The principles of cancer treatment by chemotherapy

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Abstract

Chemotherapy drugs exert their effects by interfering with the processes involved in cell division. Their therapeutic use stems from their ability to cause a greater proportion of cell kill in cancer cells as opposed to normal cells. In this article we discuss the clinical uses of chemotherapy, their mechanisms of action, important toxicities, and patterns of resistance.

Keywords Adjuvant; cell cycle; chemotherapy; clinical trials; palliative; resistance; toxicities

Cancer treatment involves one or more of surgery, radiotherapy and systemic therapy. In early stage disease, low-risk patients are often cured with surgery alone, but in many other cases a combination of treatments is required. In metastatic disease, systemic therapy is the principal therapeutic modality, as delivery through the blood stream facilitates access to disseminated cancer sites. Systemic therapies include hormonal therapy, targeted therapy, immune therapy and chemotherapy.

It is beyond the scope of this review to discuss all forms of systemic therapy. However, it is important to note that hormone therapy plays a significant role in the treatment of breast and prostate cancer. In addition targeted therapies, which have been developed from our understanding of cancer molecular biology and aberrant signaling pathways, are playing an increasingly important role in a number of tumour types. Tyrosine kinase inhibitors have shown promise in chemotherapy resistant tumours, such as renal cell carcinoma and gefitinib for epidermal growth factor receptor (EGFR) mutation-positive lung cancer. Immune therapy has also seen some major recent developments and monoclonal antibodies now play a key role in treatment for several cancers including B cell lymphomas, HER2 positive breast cancer and colon cancer. New antibodies targeting inhibitors of the immune system itself are showing great promise in several malignancies. One of these immunomodulatory antibodies, ipilimumab, is now approved after showing a significant survival benefit in metastatic melanoma.

In this article we review the classes of chemotherapy agents and their mechanism of action, clinical uses of chemotherapy, important toxicities and patterns of resistance.

Mechanisms of action

All cytotoxic chemotherapy agents exert their effects by disrupting the cell cycle by one or more processes. Cancer cells differ from normal cells by their ability to grow and survive. Acquired mutations to proto-oncogenes and tumour suppressor genes promote cell division because the normal cell cycle controls are lost. The cells become insensitive to growth inhibitory signals, and evade cell death.

The cell cycle has four stages: mitosis, gap-1, synthesis phase (S-phase) and gap-2. DNA synthesis occurs in S-phase, chromosomes then align, separate, and cell division takes place during mitosis.

Chemotherapy drugs cause cell death by apoptosis, either by directly interfering with DNA, or by targeting the key proteins required for cell division. Unfortunately, they can also be 'cytotoxic' to normal dividing cells, particularly those with a high turnover, such as the bone marrow and mucous membranes.

Chemotherapy drugs are classified in one of two ways — by their cell cycle effects, or by their biochemical properties. Those in the same biochemical class have a similar mechanism of action (Table 1). Classifying by their cell cycle specificity is useful because it influences how drugs are scheduled and combined for maximal effect (Figure 1). One example of a phase-specific agent is 5-fluorouracil (5-FU). Metabolites of 5-FU can both inhibit thymidylate synthase (an enzyme involved with DNA synthesis) or can be mis-incorporated into DNA in place of thymidine during DNA synthesis.[1] It is important that cancer cells are exposed to this drug during S-phase. Therefore, it is usually given as a prolonged infusion over days or as a daily tablet over weeks, maximizing its chances of exposure to tumour cells circulating into S phase over time. Other drugs such as cisplatin simply cause DNA damage at any point in the cell cycle and therefore prolonged exposure is not necessary.

The phase-specific agents usually have a dose—response effect up to a threshold, at which point dose escalation does not improve cell kill. The alkylating agents in contrast are non-phase specific, display a dose—response relationship and usually the threshold dose is limited by the toxicity to normal tissues.[2] These agents are used in high-dose chemotherapy regimes in chemosensitive disease, where the dose intensity is important to achieve a cure.

Combination chemotherapy

Most chemotherapy regimes in clinical practice consist of several agents from different classes in combination. There are a number of principles in generating an effective combination regimen:

- Different phases of the cell cycle are targeted to achieve maximal cell kill and there is less likelihood of resistance emerging.[1]
- The drugs used in combination should have activity against the tumour when used alone and those with maximal efficacy are preferred.
- Their mechanisms of action should be different to allow for additive or synergistic effects and dosed at their optimal dose and schedule.
- The toxicities should also be minimally overlapping, thus reducing the risk of life threatening toxicity to a single organ system.

