Cancer Chemotherapy

Subjects: Others

Contributor: Neeraj K. Singh , Jeffrey M. Beckett , Krishnakumar Kalpurath , Muhammad Ishaq , Tauseef Ahmad , Rajaraman D. Eri

Chemotherapy is still the first line of treatment for most cancer patients. Patients receiving chemotherapy are generally prone to infections, which result in complications, such as sepsis, mucositis, colitis, and diarrhoea.

cancer chemotherapy probiotics Prebiotic Synbiotic

1. Introduction

Cancer is the leading cause of mortality in Australia, leading to approximately 50,000 deaths in 2020. Currently, there are more than 1 million people in Australia who have been diagnosed with cancer at some point in time. It was estimated that around 150,000 new cases would be diagnosed in Australia in 2020 [1]. The World Health Organization (WHO) has estimated that cancer diagnoses will increase by 45% between 2008 and 2030. Major causes of cancer involve heavy smoking, poor diet, physical inactivity, and environmental pollutions. In 2018, the most common cancers diagnosed globally were lung cancer (2.09 million), followed by colorectal (2.09 million), prostate (1.28 million), skin (1.04 million), and then stomach cancer (1.03 million). The financial burden of cancer is enormous and the global burden in 2010 was estimated to be approximately USD 1.16 trillion [2].

Cancer is defined as the uncontrolled growth of cells in the body and, clinically, is termed as a malignant neoplasm. Cancer starts via genetic and epigenetic variations that result in the unlimited multiplication of cells which evade the mechanisms that normally control cell growth and division. This uncontrolled growth and multiplication of cells finally appear as a collection of cells called a tumour. These cells can metastasise to the other parts of the body through the bloodstream or lymphatic system. Cancer treatment depends on the type and stages of the disease [3][4]. Cancer treatment options include chemotherapy, radiotherapy, surgery, immunotherapy, and monoclonal antibody therapy [5]. Despite recent advances in cancer treatments, chemotherapy is still a cornerstone of cancer therapy [5][6].

2. Cancer Chemotherapy

The term “chemotherapy” was coined by Paul Ehrlich in the early 1900s for drug therapy in the treatment of diseases. He also documented the efficacy of certain chemicals against diseases in animal models, which later led to the development of cancer drugs. Chemotherapy was first introduced in cancer treatment in the 1940s and 1950s [7]. Chemotherapy is an essential part of cancer treatment, and the development of new anticancer drugs represents one of the major areas in pharmaceutical research [8]. Chemotherapy is often the only option for the

oncologist when cancer has widely metastasised to other parts of the body [9]. The major disadvantage of chemotherapy is unwanted cytotoxicity, as it cannot discriminate between rapidly dividing cancer cells and normal cells undergoing cell division [10]. However, cancer cells are generally more sensitive to the cytotoxic action of chemotherapy agents when compared to normal cells. A combination of drugs used at regular intervals can cure some cancers while others can be palliatively managed in order to improve the patient's symptoms and quality of life [3][11]. The main aim of chemotherapy is to reduce the cancer cell population to a minimal level. The fractional cell kill hypothesis, primarily offered for haematological and lymphatic malignancies, has been accepted as the protocol for various other cancer types, including solid tumours. As per this hypothesis, a specific concentration of drug in a defined period will kill a constant number of the cell population, irrespective of the absolute number of tumour cells [12][13]. The treatment efficacy depends on the dose of drug, as well as on the number and frequency of chemotherapy cycles as each successive cycle of chemotherapy will eliminate only a fixed number of remaining cells [14]. Hypothetically, a tumour size of 10^{11} cells will be reduced to less than one cell after six cycles of chemotherapy, if 99% of the cells are killed per cycle [15]. The ability of normal tissues, such as in bone marrow and the gastrointestinal tract, to recover after chemotherapy decides the timing of chemotherapy cycles; this is usually about three to four weeks [15][16].

The majority of chemotherapeutic drugs target dividing cells and thus are more effective in tumours with rapidly dividing cells. Some drugs act on a specific phase of the cell cycle in dividing cells, while a few target only the non-dividing cells. A sudden decrease in tumour size by surgery (debulking), radiotherapy, or chemotherapy induces cell division and consequently increases the susceptibility of the tumour to chemotherapy.

