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Principles of Chemotherapy

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The history of the development of chemotherapy

Chemotherapy is the term given to refer to any drug or chemical treatment used to treat any disease. Cytotoxic (or anti-neoplastic) chemotherapeutic agents are used to treat malignancy.

The development of cytotoxic chemotherapy at the beginning of the twentieth century revolutionised the treatment of cancer, especially the treatment of disseminated disease such as leukaemia. Crucial to the development of cytotoxic chemotherapy was the discovery that certain chemicals acted chiefly on any rapidly dividing cells, and this includes cancer cells. During the First World War it was noted that soldiers who were exposed to nitrogen gas developed an abnormally low white cell count. A derivative of nitrogen gas, nitrogen mustard was first used as an anti-cancer treatment in the 1940s. Many of the cytotoxic drugs used today were discovered incidentally when developing drugs for other purposes, while others have been developed specifically to interfere with metabolic pathways.

Cell cycle

To understand the principles of chemotherapy and how it works, it is important to have a basic understanding of the normal cell cycle. The cell cycle is an ordered series of events that involves several sequential phases. The purpose of the cell cycle is for cells to reproduce themselves, to replace dead or injured cells and add new ones during tissue growth.

There are two types of cell division, somatic and reproductive, and these have different goals. Somatic cell division involves all cells except for germ cells involved in reproduction. In somatic cell division, each cell duplicates its contents and divides into two identical cells through a nuclear division process called mitosis. The cell cycle consists of two main periods: interphase, when the cell is not dividing, and the mitotic (M) phase when the cell is dividing.

Interphase

The cell replicates its DNA during this period of rapid growth. Interphase has three phases: G¹, S

and G^2 . S phase is concerned with the synthesis of DNA and the G phases are gaps or interruptions in DNA replication.

1. G^1 phase. This is the interval or gap between the mitotic stage and the S phase. The cell is preparing for DNA synthesis and is metabolically active through the synthesis of RNA and protein. This stage may last from 8 to 10 hours; however, some cells remain in this phase for a longer time and are considered to be in the G^0 or resting phase.
2. S phase. Once a cell enters this phase, it is committed to go through cell division. The S phase is between G^1 and G^2 and lasts approximately 8 hours. This is the phase of DNA synthesis when the DNA replicates, ensuring that the two cells being formed are made of the same genetic material.
3. G^2 phase. This is the gap between S phase and mitosis, which will give rise to two daughter cells. This phase may last for 4 to 6 hours. Cell growth continues and enzymes and other proteins are synthesised in preparation for cell division.

M phase (Mitosis)

This phase results in the nucleic and cytoplasmic division that produces two identical, or daughter, cells. This may be broken down into four distinct phases: prophase, metaphase, anaphase and telophase, culminating in cytokinesis or the division of cytoplasm that creates two new cells.

The sequence of events in the cell cycle is shown in Figure 1.1:

G^1 Phase $\rightarrow$ S phase $\rightarrow$ G^2 phase $\rightarrow$ M phase
(Mitosis) $\rightarrow$ Cytokinesis $\rightarrow$ two new cells

Most cancer cells are characterised by their ability to divide uncontrollably. Cytotoxic chemotherapy interferes with cell division at various points in the cell cycle, affecting both cancer cells and other rapidly reproducing cells. This knowledge has enabled the development of drugs which either act specifically during one point of the cell cycle (cell cycle phase-specific) or which have some effect during all phases of the cell cycle (cell cycle non-phase-specific). Cell cycle non-specific

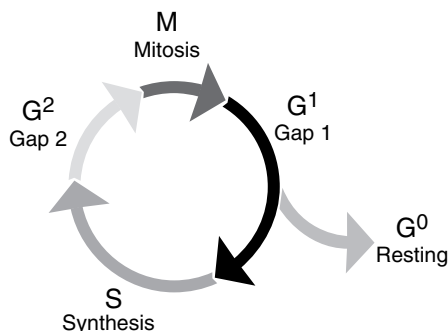


Figure 1.1 The cell cycle.

Source: Tortora & Derrickson; 2005; Fischer *et al.*, 2003; Rang *et al.*, 2003

chemotherapeutic agents (specifically the alkylating agents and platinum compounds) are also effective against cells in the G^0 phase which are not actively dividing. This group of drugs has been particularly effective against slow-growing tumours (Fischer *et al.*, 2003).

Cell cycle time

The overall objective in any cancer treatment plan is patient survival and the eradication of tumour cells, with minimal disruption to normal cell activity. It is known that tumours have a steady, progressive growth pattern which is affected by cell cycle time, growth fraction and cell loss. Chemotherapy has a greater effect on rapidly dividing cells. Cancer cells appear to have an initial rapid, proliferative phase during which time cells will be cycling quite quickly from mitosis to mitosis. The time it takes for each cycle to complete varies between 24 and 120 hours, depending on cell type.

