Cancer Chemotherapy

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INTRODUCTION

Cancer is the second leading cause of death worldwide and its management continues to be a challenge for the medical community. Of approximately 50% of patients cured of cancers, 10-15% are contributed by chemotherapy[1]. Alongside surgery, radiotherapy and immunotherapy, chemotherapy has become one of the most vital tools in the management of malignancies especially in developing resource-poor countries where, in addition patients present late. Even though cancer cells demonstrate exponential growth pattern in-vitro; nutrient and space limitations in-vivo means that growth is not purely logarithmic[2]. Understanding tumour growth kinetics has thus led to the designs of more effective combination therapy and the necessity of monitoring minimal residual disease. Cancer drugs interfere with tumour growth by various mechanisms. Conversely, tumours may develop either primary or secondary (acquired) resistance to these drugs, hence the need for combinations[3]. Primary resistance is usually due to inherent genetic variation or mutation reducing the effective dose of the drugs; while secondary resistance develops after exposure to the drugs. Due to intrinsic differences in cancer cells and genetic differences in host pharmaco-kinetics and dynamics, chemotherapy is not uniformly beneficial in all patients just as the incidence and severity of side effects vary[2]. Table 1 shows the degree of response of common cancers to chemotherapy.

GENERAL PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer drugs are relatively non-specific, thus killing some normal cells that are rapidly-dividing; haematopoietic, gastrointestinal epithelium, lymphoid, hair follicles, spermatozoa and foetuses[2, 4]. Selectivity has therefore been an issue; with respite coming only recently with the development of molecularly-targeted drugs. However, cancer chemotherapy broadly aims to achieve differential tumour cell kill with minimal morbidity. To achieve this, unique leverages must be sought in innovative drug synergism. Table 2 outlines the principles of combination chemotherapy. Treatment protocols are usually in cycles lasting 2-4 weeks, with 4-6 cycles making up a course. This allows normal body tissue recovery while maintaining therapeutic efficacy. The implication of cell cycle kinetics on chemotherapy is shown in Table 3.

CLASSIFICATION OF CHEMOTHERAPEUTIC AGENTS BY MECHANISM OF ACTION

Alkylating Agents

They transfer alkyl groups to DNA, RNA and proteins, forming covalent bonds with the amino, carboxyl, sulfhydryl and phosphate groups[5]. Though CCnSA, they depend on cell division for activity. They have radio-mimetic properties and strong local vesicant effects causing local tissue necrosis, cytopenias, pulmonary fibrosis and haemorrhagic cystitis. Nitrosoureas in addition are highly lipid-soluble, easily crossing the BBB making them useful in neural tumours. They all exhibit cross-resistance except for the nitrosoureas[6]. The commoner chemotherapeutic complications are outlined in Table 4.

Nitrogen Mustards

Cyclophosphamide (CP) is the most widely used agent; converted to its active form in the liver. Some degree of neutropenia is an indication of drug absorption. The drug is highly lipid-soluble and so crosses the BBB. CP has prominent immunosuppressive action and causes alopecia and hemorrhagic cystitis; the latter being usually responsive to mesna. It is used mainly for haematologic, ovarian and breast cancers, and retinoblastoma[5]. Ifosfamide is a congener of CP with similar side effects but usually causing more cystitis (thus, it is routinely given with mesna). However, it causes less alopecia and is less emetogenic. It is useful for germ-cell testicular cancers. Chlorambucil is a slow-

malignancies. Melphalan is popularly used for myeloma, breast and ovarian cancers, and sarcoma[7]. Other nitrogen mustards are mechlorethamine and estramustine[8].
Busulfan (an alkyl sulphonate), unlike CP is more myelosuppressive and was used mainly for CML, but especially now for BMT in myeloproliferative disorders[9].

