

- Retains activity in cisplatin andOxaliplatin Resistant cells
- Activity by Intravenous and Oral routes
- Phase 3 trials small cell lung cancer and colorectal cancer

Aroplatin:

- Liposomal oxaliplatin
- Incorporated in multimellarliposome's
- Good biodistribution
- Well tolerated

ANTIMETABOLITES:

- Acts on S phase (i.e.) of cell cycle (CCS)[12]

(A) Antifolates:

- Transported intracellularly – folate transporter
- Inhibit DHFrase – Purine synthesis
- Inhibit thymidylate synthase – Thymidine synthesis
- Intracellular formation of polyglutamate metabolites by FPGS

Currently used agents:

- **Methotrexate –** Choriocarcinoma ,Acute Lymphoblastic Leukemia (ALL), Cancer breast, head & neck cancer, ovary, bladder
- **Pemetrexed –** Mesothelioma, Non SmallCell Lung cancer
- **Adverse effect:** Bone marrow suppression, mucositis, hepatotoxicity: Pulmonary fibrosis (methotrexate), rashes (pemetrexed)

Development and resistant:

- Decrease transport via folate carrier
- Decrease formation of polyglutamates
- Increase formation of DHFrase
- Altered DHFrase with decrease affinity

Newer drugs:

Trimetrexate:

- Lipid soluble
- Crosses blood brain barrier
- Bypasses membrane transport system – transport deficient MTX – resistant tumor cells
- Leiomyosarcoma& skin cancer

Pralatrexate:

- Enters cells expressing decrease folate carrier Type1 (RFC-1)
- Relapsed or refractory peripheral T-cell lymphoma

Raltitrexed:

- Quinazoline folate analogue
- Selectively inhibit thymidylate synthase (TS)
- Advanced colorectal cancer

Lometrexol:

- Inhibit GARFT as well as AICART
- Inhibit of de novo synthesis of purines

(B) Purine analogues:[13]

Mechanism of action:

- Purine antimetabolites activated by HGPRTase
- Incorporated into DNA and RNA nucleotides
- Inhibit various enzymes of purine synthesis

Newer drugs:

Clofarabin:

- Paediatric patient for relapsed or refractory Acute Lymphoblastic Leukemia (ALL)
- Side effect : Tumor lysis syndrome, bone marrow suppression, systemic inflammatory response (SIRS)

(C) Pyrimidine Analogues:

Mechanism of action:

- **Cytarabin**activated to arabinoside CTP – inhibit DNA polymerase/β
- **5-FluroUracil (FU)**converted to 5-dUMP – inhibit thymidylate synthetase
- **Azacytidine&Decitabine**DNA hypomethylation by inhibiting DNA methyl transferase

Newer drugs:

Tegafur Uracil:[14]

- Tegafur is 5-FU prodrug developed in 1967
- unacceptable CNS toxicity & discontinued
- Combination of tegafur& uracil (1:4)
- Uracil – inhibitor or Dihydropyrimidine Dehydrogenase
- Increase of 5-FU without toxic levels of tegafur
- Given orally
- Approved in Japan for last 15 years
- Gastric cancer, colorectal cancer, Hepatocellular Cancer

Carmofur:

- Oral lipophilic derivative of 5-FU
- Managable toxicities (Urinary frequency)
- Serious toxicity- Leucoencephalopathy
- Adjuvant chemotherapy for curatively resected colorectal cancer.

MITOTIC SPINDLE INHIBITORS:

(A) Vinca Alkaloids:

Mechanism of action:

- Bind to microtubule protein- tubulin
- Dissolve the assembly[15]
- Chromosome cannot align along the division plate

Currently used agents:

- **Vinblastine, Vinorelbine –** Hodgkin's, Non- Hodgkin Lymphoma(NHL), Breast, Lung, Testis cancer
- **Vincristine –** ALL, Neuroblastoma, Wilms tumour, Rhabdomyosarcoma, Hodgkin's, NHL

Adverse Effects:

- Vinblastine &Vinorelbine – Bone marrow depression (leukopenia)
- Vincristine – Peripheral neuropathy

Newer agents [16,17]

Vinflunine:

- More activity than vinblastine/ vinorelbine
- No peripheral neuropathy
- Use : Advanced bladder cancer, advanced breast cancer

Vindesine:

- All types of cancers, Non-small cell lung cancer (NSCLC) cancer
- Side effect : local vescicant, myelosuppression, peripheral neuropathy

(B) Taxanes:

Mechanism of action:

- Binds to β-tubin subunit of micro-tubules
- Antagonises its disassembly
- Enhancement of tubulin polymerisation
- Metaphase arrest

Currently used drugs:[18]

- **Paclitaxel, Docetaxel-** Ovarian, Breast, Prostate, Bladder, Lung, Head and Neck
- Adverse effect : Hypersensitivity reactions, myelosuppression, peripheral neuropathy

Resistance:

- Increase of mdr-1 gene- increase p-glycoprotein
- Increase survivin – anti apoptotic factor
- B tubulin mutation