Currently, a newer anticancer therapy, known as targeted therapy, is also widely in use. The goal of targeted therapy is to deliver the drug to specific molecules of interest in cancer cells or in the tissue environment, thereby regulating the growth and development of the cancer. This molecule-specific action of treatment has been shown to be beneficial in many cancers and is now used globally [10][17]. Monoclonal antibodies (immunotherapy) and small molecule inhibitors (cellular kinases) are the two main categories of targeted therapy. Monoclonal antibodies induce cytotoxicity by different mechanisms, such as target cell killing through the recruitment of host immune functions, by receptor or ligand binding, to disturb the essential cancer cell processes or by deadly payloads, such as radioisotopes or toxins to kill the target cells. They are administered intravenously and circumvent the first pass/hepatic metabolism [17][18]. On the other hand, small molecule tyrosine kinase inhibitors (SM-TKIs) are orally administered and known to inhibit oncological targets in many solid organ tumours. Unlike conventional chemotherapy, the SM-TKIs, which include VEGFRs (vascular endothelial growth factor receptors) TKIs, and EGFRs (epidermal growth factor receptors), TKIs can be administered orally for a longer duration (i.e., months or years) [19]. Targeted therapy also exerts side effects as it damages the normal cells that express target molecules. However, side effects in this case can also be used as surrogate markers of the treatment efficacy [10][18].

Cancer treatment generally uses a combination of chemotherapy to reduce toxicity and to reduce the risk of resistance against the drugs [15]. The majority of cancer patients undergo conventional chemotherapy treatment; however, this is associated with many complications including widespread mucositis, which can manifest as pain, inflammation, bleeding, risk of infections, and diarrhoea [20].

Chemotherapeutic Agents and Side Effects

The toxicity of chemotherapy is a major cause of concern, leading to a poor quality of life in cancer patients and may eventually result in a reduction in dose in order to manage the adverse effects of the treatment. It has been shown that reduction in dose results in low survival rates [8]. Currently, a wide range of chemotherapeutic agents are in use and exhibit a variety of side effects in cancer patients. The different classes of chemotherapy drugs, based on their mechanism of actions and side effects, are summarised below in **Table 1**.

Table 1. Classes of chemotherapy drugs, drug names, their mechanisms of action, and their common side effects, with references.

Drug Class	Drug Names	Mechanism of Action	Common Side Effects	References
Tubulin modifying agents	Docetaxel and paclitaxel	Inhibit the mitotic process of cells by interfering with the tubulin polymerisation process in order to induce cell death.	Ischaemic colitis, nausea, fatigue, flushing, fever, diarrhoea, acute abdominal pain, neutropenia, septicaemia, hyperglycaemia, gastrointestinal haemorrhage, bowel perforation, neuropathy, dyspnoea, peritonitis, and tenderness.	[21][22]
Platinum-based drugs	Cisplatin and oxaliplatin	Cause DNA damage to induce cell death.	Nausea, vomiting, diarrhoea, constipation, stomatitis, gastro-oesophageal reflux, anorexia, cachexia, asthenia, melena, dry mouth, gum inflammation, haemoptysis, colitis, ileus, pancreatitis, hepatic sinusoidal dilatation, rectal haemorrhage, haemorrhoids, tenesmus renal and neural toxicity, cardiotoxicity, ototoxicity, alopecia, and bone marrow suppression.	[23][24][25]
DNA intercalator drugs	Anthracyclines, doxorubicin, daunorubicin, idarubicin, and epirubicin	Inhibit DNA isomerase II and DNA replication to cause cell death.	Cardiac toxicity, nausea, vomiting, stomatitis, oesophageal ulceration, colonic ulceration, anorexia, and rarely tongue hyperpigmentation.	[10]

Drug Class	Drug Names	Mechanism of Action	Common Side Effects	References
Antimetabolites	5-fluorouracil, capecitabine, 6-mercaptopurine, cytarabine, gemcitabine, and methotrexate	Induce cell death during the S-phase of the cell cycle or by inhibiting the enzymes responsible for nucleic acid production	Fever, nausea, vomiting, gingivitis, pharyngitis, gastrointestinal ulceration, abdominal pain, loss of appetite, haematemesis, melena, diarrhoea, constipation, stomatitis, bowel necrosis, pancreatitis, hyperbilirubinemia. hepatic failure, hyperbilirubinemia, dyspepsia, anorexia, bone marrow suppression, and leukopenia.	[10][26][27]
Alkylating agents	Mechlorethamine, melphalan, chlorambucil, cyclophosphamide, ifosfamide, carmustine (BCNU), lomustine (CCNU), mitomycin C, dacarbazine, and procarbazine	Cause reactions with different components of DNA to induce cell death	Nausea, vomiting, abdominal pain, diarrhoea, constipation, melena, stomatitis, anorexia, dry mouth, leukopenia, thrombocytopenia, encephalopathy, bone marrow suppression, and haematuria.	[28][29][30]
Targeted biological agents (cellular kinases and monoclonal antibodies)	Alemtuzumab, bevacizumab, cetuximab, gemtuzumab, ozogamicin, tiuxetan, ^{131}I-tositumomab, panitumumab, rituximab, trastuzumab, bortezomib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, and sunitinib	Induce cell death by targeting a specific molecule in cancer cells.	Nausea, vomiting, diarrhoea, anorexia, stomatitis, abdominal pain, hepatotoxicity, cardiotoxicity, proteinuria, skin rashes, thrombosis, hypertension, myelosuppression, peripheral neuropathy, and interstitial lung disease.	[10][18]

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