What is cancer chemotherapy?

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Acta Oncologica Vol. 40, No. 2/3, pp. 166–174, 2001

The importance of chemotherapy for cure of cancer is increasing, especially with its use as adjuvans to local therapy. Furthermore, in advanced disease, when the tumour has disseminated from its place of origin, chemotherapy has an expanding role in efforts to relieve cancer-related symptoms and to prolong life. Despite its shortcomings, chemotherapy, therefore, is an important treatment modality in oncology and will probably remain so for considerable time. This presentation, within the frame of The Swedish Council on Technology Assessment in Health Care (SBU) project to review cancer chemotherapy, aims to provide a brief overview of the field cancer chemotherapy. It includes a historical perspective of cancer chemotherapy, some practical aspects and theoretical considerations with respect to the action of, resistance to and metabolism of these drugs. Furthermore, some outlooks into the nearest future with respect to ways to improve and develop cancer chemotherapy are provided as well as some aspects of chemotherapy from an employee-protection perspective.

A HISTORICAL PERSPECTIVE ON THE DEVELOPMENT OF CHEMOTHERAPY

Treatment of cancer with chemicals goes back several hundred years, but it was not until the 1940s that the first successful and documented use of systemic chemotherapy took place. Based on warfare experience of toxic effects of nitrogen mustard on the lymphatic system, this agent was used for treatment of a patient with lymphoma. Although the tumour rapidly relapsed after an initial pronounced antitumour effect, this experience marked the beginning of chemotherapy of malignant tumours (1). A number of agents have been developed since then and the 44 cytotoxic drugs approved in Sweden 2000 are detailed in Table 1 according to suggested modes of action. The introduction, defined as the year for approval by the Medical Products Agency, of new cytotoxic drugs up to 2000 seems to have been somewhat more rapid during the 1990s than earlier as shown in Fig. 1. Forty-six drugs are included in this figure, the additional two being liposomal preparations of old drugs.

Nitrogen mustard belongs to the largest group of drugs, acting through alkylation of DNA. Increasing knowledge in the biochemistry of cellular metabolism (2) led to development of the antimetabolites during the following decades, e.g. methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine and 5-fluorouracil. The 1960s and 70s saw the arrival of natural agents like the antibiotics actinomycin D and doxorubicin and extracts from the periwinkle plant, the vinca alkaloids (2).

A milestone in modern chemotherapy was the introduction of cisplatin in the late 1970s, which considerably changed the outlook for patients with, e.g. testicular cancer. It was later found to be useful also in the treatment of other solid tumours (3).

During the recent decade, some new drugs that may contribute substantially to the treatment options have been introduced, among them the taxanes (4), with high activity in breast cancer, and topoisomerase I inhibitors (5). Furthermore, the antimetabolites fludarabine and cladribine

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 ISSN 0284-186X

have extended the treatment options for some types of lymphomas (6).

The process of new drug development is slow and only a few drugs per year at best are added to the therapeutic arsenal. From the timepoint of discovery of anticancer activity of a compound to approval for use in patients, 20–30 years have elapsed for the most recently introduced drugs. Following the introduction of a new cytotoxic drug after approval, clinical studies continue to further define patient benefit with respect to, e.g. survival and symptom relief in various malignancies. The time frame for the development of new cytotoxic drugs is, thus, considerable.

CHEMOTHERAPY IN PRACTICE

Cancer chemotherapy refers to the administration of cytotoxic chemicals, i.e. chemicals with cell killing properties, with the aim to, in some cases, eradicate the tumour or, at least, reduce the tumour burden and, thereby, reduce the tumour-related symptoms and perhaps prolong life. Cytotoxic drugs are mostly given by the intravenous route. This has proven to be the safest way to safeguard tumour exposure to cytotoxic drugs but oral administration is an alternative for some drugs. In the case of tumours limited to an anatomical region, cytotoxic drugs are sometimes adminstered only into this region, e.g. the abdominal cavity, the spinal fluid or via blood vessels into an extremity. In this way, the dose used can be higher, with the hope of achieving a better antitumour effect.

