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Review on the Cancer Treatment: Chemotherapy

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Abstract

Chemotherapy serves as a crucial treatment modality for various types of cancer and has made significant contributions to enhancing patient outcomes in recent decades. This abstract presents a comprehensive overview of chemotherapy, encompassing its progress, obstacles, and prospects for the future. The primary aim of chemotherapy is to selectively target and eradicate cancer cells throughout the body using cytotoxic drugs. Chemotherapeutic agents can be categorized into diverse groups, including alkylating agents, antimetabolites, anthracyclines, taxanes, and targeted therapies.

Significant advancements have emerged in the field of chemotherapy, leading to the development of more efficient and personalized treatment strategies. The introduction of targeted therapies, such as monoclonal antibodies and small molecule inhibitors, has revolutionized cancer treatment by precisely attacking cancer cells while minimizing harm to healthy tissues. Additionally, the integration of immunotherapeutic agents, like immune checkpoint inhibitors, has displayed remarkable success in augmenting the immune system's ability to identify and eliminate cancer cells.

Nevertheless, chemotherapy encounters several challenges. One of the primary limitations lies in its toxicity to normal cells, resulting in notable side effects. Efforts are underway to enhance the selectivity and specificity of chemotherapy drugs, aiming to reduce adverse effects on healthy tissues. Furthermore, drug resistance remains a critical concern in chemotherapy, as cancer cells can develop mechanisms to evade the cytotoxic impact of drugs. Despite these challenges, chemotherapy remains a crucial component of cancer treatment, and recent advancements have paved the way for more effective and personalized therapeutic approaches. Overcoming the obstacles associated with toxicity and drug resistance remains a priority, with future research focused on optimizing treatment strategies to improve patient outcomes. By harnessing the potential of emerging technologies and innovative approaches, chemotherapy holds promise for further advancements in the battle against cancer.Keywords: chemotherapy, cancer treatment, advancements, challenges, drug resistance, targeted therapies, immunotherapy, toxicity, drug delivery, personalized medicine.

Key words: Cancer, Chemotherapy, Treatment

Introduction

Chemotherapy, also known as chemo or CTX/CTx, is a form of cancer treatment that utilizes anti-cancer drugs, such as chemotherapeutic agents or alkylating agents, as part of a standardized chemotherapy regimen. It can be administered with the intention of curing the disease (often using drug combinations) or to prolong life and alleviate symptoms (palliative chemotherapy). Medical oncology, a branch of medicine specializing in pharmacotherapy for cancer, encompasses chemotherapy as a major component.

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The development of cancer treatment can be traced back to three significant events in the last century. These include the discovery of X-rays by Wilhelm Konrad Roentgen, the use of transplantable animal tumour models in cancer research, and the introduction of the radical mastectomy surgical procedure by Halsted.

The term "chemotherapy" was coined by German pharmacist Paul Ehrlich, who explored the use of medicines for treating infectious diseases. He was also the first scientist to employ animal models to screen various chemicals for their potential efficacy against diseases. Historical records indicate the use of arsenicals in the 1900s. Radiotherapy and surgery were the primary treatment modalities for cancer in the 1960s. As the presence of micro metastases and cancer recurrence after surgery and radiation became apparent, combination chemotherapy gained importance.

The publication of Lindskog's study demonstrating the efficacy of nitrogen mustard in treating carcinoma had a significant impact on the development of cancer chemotherapy. It led to the development of oral derivatives like chlorambucil and eventually cyclophosphamide. The discovery of actinomycin D spurred the search for additional antitumor antibiotics, including anthracyclines, mitomycin, and bleomycin. In 1947, Farber and colleagues achieved success in treating childhood leukaemia using antimetabolites with antifolate activity, such as aminopterin, later known as methotrexate [(1)].

The successful use of methotrexate in treating choriocarcinoma and leukaemia's prompted further investigations in cancer chemotherapy. Medications like thiopurines (e.g., 6-mercaptopurine) and 5-fluorouracil became prominent in cancer treatment. Subsequently, the association of chromosome translocations with various leukaemia's, as studied by Nowell and colleagues, paved the way for the development of molecular targeted therapies, such as imatinib.

Charles Huggins was awarded the Nobel Prize in 1966 for his research on hormone therapy in prostate cancer. This work marked the beginning of a new era of hormone therapy, leading to the introduction of medications like tamoxifen and anastrozole.