Chemotherapy drugs are given at repeated, regular intervals know as treatment cycles. The scheduling of chemotherapy cycles is determined by the ability of normal tissues to recover and

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Biochemical classification of chemotherapy drugs

Drug class	Mechanism of action	Examples
Alkylating agents	Impair cell function by forming covalent bonds on important molecules in proteins, DNA and RNA. Classified by their chemical structure and mechanism of covalent bonding	Platinums (Cisplatin, Carboplatin, Oxaliplatin) Nitrogen Mustards (chlorambucil, melphalan) Oxazophosphorines (cyclophosphamide, ifosfamide)
Anti-metabolites	Structural analogues of naturally occuring metabolities involved in DNA and RNA synthesis. They either substitute for a metabolite that is normally incorporaated in to DNA or RNA or compete for the catalytic site of a key enzyme	Pyrimidine analogues (gemcitabine, 5-fluorouracil, capecitabine) Anti-folates (methotrexate, raltitrexed)
Anti-tumour antibiotics	Intercalate DNA at specific sequences, creating free radicals which cause strand breakage.Anthracyclines are products of the fungus Streptomyces, also have mechanism of action of topoisomerase I and II, required for the uncoiling of DNA required for DNA synthesis	Anthracyclines (doxorubicin, epirubicin), bleomycin, mitoxantrone
Topoisomerase inhibitors	Topoisomerases are enzymes that control the 3 —D structure of DNA. Topoisoerase I and Topoisomerase II are enzymes responsible for the uncoiling of DNA during replication	Topoisomerase I inhibitors (irinotecan, topotecan), Topoisomerase II inhibitors (etoposide)
Tubulin-binding drugs	Vinca alkaloids bind to tubulin, and prevent the formation of the microtubule, which is important during mitosis, but also for cell shape, intracellular transport and axonal function Taxoids prevents the disassembly of the microtubules, thereby inhibit normal function	Vinca alkaloids (vincristine, vinorelbine), Taxanes (paclitaxel, docetaxel)

Table 1

Actions of chemotherapy agents on the cell cycle

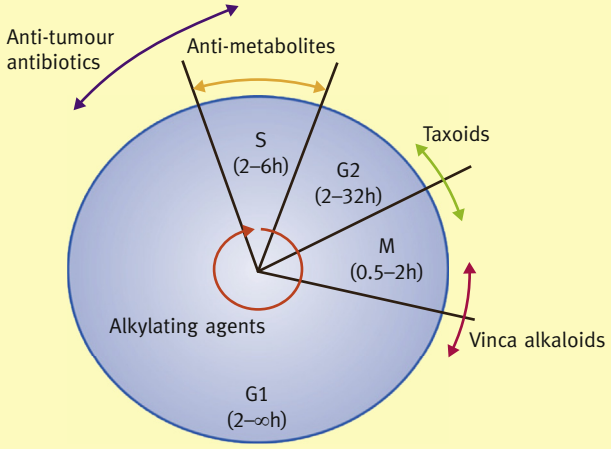

Figure 1 The cell cycle is divided into a number of phases G1, S, G2, and M, each of which can vary in length according to the type of cell and the growth rate of the cell. The activity of different classes of certain chemotherapy agents (antibiotics, anti-metabolites, taxoids, vinca alkaloids) are optimal in different phases of the cell cycle, whereas alkylating agents are relatively non-phase specific.

should be the shortest time possible. Each cycle kills a constant fraction of cells, not a constant number. Although there will be some repopulation between cycles, tumours have less capacity for repair than normal tissues. Therefore, repeated cycles of chemotherapy decreases the tumour population with time, but the interval between cycles allows normal cells to repopulate.

By the time a cancer is detectable, it contains approximately 10^8—10^9 cells and has undergone over 30 doublings to get to that stage.[1] Thus there is still a significant cancer burden once it has become undetectable and this is why many patients who have an apparent complete radiological response can relapse after a short interval.

Clinical uses of chemotherapy

Since their introduction in the 1940s there are now over 50 licensed drugs for the management of malignant disease.[3] The clinical uses for chemotherapy are determined by patient and tumour characteristics. In general, cure is only possible when chemotherapy is used in combination with surgery, either in the adjuvant or neoadjuvant setting. Treatment of metastatic disease is mostly with palliative intent, although there are some notable exceptions.

There is a wide spectrum of sensitivity to chemotherapy amongst different tumour types. As a general rule, rapidly dividing neoplasms are more chemosensitive. Although specific tumour sites such as testicular are generally regarded as