Platinum complexes

These include cisplatin, carboplatin and oxaliplatin. Cisplatin-based therapies have been quite successful in the treatment of testicular, ovarian, bladder and colorectal cancers. Carboplatin and cisplatin are structurally different accounting for their different toxicity profiles. Oxaliplatin shows no cross-resistance with the others[10] and has dose-limiting but reversible neurotoxicity. They may induce nephrotoxicity which is reduced by hydration.
Other alkylators include the nitrosoureas (carmustine, lomustine and streptozocin) and aziridine (thiopeta)[2,8].

Non-Classic Alkylators

Procarbazine is mainly used for HL but has leukaemogenic, teratogenic and mutagenic properties. Darcabazine is activated by liver enzymes and also used for HL and malignant melanoma. They also inhibit the synthesis of nucleic acids and proteins. Others include altretamine and temozolomide[11].

Antimetabolites

These are structural analogues of nucleic acid synthetic metabolites. Analogues of folate include methotrexate and premetrexed; of purines, mercaptopurine (6MP), thioguanine (6TG), fludarabine, cladribine and pentostatin; of pyrimidines, cytarabine, fluorouracil (5FU), floxuridine, cepacitabine and gemcitabine; and hydroxyurea (HU) which is a substituted urea[2,4]. HU is a versatile agent that was until recently the first-line drug for CML(12).

Folate analogues

These usually cause megaloblastic anaemia which can be reversed with folinic acid. Methotrexate is a very versatile agent used in breast, head and neck, GI and lung cancers. It is also effective for ALL, CNS leukemia, GTD and NHL[2].

Purine analogues

6-Mercaptopurine and 6TG, inhibit purine nucleotide inter-conversion. 6MP is commonly used for ALL, AML and CML; and 6TG for AML. Azathioprine, its analogue is an immunosuppressive agent. The dose of 6MP unlike 6TG should be reduced when co-administered with allopurinol to reduce toxicity. Fludarabine acts by inhibiting nucleic acid synthesis and causes apoptosis, and is mainly used for CLL. Cladribine causes DNA strand breakage. It is used commonly (as is pentostatin) for hairy cell leukemia[2,4].

Pyrimidine analogues

They also inhibit DNA synthesis. 5-Flourouracil (5FU) is a pro-drug whose activity is slightly reversed by thymidine. It is widely used for colorectal, stomach, pancreatic and breast cancers. Cytarabine is used for AML[8].

Natural Products

This broad category of naturally-occurring or semi-synthetic chemicals with anti-tumour activity. This includes antibiotics, microtubule agents, epipdophyllotoxins, camptothecin analogues and enzymes[2,4,8].

Antibiotics

Anthracyclines comprise two congeners daunorubicin and doxorubicin. They produce oxygen free radicals which may be responsible for their cardiotoxicity. Daunorubicin is less cardiotoxic but may cause discoloration of the sclera, finger-nails and urine. Both drugs cause more neutropenia than thrombocytopenia and are more efficacious in combination regimens. They undergo hepatic metabolism and induce RRR. They are commonly used for AML, ALL, breast and ovarian cancers.
Dactinomycin inhibits nucleic acid biosynthesis. It is useful in treating paediatric tumours and GTD. Like anthracyclines, it also induces RRR.
Bleomycin destroys nucleic acids. Its use is mainly for sarcoma, squamous cell and testicular cancers. It causes pulmonary toxicities and may contribute to renal dysfunction.
Other less commonly used antibiotics include mitoxantrone, mitomycin, epirubicin, idarubicin and valrubicin.

Microtubule agents

Vinca alkaloids are derived from the plant *Vinca rosea;* they arrest mitosis at metaphase. Vincristine is

commonly used for ALL, HL, NHL and childhood germ cell tumours. Unlike vinblastine, it is more neurotoxic than myelosuppressive. In addition to HL and NHL, vinblastine is used for GTD, testicular and breast cancers and Kaposi's sarcoma. Vinorelbine is active for non-small cell lung cancers (NSCLC)[13].

Taxanes are derived from yew plants and they enhance polymerization of tubulins. Paclitaxel and docetaxel have significant activity in NSCLC, Kaposi's sarcoma, and in relapsed breast and ovarian cancers[14]. Pre-medication is important to prevent hypersensitivity reactions.