Table 1

Cytotoxic drugs approved for marketing in Sweden in 2000 according to generic names and principal mechanism of action

Alkylators and alkylator-like drugs	Topoisomerase inhibitors
Cyclophosphamide	Etoposide
Ifosfamide	Teniposide
Chlorambucil	Topotecan
Melphalan	Doxorubicin
Epirubicin	Daunorubicin
Busulfan	Idarubicin
Thiotepa	Amsacrine
Mitoxantrone	Actinomycin D
Lomustine	Irinotecan
Cisplatin	
Carboplatin	
Mitomycin C	
Dacarbazine	
Temozolomide	
Altretamine	
Oxaliplatin	
Antimetabolites	Microtubule interacting agents
Methotrexate	Vincristine
Mercaptopurine	Vinblastine
Thioguanine	Vindesin
Cladribine	Vinorelbine
Fludarabine	Paclitaxel
Cytarabine	Docetaxel
Fluorouracil	Estramustine
Gemcitabine	
Hydroxycarbamide	
DNA interaction	Amino acid depletion
Bleomycin	Asparaginase
Membrane perturbation	
Miltefosine	

Cytotoxic drugs are mostly given in specified combinations of two or more drugs with the aim to increase the possibility to overcome tumour cell resistance, procure the activity of the regimen against different tumour cell clones and to avoid pronounced toxicity from normal tissues (7). Development of the various chemotherapy regimens has so far mainly been based on empirism.

The selection of a chemotherapeutic regimen for an individual patient has so far been based on tumour histology and data from clinical trials including many patients, indicating which therapeutic option is the best for the average patient. According to this concept, the individual patient's treatment response can only be determined after some cycles of chemotherapy have been attempted. This is problematic in that a patient with an often short expected survival has a high risk of contracting serious side-effects, leading to decreasing quality of life before a possible gain from the therapy can be evaluated.

Unfortunately, the tumour types in which cytotoxic drugs may provide cure from metastatic disease are few and encompass a minority of patients with advanced disease, as indicated in Table 2. In more tumours, including some of the major types of the western world, chemotherapy prolongs survival and provides symptom relief. For a third group of tumours, chemotherapy at best provides relief from some tumour-associated symptoms. A considerable proportion of patients will not achieve a substantial tumour response but will only experience side-effects. For some tumour types, the proportion of patients that benefit may be as low as 20%, even when choosing the best established therapeutic regimen. No medication in common use has a narrower therapeutic index than the antineoplastic drugs, i.e. the difference between doses giving an antitumour effect and those giving life-threatening toxicity is very small. In fact, it is essentially impossible to achieve tumour remission without a risk for potentially life-threatening adverse effects.

The standard method for evaluation of the efficacy of chemotherapy has been the objective evaluation, mostly by means of radiology, of the change in tumour volume over treatment time. The complete disappearance of the tumour, denoted complete remission (CR), is, with an exception for some of the more rare tumour types infrequent in advanced disease but is a prerequisite for the chance of cure. A more than 50% reduction in tumour volume, denoted partial remission (PR), may or may not lead to life prolongation, but is often accompanied by symptom relief. The sum of per cent CR and PR for a specified