Age and developmental status are known to influence cellular proliferation. Children and young people are growing, so have more body tissues with a dividing cell population; this helps to explain why paediatric malignancies appear to be more receptive to chemotherapy and more susceptible to the adverse side effects that may follow (Ettinger *et al.*, 2002).

Growth fraction

The growth fraction represents the percentage of cells undergoing division at any one time.

During early tumour development (when tumour bulk is small) there is a high fraction of dividing cells and tumours are able to double their size rapidly. As tumours grow in size, the blood, oxygen and nutrient supply become compromised and space for growth is restricted. During this time the cell growth fraction is low and the cycle time is slowed, therefore the doubling time is decreased (Ettinger *et al.*, 2002). Chemotherapy is more effective against rapidly dividing cells, so may be less effective when tumours reach this stage. It is thought, however, that it may be possible to increase both cell growth fraction and cell cycle time by achieving an initial tumour reduction, either through chemotherapy, radiotherapy or surgery. This would stimulate trigger mechanisms on the cell surfaces to recruit cells back into the cycle in an attempt to replace the lost bulk. Once this has been achieved, chemotherapy can once again become effective against reduced tumour bulk (Ettinger *et al.*, 2002). It can be concluded therefore that doubling times can vary greatly between different tumours and that chemotherapy-sensitive tumours tend to grow faster than slow-growing ones that are less sensitive to chemotherapy (Tortorice, 2000).

Pharmacokinetics and pharmacodynamics

Pharmacokinetics is the study of drug absorption, distribution, metabolism and excretion, or the movement of drugs within the body (Ettinger *et al.*, 2002). Pharmacokinetics therefore plays an important role in the successful application of cancer chemotherapy. Although some tumours may be known to be sensitive to a given cytotoxic agent, that agent may still fail to achieve a response. An understanding of how a patient's body is able to deal with a particular drug is essential in determining dose, timing and route of administration. Individual patients may demonstrate variable responses to therapies due to a variety of factors such as altered organ function. The pharmacokinetic behaviour of cytotoxic drugs has not been extensively evaluated in children; however, improved techniques have led to an increased emphasis on measuring the concentration of various drugs through pharmacokinetic studies (Balis *et al.*, 2002).

Pharmacodynamics is the study of the relationship between drug concentration and drug effect. It may therefore be possible to give a particular drug either as a bolus or as an infusion and achieve a completely different therapeutic or toxic effect (Ettinger *et al.*, 2002).

There is a very close link between the anti-tumour and toxic effects of chemotherapy; this means that the difference between an effective and a toxic dose can be very small. The aim of any chemotherapeutic schedule is therefore to gain the greatest anti-tumour effect with an acceptable level of toxicity (Ettinger *et al.*, 2002; Boddy, 2004).

An understanding of these two principles highlights the importance of careful and regular monitoring of the patient before each course of treatment so that doses can be modified accordingly.

Protocol development and clinical trials

Childhood cancer is very rare; hence the best way to search for better treatments is to conduct multi-institutional trials within a co-operative group, this may be either national or international. In the United Kingdom trials are co-ordinated by the Children's Cancer and Leukaemia Group (CCLG). It is the work of this organisation that has resulted in a 70% cure rate for all childhood cancers (Sposto, 2004). The advantage of multi-institutional collaboration is that patient accrual is quicker, allowing for faster, reliable conclusions to be made (Ablett, 2004a). Co-ordination of trials reduces duplication and allows prompt evaluation of new agents and ways of giving treatments.

Clinical trials

There are few conditions for which treatment is known to be 100% effective; this gives great potential for making improvements. Improvements to prescribed treatments can be determined via a clinical trial. A clinical trial is a planned experiment that is designed to discover the most appropriate treatment for patients with a given condition (Ablett, 2004a).

All clinical trials are described in a protocol document. This protocol will outline information

relating to the purpose, design and conduct of the trial, including which patients are eligible, which treatments are to be evaluated and how each patient's response will be evaluated. Trial data will be analysed to evaluate the patient outcome with a given treatment regime. The patient outcome may be measured in terms of length of time to death or relapse. As outcomes improve, many childhood cancer trials aim to reduce the morbidity of treatment while maintaining its efficacy (Sposto, 2004).

Any research involving human subjects is subject to strict regulations. The European Union Directive on Good Clinical Practice (GCP) was implemented in May 2004. This is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. GCP affects everyone working in clinical trials, whether in the pharmaceutical industry or academia. Failure to comply with certain elements of the legislation constitutes a criminal offence. These regulations have therefore affected all staff working with clinical trials involving the treatment of childhood cancer and resulted in additional training and working within agreed standard operating procedures (Ablett, 2004b).