Epipodophyllotoxins

These semi-synthetic drugs are derived from *Podophyllum peltatum* and inhibit topoisomerase II causing DNA strand breakage. They are highly protein-bound and widely distributed. Examples include etoposide and teniposide[2, 4]. They are used in SCLC and as second-line drugs in childhood ALL and testicular cancer.

Other natural products

L-Asparaginase is an enzyme used mainly in ALL. The camptothecin analogues, irinotecan and topotecan are used for colorectal and ovarian cancers respectively[15].

Other Anticancer Drugs

Retinoic acid derivatives: Tretinoin is specific for AML-M3 (APL); causing terminal differentiation of the promyelocytes, and is thus used in combination with other remission-inducing agents[4, 8]. Among other toxicities, it is teratogenic. Arsenic trioxide also induces differentiation and apoptosis in APL. It's also used in relapsed myeloma.

Mitotane is specifically cytolytic for adrenocortical cells and has found use in the treatment of adrenocortical cancer[16, 17].

Steroids and Hormonal Agents

Though, these are not cytotoxic drugs per se, but they play a prominent role in cancer chemotherapy usually as palliatives. They are also useful for hormone-dependent tumours and in lymphoid malignancies where they exert a direct lympholytic effect at high doses[18]. Hormones are valuable in the management of cancer-related hypocalcaemia, nausea and vomiting. Hormonal therapy is has its effect by receptor blockade or ablation of appropriate organs.

Oestrogen and Androgen Inhibitors

Tamoxifen is an oestrogen inhibitor for treating oestrogen-responsive tumours, though concurrent ablation surgery may be needed. Its metabolites also possess anti-tumour properties. Luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide or goserelin plus flutamide, bicalutamide and nilutamide are used to achieve complete androgen blockade in the treatment of prostate cancer[2, 4, 8]. They act by inhibiting a negative feedback mechanism.

Aromatase Inhibitors

Aminogluthetimide inhibits adrenal steroidogenesis and the conversion of androgens to oestrogens. Anastrozole is a more selective aromatase inhibitor and particularly useful in cancers that have progressed in spite of tamoxifen therapy. Exemestane, a steroid inactivator of aromatase, seems to lack cross-resistance with the other steroid inhibitors[4].

Immunotherapeutic and Molecular Targeting Agents

These are usually highly effective and selective free or conjugated agents.

Imatinib, a tyrosine kinase inhibitor specifically designed for Philadelphia-positive CML[4, 19] and Kit-positive GI stromal tumours[20], has been a huge success.

Monoclonal antibodies have also recently been added to the oncologists' arsenal. In this category, Rituximab (for $CD20^+$ B-cell NHL), alemtuzumab (B-cell CLL), trastuzumab ($Her2^+$ breast cancer), cetuximab ($EGFR^+$ colorectal cancer) and bevacizumab (colorectal cancer) have come into use.

Ancilliary medicaments

Amifostine is preferentially cytoprotective against xerostomia in patients receiving radiotherapy for head and neck cancers[4,8].

Growth factors

These are agents that have helped to reduce periods of cytopenia thereby ensuring the certainty of uninterrupted chemotherapy. Examples include filgrastim (G-CSF), sargramostim (molgramostim, GM-CSF) for neutropenia[21], thrombopoietin for thrombocytopenia[22] while darbopoietin and erythropoietin (Epo) are for anaemia[23].

TUMOUR LYSIS SYNDROME

This is one of the commonest complications in the clinical oncology. It tends to occur in the presence of large tumour load and associated necrosis which may be spontaneous or induced by cytotoxic therapies. It is caused by the rapid release of intracellular electrolytes and metabolites into the bloodstream which if uncorrected may lead to renal failure or even sudden death. The syndrome comprises hyperuricaemia, hyperkalaemia, hyperphosphataemia , hypocalcaemia and metabolic acidosis. A high index of suspicion helps to identify at-risk patients. Prophylaxis is with adequate hydration, urinary alkalinization and allopurinol at least 24-48 hours before therapy. Serial serum chemistries are important. Established cases will require aggressive electrolyte correction, hydration, haemodialysis and lately rasburicase, a new drug that degrades uric acid[2,4].