Newer agents:[19, 20]

Nab – Paclitaxel:

- Protein bound paclitaxel – decrease hypersensitivity reactions

Cabazitaxel:

- Poor substrate for p- glycoprotein efflux pump
- With prednisolon – Hormone refractory metastatic prostate cancer previously treated with docetaxel containing regimen
- Food and Drug Administration approved in June 2010
- Adverse effect : Myelosuppression, hypersensitivity reaction, diarrhea

Ortataxel:

- Blocks its own efflux from gpP – overexpressing cells
- Phase2 trials
- Tried for taxene refractory solid tumours (Lungs, breast, Kidney)

Larotaxel:

- Active against taxene – resistant and multidrug – resistant tumours
- Crosses the blood brain barrier
- Advanced pancreatic cancer and advanced bladder cancer with brain metastasis

- Phase 3 trials

Tesetaxel:[21,22]

- Orally available
- Eliminates transfusion reaction
- Decrease incidence of peripheral neuropathy
- Tried in advanced gastric and advanced breast cancer
- Phase 3 trials

(C) Epothiolones:

Mechanism of action :

- Bind to β tubulin
- Stabilise the microtubules
- G2M interphase arrest

Advantages:

- Less susceptible to gpP mediated multi drug resistance
- Superior cytotoxic potential compared to taxenes

Currently used drugs:[23]

Lxabepilone:

- With capecitabine : Locally advanced or metastatic Breast cancer not responding to Anthracyclins and taxanes
- Monotherapy : metastatic Breast cancer progressed through treatment with anthracyclins, taxanes and peripheral neuropathy
- Adverse effect : neutropenia, peripheral neuropathy

Sagopilone:

- Natural product of epothilone B
- Increase effective in stabilizing performed microtubules
- Taxane-resistant settings
- Crosses the blood brain barrier
- Use : Gastric cancer, NSCLC

KOS 1584/21 Aminoepothiolone: [24,25]

- Phase 1 trials

Patupilone:[26]

- Paclitaxel-resistant cancer cells

- Target vasculature of solid tumor- immature endothelial cells have strong dependence on tubulin in maintaining their shape
- Phase 2 trials for solid tumours example : ovarian cancer

TOPOISOMERASE INHIBITORS:

(A) Camtothecins:

Mechanism of action:

- Inhibit topoisomerase 1
- Collision of replication fork with SS breaks – DNA break
- S phase specific

Currently used agents:

Irinotecan, Topotecan: Colon, lung, ovary cancer

Adverse effect:

- Topotecan – Neutropeenia
- Iritocan – diarrhea, cholinergic syndrome

Newer agent:[26]

Belotecan:

- Use in ovarian cancer, small cell lung cancer

(B) Antitumor Antibiotics:

Mechanism of action:

- Inhibit of topoisomerase II
- Binding to DNA through intercalation- blockage of DNAandRNA
- Bind to cell membrane-After fluidity and ion transfer

Currently used agents: [27]

Doxorubicin	Breast Ca, HL & NHL, soft tissue sarcoma, Ovarian Ca, Lung Ca, Wilm's tumor & Neuroblastoma
Daunorubicin	AML, ALL
Idarubicin	AML, ALL, CML in blast crisis
Epirubicin	Breast Ca, Gastro-esophageal Ca
Mitoxantrone	Hormone Refractory Prostate Ca, NHL, AML

Adverse effect:

Cardiotoxicity, myelosuppression, mucositis, radiation recall syndrome

Newer drugs:

Aclarubicin:

- Inhibits RNA synthesis more strongly than DNA
- Cardiotoxicity less
- Relapsed / Resistance Acute myeloid leukemia(AML)

Amrubicin:

- Marketed in Japan for small cell lung cancer
- Superficial bladder cancer and lymphoma

Pirarubicin:

- More lipophilic derivative
- Higher uptake rate of cells & better antitumor efficacy
- Lower cardio toxicity
- Breast cancer , acute leukemia's and lymphomas
- Phase 3 trials

Zorubicin:

- Four times less cardio toxic
- Less myelosupression
- Acute leukemia’s and breast cancer
- Phase 3 trials

Valrubicin[28]

- United State Food and Drug Administration approved(USFDA) – BCG refractory bladder cancer inset
- Administered intravescically
- Systemic absorption decrease
- Adverse effect: Urinary frequency, urgency, dysuria

CONCLUSION:

The period from 1980 to the present has seen a remarkable growth in the understanding of many of the cellular and molecular mechanisms underlying malignant transformation of a cell. Given our increasing knowledge about the biology of cancer, it is clear that no single therapy will serve as a panacea & it is most likely that in near future, agent directed against the molecular events will have to be combined with the existing standard chemotherapies for the desired outcome.

FUTURE PERSPECTIVES

The outcomes in pre-clinical research should be studied and correlated at the clinical level and in future there is a huge scope for researchers in the clinical anticancer research and development study.

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