Clinical trials fall into four phases:

1. Phase I to determine an acceptable drug dosage
2. Phase II to provide evidence of efficacy of treatment
3. Phase III to compare efficacy/side effects with those of other drugs/treatments
4. Phase IV large-scale epidemiological study (mainly industry).

Phase I studies

Phase I studies are the first trials in humans. They may be viewed as toxicity screening studies, where following testing in laboratories, a new drug is administered to human subjects to determine the maximum tolerated dose and any dose-limiting toxicities. The first human studies are undertaken in adults, but as children often have different tolerance patterns for chemotherapy drugs, the paediatric dose cannot be accurately extrapolated from the results of adult trials. Phase I trials are undertaken in paediatrics, but only children who have failed to respond to conventional treatments

are eligible for entry. Pharmacokinetic data are frequently collected, via serial blood and urine sampling, to determine the absorption, bioavailability and excretion patterns for the new drug.

Phase II studies

These aim to determine the potential efficacy of the new drug in different types of cancer. The maximum tolerated dose is given to a statistically defined number of children with a variety of relapsed or refractory cancers, and response is monitored. The goal of a phase II study is to identify which drugs warrant further study in a given tumour type.

Phase III studies

In childhood cancer, these phase III studies are the large-scale multicentre or international randomised trials into which the majority of children in the United Kingdom will be entered at the time of diagnosis. Large numbers of children will either be given a new drug or previously used drugs in a new combination or at a new dose. These new elements are usually in combination with standard therapy, to determine whether significant survival benefit is achieved by its addition to the previous 'best known' treatment or whether the new treatment is better than the standard one (Ablett, 2004a).

Considerations when planning chemotherapy treatments

Drug resistance

There is a wide variety of therapeutic responses and unacceptable toxicities in patients receiving chemotherapy (Tortorice, 2000). Some cancer cells demonstrate either an intrinsic or an acquired resistance to chemotherapy. Several mechanisms of drug resistance in cancer cells have been identified:

- decreased drug uptake by the cell;
- increased efflux (flow outwards) of drug out of the cell;

- detoxification of drugs in the cell secondary to metabolic changes;
- increased DNA repair;
- alterations in the structure of drug receptor sites or targets;
- decreased sensitivity to apoptosis (programmed cell death);
- multidrug resistance gene from genetic mutation following exposure to particular chemotherapeutic agents.

(Ettinger *et al.*, 2002)

It has been identified that resistant malignant cells contain the gene known as the multidrug resistance (MDR) gene. In intrinsic resistance the MDR gene is present from the onset, whereas the gene is the result of genetic mutation following exposure to chemotherapy in acquired cases. These resistant cells have a protein called P-glycoprotein present on the cell surface. This protein acts as an efflux pump, rapidly pushing through and eliminating the chemotherapeutic agents from within the cell, preventing their therapeutic effect.

In order that the risk of resistance is kept to a minimum, it is recommended that chemotherapy is administered at maximum dose intensity. This means that chemotherapy schedules should be constructed to offer the maximum tolerated dose with the smallest possible interval between doses. Advances in supportive care, such as colony stimulating factors and powerful antibiotics, have helped to make these dose-intensive protocols possible (Balis *et al.*, 2002; Ettinger *et al.*, 2002).

Toxicities

Chemotherapeutic agents have the same cytotoxic effect on both normal and malignant cells. This cell toxicity is often dose-limiting and restrictive. Normal cells need to have the opportunity for recovery between treatments to avoid life-threatening toxicities or those threatening quality of life which may be unacceptable to patients, both in the short and long term. Even in the presence of drug resistance, unacceptable toxicities may still occur because of the toxic effects of chemotherapy on normal cells.

Several toxicities are common to the majority of cytotoxic drugs, for example, myelosuppression,

nausea and vomiting, and alopecia. These acute toxicities are usually reversible. Some drugs also have unique toxicities affecting specific organs or tissues, such as cardiotoxicity which is associated with anthracyclines. Many of these unique toxicities are cumulative and in some cases irreversible (Balis *et al.*, 2002).

The severity of any toxicity is an important factor when planning a treatment protocol. It is usual therefore to combine drugs that have differing side effects, for example, a non-myelosuppressive drug such as vincristine may be combined with myelosuppressive ones without compromising the dose of either drug (Balis *et al.*, 2002).

In the palliative stages of disease, when cure is no longer the aim of treatment, careful consideration needs to be given to ensuring that the balance between an achievable quality of life is weighed up against the toxic side effects of any treatments given. It is possible that toxicity deemed acceptable during active therapy may prove unacceptable for the dying child (Hain and Hardy, 2004).