Table 1: Relative response of cancer cells to chemotherapy

High complete response High cure	High complete response Low cure	Low complete response Low cure
Hodgkin's lymphoma	AML	Non-small-cell lung cancer
ALL	Breast cancer	Colon cancer
Retinoblastoma	CML	Liver cell carcinoma
Testicular cancer	Ovarian cancer	Stomach cancer
Choriocarcinoma	Small cell lung cancer	Prostrate cancer
Childhood cancer	Sarcoma	Pancreatic cancer
Burkitt's lymphoma	Myeloma	Glioblastoma

Adapted from Stewart BW and Kleihues P, eds. World Cancer Report, Lyon, WHO/IARC, 2003 p. 281

Table 2: Principles of combination chemotherapy

1	Drugs active as single agents should be used; especially those that induce complete remission.
2	Drugs with different mechanisms of action; with additive or synergistic cytotoxic effects on the tumor.
3	Drugs with different dose-limiting toxicities, so that full therapeutic doses can be used.
4	Drugs should be used at their optimal dose and schedule.
5	Drugs should be given at consistent intervals, and the treatment-free period should be as short as possible to allow for recovery of the most sensitive normal tissues.
6	Drugs with different patterns of resistance should be used to minimize cross-resistance.

Adapted from Takimoto CH, Calvo E. Principles of oncologic pharmacotherapy. In: Cancer management: a multidisciplinary approach.; 2006. p. 23-42.

Table 3: Relationship of cell cycle to chemotherapy

Categories	Cell cycle-specific agents CCSA	Cell cycle-nonspecific agents CCnSA
Properties	Increasing EXPOSURE increases total cell kill	Increasing DOSE increases total cell kill
Examples	Vinca alkaloids; M-phase Antimetabolites; S-phase Antimitotic antibiotics; S-phase	Alkylating agents Steroids and Hormones Platinum complexes

Table 4: Major complications of cytotoxic chemotherapy

Common drugs in various Classes	Complications
Alkylating Agents	
Busulfan	Hyperpigmentation, pulmonary fibrosis, oligospermia & amenorrhoea
Cyclophosphamide	Haemorrhagic cystitis, oligospermia & amenorrhoea
Chlorambucil	Hepatotoxicity & dermatitis
Cisplatin	Nephrotoxicity & peripheral neuropathy,
Melphalan	Infertility & amenorrhoea
Anti-Metabolites	
Dactinomycin	Vesicant, hyperpigmentation, stomatitis & anorexia
Cytarabine	Megaloblastic anaemia, hepatotoxicity, abdominal pain, conjunctivitis, mucositis & anorexia
5-Flourouracil	Mucositis, gastroenteritis, malabsorption, hyperpigmentation, dermatitis & cerebellar ataxia
6-Mercaptopurine	Stomatitis, anorexia & cholestatic jaundice
Methotrexate	Mucositis, diarrhoea, haemorrhagic enteritis, hepatotoxicity, nephrotoxicity, pneumonitis & cerebral atrophy
Hydroxyurea	Rash, stomatitis, nephrotoxicity & megaloblastic anaemia
Vinca Alkaloids	
Vincristine	Neuropathies, constipation, abdominal pain & tissue necrosis
Antibiotics	
Adriamycin	Vesicant, red urine, hyperpigmentation, stomatitis & dose-limiting cardiomyopathy
Bleomycin	Pneumonitis, pulmonary fibrosis, hyperpigmentation, pruritus & nail changes
Corticosteroids	
Prednisolone, dexamethasone, hydrocortisone, etc	Peptic ulcer, GIT bleeding, DM, Cushing's syndrome, psychosis, hypertension, electrolyte imbalance, weakness, osteoporosis, childhood growth retardation, infections, polycythaemia & leucocytosis

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