With an enhanced understanding of cancer biology, there are now several therapeutic monoclonal antibodies available. Rituximab and trastuzumab were approved in the late 1990s for the treatment of lymphoma and breast cancer, respectively. Molecular targeted therapy has emerged as a novel approach to cancer treatment, with several agents receiving FDA approval in the last decade. Researchers are designing targeted therapies to inhibit specific pathways involved in cancer growth, such as cell signaling, angiogenesis, and protein degradation. Immunotherapy, including immune checkpoint inhibitors (e.g., PD-1, PD-L1, CTLA-4), which enhance the immune response against cancer cells, is also being extensively employed in various cancers. Immunotherapy is considered a separate field of treatment. [(2)]

Function

- The primary objective of chemotherapy is to impede cell proliferation and tumor growth, thereby preventing invasion and metastasis. However, the toxic effects of chemotherapy also impact normal cells. Inhibition of tumor growth can occur at various stages within the cell and its microenvironment.
- Traditional chemotherapy agents primarily affect the synthesis and functioning of macromolecules in neoplastic cells by interfering with DNA, RNA, or protein synthesis or by disrupting their proper function. When inhibition of macromolecular synthesis or function is sufficient, it can lead to cell death either directly or by inducing apoptosis. With traditional agents, cell death may be delayed as only a proportion of the cells die in response to treatment. Thus, repeated doses of the drug may be necessary to achieve a response. The cytotoxic effects of these medications are most significant during the S phase, which is the DNA synthesis phase of the cell cycle. Vinca alkaloids and taxanes act during the M phase and interfere with mitotic spindle formation. [(3)]
- Combination chemotherapy is often employed to achieve desirable responses. It appears to hinder the development of resistant clones by promoting cytotoxicity in both resting and dividing cells. Cellular mechanisms governing cell proliferation and division are

complex, involving numerous genes, receptors, and signal transduction pathways. Advances in cancer cell biology have provided valuable insights into mechanisms such as apoptosis, angiogenesis, metastasis, cell signaling, division, and modulation of growth factors. Researchers are developing molecular targeted therapies that aim to inhibit these pathways, including cell signalling, angiogenesis, and protein degradation.

❖ Chemotherapy can be administered in neoadjuvant, adjuvant, combined, or metastatic settings. Neoadjuvant therapy is given before the primary treatment, while adjuvant therapy is given alongside the primary treatment to suppress or eliminate the growth of hidden cancer cells. Adjuvant therapy has become the standard approach for bone, lung, colorectal, and ovarian cancers. Combined modalities, such as chemotherapy and radiation, are used to shrink tumors before surgery or as a curative treatment in cancers like head and neck, lung, and anal cancer. [3]

❖ The combination of chemotherapeutic agents is administered cyclically based on three fundamental principles. The fraction kills hypothesis states that a uniform dose of a drug kills a constant fraction of tumour cells, rather than a constant number, regardless of tumour burden. Neoplastic tumour cells exhibit a linear response to the administered dose in terms of efficacy. The Goldie-Coldman hypothesis suggests that cancer cells acquire spontaneous mutations that lead to drug resistance. Therefore, combination or multitargeted therapies are generally superior to single-agent treatments in most cancer cases.

❖ Additionally, combination chemotherapy agents with different mechanisms of action and non-overlapping toxicity profiles can be selected to minimize resistance and toxicity. For instance, the therapeutic regimen of bleomycin/vinblastine/cisplatin for testicular cancers exemplifies combination chemotherapy. [4]

Chemotherapeutic agents can classify according to the mechanism of action:

Alkylating Agents

Exemplifications of alkylating agents are as follows

- Nitrogen mustard- bendamustine, cyclophosphamide, ifosfamide
- Nitrosoureas – carmustine, lomustine
- Platinum analogs – carboplatin, cisplatin, oxaliplatin
- Triazenes- Dacarbazine, procarbazine, temozolamide
- Alkyl sulfonate- Busulfan
- Ethyleneimine- Thiotepa

Medium of action (MOA): -These medications produce an unstable alkyl group, R-CH2, which reacts with nucleophilic centres on proteins and nucleic acids, thereby inhibiting DNA replication and synthesis.

The toxic effects of chemotherapy include dose-limiting toxicity, such as myelosuppression, which leads to neutropenia (lowest neutrophil count) within 6 to 10 days and recovery in 14 to 21 days. Other side effects include mucositis, nausea and vomiting, neurotoxicity, and alopecia (hair loss). In the long term, chemotherapy can cause pulmonary fibrosis, fertility issues, and secondary malignancies. [5]

Antimetabolites

Mechanism of Action: Inhibit the replication of DNA

A) **Cytidine analogs** – azacitidine, decitabine, cytarabine, gemcitabine

- DNA methyltransferase inhibitors - Azacitidine, Decitabin
- Mechanism of Action: Directly incorporate into DNA and inhibit DNA methyltransferase.
- Suggestions: Azacitidine and Decitabine for Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML). Cytarabine for MDS and AML. Gemcitabine for bone cancer, Non-Small Cell Lung Cancer (NSCLC), ovarian cancer, pancreatic cancer, bladder cancer, sarcoma, Hodgkin's lymphoma (HL), and Non-Hodgkin's lymphoma (NHL).
- Toxicity: Myelosuppression is a common side effect. High-dose cytarabine can cause neurotoxicity and conjunctivitis. Gemcitabine may lead to liver enzyme elevations and interstitial pneumonitis. [6]