Treatment approaches

The ultimate aims of treatment for all patients are cure and quality of life. There are many approaches to treatment that will be used to achieve this aim.

Single agent versus combination

It has long been acknowledged that combination drugs regimes significantly increase the chance of complete remission (Balis *et al.*, 2002). This is because combination regimes offer a way to overcome drug resistance to individual agents. When different drugs are used to treat a particular tumour, it is usual to select those that have different toxic effects, as this helps to reduce the treatment-related morbidity.

Adjuvant chemotherapy

Adjuvant chemotherapy is a term sometimes used to describe therapy that is used in addition to other modalities of treatment, such as surgery or radiotherapy. This is particularly effective in patients

who have a high risk of relapse at metastatic sites, for example, those with solid tumours (Ettinger *et al.*, 2002).

Neo-adjuvant chemotherapy

This is the term used to describe chemotherapy that is given prior to definitive localised therapy such as surgery or radiotherapy in an attempt to reduce the tumour bulk, thus facilitating less radical surgical or radiotherapeutic interventions. Chemotherapy used in this way will also provide earlier treatment of micrometastatic disease (Balis *et al.*, 2002; Ettinger *et al.*, 2002). It is also possible to identify which chemotherapeutic agents are effective against a particular tumour in a particular patient. Further courses of chemotherapy are frequently prescribed once recovery from definitive localised treatment has been attained.

Dose-intensive regimes

One way of overcoming drug resistance is to ensure that drugs are administered at the maximum drug intensity. Dose intensification can be achieved in two ways. By alternating myelotoxic drugs with non-myelotoxic ones, given at the neutropenic nadir, it is possible to continue cytotoxic onslaught on malignant cells while permitting bone marrow recovery. Another approach is to reduce the duration of marrow aplasia by combining intensive chemotherapy with the administration of colony-stimulating factors (Scurr *et al.*, 2005).

Combination chemotherapy

Drugs used in combination may have an enhanced effect against malignant cells; however, it is not completely understood why this is (Ettinger *et al.*, 2002). Tumour cells do not progress through the cell cycle at the same time, so it is important to select agents that exert their antineoplastic effects at different stages of the cell cycle. The objective of any regime is to achieve maximum tumour cell kill without excessive toxicity. Drugs with

different toxicities will be chosen wherever possible, however, if overlapping toxicities are unavoidable, for example, bone marrow depression, it may be necessary to reduce doses or extend the period of time between cycles (Tortorice, 2000).

Reducing doses

High-dose therapies have been responsible for many of the improvements seen in the treatment of childhood cancers. Randomised studies are now being conducted which set out to identify whether some children can be treated at lower doses without reducing efficacy, for example, the current treatment trial for treating acute lymphoblastic leukaemia (Medical Research Council, 2003) sets out to identify low-risk children by looking at minimal residual disease at various points in the induction period of treatment. The main focus is to attempt to reduce the cumulative, dose-related cardiotoxic effects of the anthracyclines and the risk of infertility and secondary malignancies associated with alkylating agents. It is hoped that the optimum balance between effective treatment and low toxicity can be achieved by reducing the total doses given, by substituting less toxic analogues of effective drugs and, where possible, by avoiding anthracyclines or alkylating agents completely. Children who are participating in these studies will require particularly close monitoring for response, in order that treatment may be modified back to the standard therapy if necessary.

Chemoprotective agents

Cytotoxic chemotherapy is extremely toxic and has many unwanted side effects. Some side effects, such as nausea and vomiting and alopecia, are unpleasant but are reversible and not life-threatening. Bone marrow depression can be life-threatening but is usually reversible, especially if doses are modified. There is a group of toxicities that are potentially life-threatening and can cause irreversible damage to normal cells, for example, the cardiotoxic effects of anthracyclines. Much interest has therefore been generated in the development of drugs that may block the toxic effects of chemotherapeutic agents while

maintaining their antineoplastic properties. These developments include both chemoprotective and rescue agents for drugs such as doxorubicin (liposomal preparations and cardio-protective agents), ifosfamide (mesna) and methotrexate (folinic acid) (Boddy, 2004).

Administration schedules

Prolonged drug administration has been explored as an additional way of reducing toxicity. The toxicity associated with peak serum levels in some drugs, such as the anthracyclines, is thought to be reduced by slow administration; this may be over several days. However, the relative benefits of these regimes over shorter infusions have yet to be substantiated, mainly because other short- to medium-term side effects, such as mucositis, are enhanced with prolonged infusion time (Boddy, 2004; Scurr *et al.*, 2005).

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