Cytotoxic chemotherapy: clinical aspects

Rob Jones

Abstract

Chemotherapeutic 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 than normal cells. In this review we discuss the clinical uses of chemotherapeutic agents, their mechanisms of action, important toxicities and patterns of resistance.

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

What's new?

- Molecular characterization of tumours is leading to better personalization of systemic therapies
- Biopsying of multiple metastatic sites in the same patient has proven a high degree of tumour heterogeneity within each patient
- Understanding of tumour immunology has led to the development of immune checkpoint inhibitors
- Immune checkpoint inhibitors have improved survival in lung cancer and melanoma

Introduction

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 bloodstream facilitates access to disseminated cancer sites. Systemic therapies include hormonal therapy, targeted therapy, immune therapy and chemotherapy. Hormone therapy plays a significant role in the treatment of breast and prostate cancer and is discussed in *Hormonal Therapy for Cancer* on pages 30–33 of this issue.

In addition targeted therapies, which have been developed from our understanding of cancer molecular biology and aberrant signalling pathways, are playing an increasingly important role in a number of tumour types (see *The Biology of Cancer* and *Targeted Therapy in Cancer* on pages 1–5 and 34–38 respectively of this issue). Tyrosine kinase inhibitors have shown promise for chemotherapy-resistant tumours, such as renal cell carcinoma, as has 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, human epidermal growth factor receptor-2 (HER-2)-positive breast cancer and colon cancer. New antibodies targeting inhibitors of the immune system itself are showing huge promise in several malignancies. Three classes of immunomodulatory antibodies targeting programmed death ligand-1 (PD-L1), programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA4) are entering clinical practice for lung cancer and metastatic melanoma types (see *The Biology of Cancer* and *Targeted Therapy in Cancer* on pages 1–5 and 34–38 respectively of this issue).

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In this article we review the clinical uses of conventional cytotoxic chemotherapy, important toxicities and patterns of resistance.

Combination chemotherapy

Most chemotherapy regimens in clinical practice consist of several agents from different classes used in combination (see *Principles of Systemic Anticancer Therapy* on pages 20–24 of this issue). A summary of different drug classes and how they act on the cell cycle can be seen in Figure 1 and Table 1. 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 they should be 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.

Chemotherapeutic drugs are given at repeated regular intervals known as treatment cycles. The scheduling of chemotherapy cycles is determined by the ability of normal tissues to recover and should be the shortest time possible.

Clinical uses of chemotherapy

From their introduction in the 1940s there are now over 50 licensed drugs for the management of malignant disease.[2] The clinical uses of 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 among different tumour types. As a general rule, rapidly dividing neoplasms are more chemosensitive. Although specific tumour sites such as testicular tumours are generally regarded as exquisitely chemosensitive, it is becoming increasingly clear that

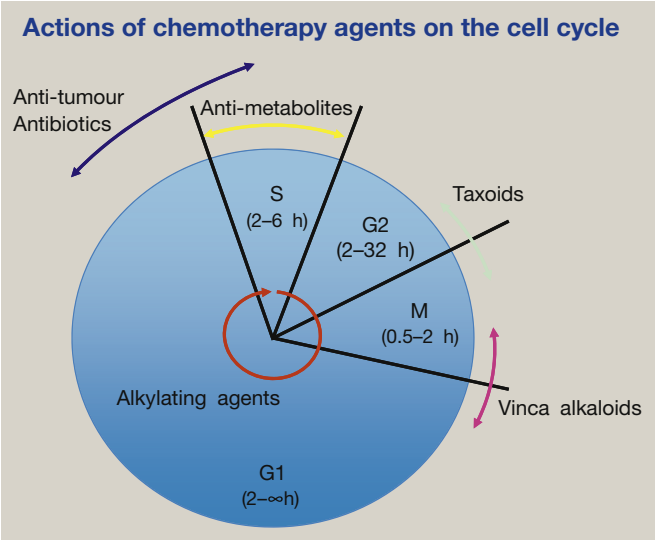

Figure 1 The cell cycle is divided into a number of phases — G1, S, G2 and M — each of which can vary in length according to the type of cell and the growth rate of the cell. The activity of different classes of certain chemotherapeutic agents is optimal in different phases of the cell cycle, whereas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

tumours of the same histological type can also display different patterns of chemosensitivity and behaviour. Cancer diagnosis is thus evolving from an emphasis on the organ and morphology, to include biological features based on the differential expression of proteins in or on cancer cells. This is of particular relevance to the new targeted therapies. For example, breast cancer patients are now routinely tested for the presence of the oestrogen receptor and expression of *HER-2*, which will predict their response to hormonal therapy and trastuzumab and also provides prognostic information. In colorectal cancer, the absence of the RAS mutation can predict the response to cetuximab, an antibody targeting the EGFR.

Metastatic disease

Excluding germ cell tumours and lymphomas, most patients with solid tumours diagnosed with metastatic disease are not curable and treatment is with palliative intent. In the case of germ cell tumours and a number of haematological malignancies maintaining dose intensity during treatment is paramount, and in cases where conventional dose chemotherapy fails, high-dose chemotherapy is often used to try and enhance the chance of cure.

For all other tumour types cure is not possible with chemotherapy alone. However in certain circumstances, such as those patients who have oligo-metastases, eradication of the cancer can be occasionally achieved if there is a good response to chemotherapy and a subsequent successful surgical resection. A good example of this is the treatment of potentially resectable liver metastases in colorectal cancer. For other cases of metastatic disease the aim of treatment is to prolong survival, delay the time to disease progression and improve quality of life. Examples of well-established palliative chemotherapy regimens are found for breast, colorectal, lung, ovarian, prostate, bladder and head and neck cancers.

Response rates for single-agent therapy are usually around 15–20%, and although there are some patients who have a substantial response with a significant improvement in symptoms and survival, there are also those who do not get any benefit from treatment and only suffer its adverse effects. Treatments are only continued if patients are genuinely benefitting and the toxicities are acceptable. Combination chemotherapy improves the response rates at the cost of increasing toxicity and is decided

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.	Cisplatin, carboplatin, chlorambucil, cyclophosphamide, ifosfamide
Anti-metabolites	Structural analogues of naturally occurring metabolities involved in DNA and RNA synthesis. They either substitute for a metabolite that is normally incorporated into DNA or RNA or compete for the catalytic site of a key enzyme.	5-Fluorouracil, methotrexate, pemetrexed, mercaptopurine, gemcitabine
Antitumour 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.	Bleomycin, anthracyclines (doxorubicin, epirubicin)
Topoisomerase inhibitors	Topoisomerases are enzymes that control the 3-D structure of DNA. Topoisomerase 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. Taxanes prevent the disassembly of the microtubules, thereby inhibiting normal function.	Vinca alkaloids — vincristine, vinorelbine Taxanes — docetaxel, paclitaxel

Table 1