B) Folate antagonists - Methotrexate, Pemetrexed
• Mechanism of Action: Reduces folate, which is essential for the synthesis of purine nucleotides and thymidylate.
• Suggestions: Methotrexate for Acute Lymphoblastic Leukaemia (ALL), NHL, central nervous system (CNS) tumours, and sarcoma. Pemetrexed for malignant pleural mesothelioma and Non-Squamous Non-Small Cell Lung Cancer (NSCLC).
• Toxicity: Myelosuppression, mucositis, hepatotoxicity, nephrotoxicity, and cutaneous reactions.
• Toxin Prevention: Hydration and alkalization of the urine, leucovorin rescue.

C) Purine analogs - Cladribine, Clofarabine, Nelarabine
• Mechanism of Action: Structural analogs of guanine and act as false metabolites.
• Suggestions: Cladribine for hairy cell leukaemia, AML, CLL, and NHL. Clofarabine for ALL and AML. Fludarabine for CLL, AML, NHL, and as a conditioning agent for bone marrow transplantation (BMT). Nelarabine for T-cell ALL and T-cell lymphoblastic lymphoma. Pentostatin for hairy cell leukemia, cutaneous T-cell lymphoma (CTCL), and CLL.
• Toxicity: Myelosuppression and immunosuppression (suppresses CD4 cells), which puts patients at risk for opportunistic infections. [7]

D) **Pyrimidine analogs** - Fluorouracil (5-FU), Capecitabine (prodrug of 5-FU)
• Mechanism of Action: Active metabolite (F-dUMP) forms a stable covalent complex with thymidylate synthetase in the presence of reduced folate, thus interfering with DNA synthesis and function.
• Suggestions: 5-FU for colorectal cancer, anal cancer, pancreatic cancer, and gastric cancer. Capecitabine for colorectal cancer and breast cancer.
• Toxicity: Hand-foot syndrome, mucositis, and diarrhoea are common. Myelosuppression can also be a dose-limiting toxicity. Severe toxicity of 5-FU can occur in cases with Dihydropyridine Dehydrogenase (DPD) deficiency or medication overdose, leading to cardiac dysfunction, colitis, neutropenia, and encephalopathy. Uridine triacetate is approved for the treatment of these toxicities. [8]

Antimicrotubular Agents
Exemplifications of antimicrotubular agents are as follows

A) Topoisomerase II inhibitors - Anthracyclines (Doxorubicin, Daunorubicin, Idarubicin, Mitoxantrone)
• Mechanism of Action: Inhibit RNA and DNA synthesis. Additionally, they inhibit topoisomerase II, leading to the inhibition of DNA replication and DNA-protein complex formation.
• Suggestions: Daunorubicin for Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML), Acute Promyelocytic Leukaemia (APL). Doxorubicin is used for ALL, AML, Wilms tumour, neuroblastoma, sarcomas, bone cancer, ovarian cancer, bladder cancer, thyroid cancer, Hodgkin's lymphoma (HL), and Non-Hodgkin's lymphoma (NHL). Liposomal doxorubicin has a longer half-life and is less cardiotoxic.
• Toxicity: Myelosuppression and cardiotoxicity (cumulative dose-dependent). The maximum cumulative dose of doxorubicin is typically around 550 mg/m2. Secondary malignancies like treatment-related Myelodysplastic Syndrome (t-MDS) and Acute Myeloid Leukaemia (t-AML) are rare but reported complications, particularly with alkylating agents and topoisomerase II inhibitors. These secondary malignancies often present 5 to 7 years after exposure to the medications. [9]

B) Topoisomerase I inhibitors - Irinotecan, Topotecan
• Mechanism of Action: Prevent DNA unwinding by blocking the release of Topoisomerase I from the cleavable complex, forming a ternary complex. [10]
• Suggestions: Irinotecan for colorectal cancer, cervical cancer, oesophageal cancer, sarcoma, pancreatic cancer, and lung cancer. Topotecan for cervical cancer, ovarian cancer, and Small Cell Lung Cancer (SCLC).

• Toxicity: Irinotecan causes dose-limiting diarrhoea. Topotecan causes dose-limiting neutropenia and thrombocytopenia.

C) Taxanes - Paclitaxel, Docetaxel, Cabazitaxel
• Mechanism of Action: Disrupt the equilibrium of microtubule polymerization and depolymerization, leading to abnormal cellular function and disruption of cell replication, ultimately inducing apoptosis. They inhibit microtubule assembly and are M-phase specific.
• Suggestions: Docetaxel for bone cancer, lung cancer, prostate cancer, ovarian cancer, cervical cancer, and sarcoma. Paclitaxel for breast cancer, lung cancer, and ovarian cancer. Abraxane is a protein-bound form of paclitaxel. Cabazitaxel for prostate cancer.
• Toxicity: Hypersensitivity reactions, myelosuppression, and peripheral neuropathy. [11]

D) Vinca alkaloids - Vinblastine, Vincristine, Vinorelbine
• Mechanism of Action: Bind to tubulin and inhibit microtubule formation, arresting cells in metaphase. They are M-phase specific.
• Suggestions: Vincristine for ALL, Hodgkin's lymphoma (HL), Non-Hodgkin's lymphoma (NHL), neuroblastoma, and Small Cell Lung Cancer (SCLC).
• Toxicity: Peripheral neuropathy (affects both motor and sensory functions) and myelosuppression. [12]

Antibiotics
Examples of antibiotics used as chemotherapy agents are as follows:
Actinomycin D, Bleomycin, Daunomycin.
• Mechanism of Action: They inhibit RNA and DNA synthesis.
• Bleomycin specifically binds to DNA, causing single and double-strand DNA breaks.
• Suggestions: Testicular cancer, Hodgkin's lymphoma (HL), head and neck cancers.
• Toxicity: Bleomycin has the potential for cumulative pulmonary toxicity and may cause hyperpigmentation.

A) Hydroxyurea
• Mechanism of Action: Inhibits ribonucleoside diphosphate reductase, leading to decreased DNA synthesis. It is S-phase specific.
• Suggestions: Acute Myeloid Leukaemia (AML), Chronic Myeloid Leukemia (CML), sickle cell disease.
• Toxicity: Myelosuppression, dermatologic reactions.

B) Tretinoin
• Mechanism of Action: Acts as a vitamin A derivative, targeting the retinoic acid receptor-alpha (RAR-α) and promoting cell differentiation.
• Suggestion: Acute Promyelocytic Leukaemia (APL).
• Toxicity: APL differentiation syndrome may occur, leading to complications and cardiopulmonary symptoms.

C) Arsenic trioxide
• Mechanism of Action: Induces cell differentiation and apoptosis.
• Suggestion: Acute Promyelocytic Leukaemia (APL).
• Toxicity: QT interval prolongation, requiring careful monitoring and electrolyte replacement (potassium, magnesium). APL differentiation syndrome may also occur.

D) Proteasome inhibitors
• Suggestion: Bortezomib is used in multiple myeloma.
• Toxicity: Peripheral neuropathy is a common side effect of proteasome inhibitors.

Clinical Significance
The side effects of cancer chemotherapy can be acute or prolonged and may require monitoring. It is important to have a multidisciplinary approach to monitoring, as certain patient populations may be at a higher risk of complications. Here are some common side effects of chemotherapy and their management options: [13]

Infusion reactions: These can be managed by using pre-medications such as diphenhydramine, methylprednisolone, or epinephrine.

Chemotherapy-induced nausea and vomiting (CINV): Treatment options include medications

like prochlorperazine, haloperidol, metoclopramide, lorazepam, dexamethasone, ondansetron, granisetron, dolasetron, palonosetron, dronabinol, aprepitant, and fosaprepitant. Palonosetron is known to have a longer half-life, better efficacy, and higher binding affinity than granisetron. [(14)]

Mucositis: Management strategies include using magic mouthwash, avoiding commercial mouthwashes, and using glycerine-based products to soothe the mouth.

Fatigue: Interventions such as exercise, optimizing sleep quality, and behavioral therapies like relaxation techniques can help manage fatigue.

Chemotherapy-induced diarrhoea: Agents like loperamide, diphenoxylate with atropine, and octreotide can be used to manage chemotherapy-induced diarrhoea[(15)].

Chemotherapy-induced constipation: Agents such as docusate, senna, milk of magnesia, bisacodyl, lactulose, polyethylene glycol, and enemas can be used to manage constipation.

Neurotoxicity: Depending on the specific neurotoxicity, management options may include vitamin B6, glutamine, gabapentin, pregabalin, carbamazepine, or tricyclic antidepressants (such as amitriptyline).

In cases of **5-fluorouracil** (5FU) toxicity, which can occur in individuals with Dihydropyridine Dehydrogenase (DPD) deficiency or drug overdose, it can lead to cardiac dysfunction, colitis, neutropenia, and encephalopathy. Uridine triacetate is approved for the management of these cases. [(16)]

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