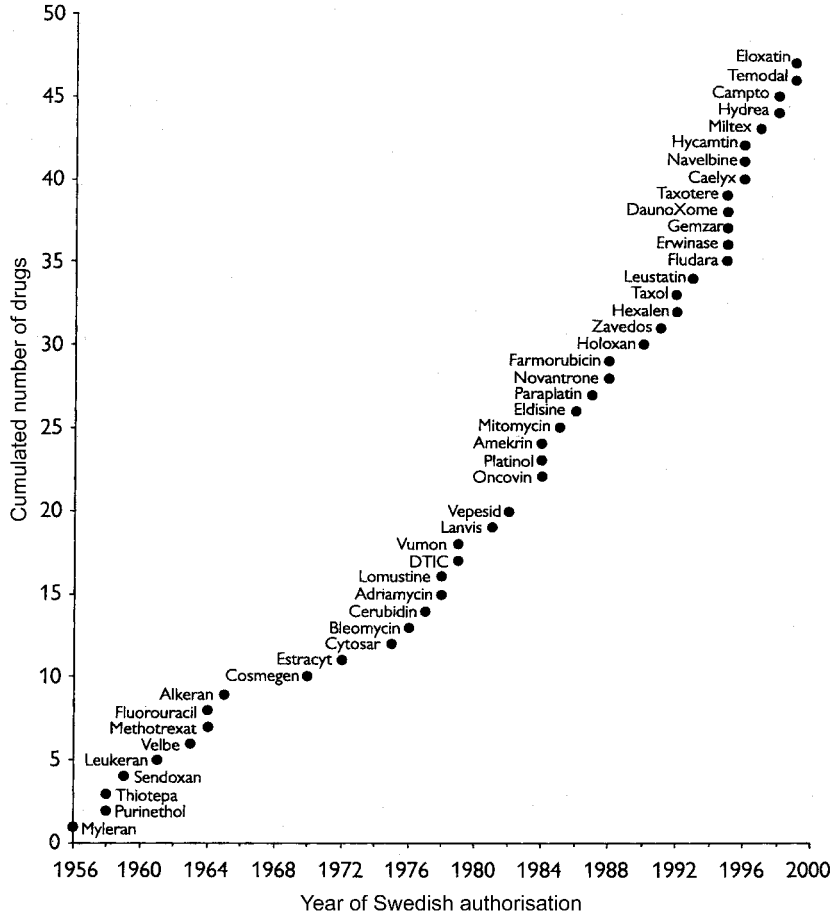

Fig. 1. Cytotoxic drugs (Swedish trade names) available for use in Sweden 1999 according to year of authorisation.

treatment and diagnosis has been the standard measure to indicate therapeutic efficacy. Unfortunately, the true value of tumour remission as a surrogate for patient benefit, e.g. in terms of symptom relief and survival prolongation, has not been extensively studied (see also (9) for a more extensive discussion).

Chemotherapy is currently used in 4 principally different settings (7). In advanced and in some cases also localised disease, chemotherapy is used as *induction therapy* with the aim to reduce the tumour volume as much as possible and achieve clinical effects ranging from symptom relief to cure, depending on tumour type. In *adjuvant therapy* the chemotherapy is added after controlling the primary tumour with, e.g., surgery or radiotherapy, with the aim to eradicate any tumour cells that might have escaped from the primary tumour and could regrow to form metastases in the future. In this setting, the aim is to increase the number of cured patients. In *preoperative therapy* the chemotherapy is given for a localised inoperable tumour prior to surgery, with the aim to increase the chance of achieving local tumour control. In *neoadjuvant therapy*, which is also given preoperatively, the aim is to achieve a better long-term tumour control of a tumour that is operable by effects on microscopic disesase. Chemotherapy can also be given as *instillations*, usually as an add-on to general therapy, into sanctuarities with the aim to increase the chance for tumour cell eradication and control at that site.

The adjuvant setting is principally different from the others in that the patients treated often are cured by the local treatment only. This poses a special ethical dilemma in that a number of already cured patients have to go through a treatment with potentially serious acute and long-term adverse effects.

A chemotherapy regimen is specified with respect to cytotoxic drugs included, the doses to be used, mostly expressed as mg/m^2 body surface, and relative time-points for, and methods of, administration. The time between the start days for each course of chemotherapy, i.e., the cycle time, is mostly 21 or 28 days but, weekly administration of various drug combinations is frequently used in, e.g. chemotherapy for lymphomas. The frequently used cycle-time of 3 weeks is mainly based on the empirical knowledge that the average patient needs this time to recover enough from the adverse effects from the prior course to be able to manage those of the next.

The drugs included in the regimen are often administered as intravenous injections or infusions during 1–5 days in the beginning of each course, but additional administration later in the course, is included in some regimens. Modern treatment schedules frequently include algorithms, mostly based on the level of toxicity between courses, for dose reductions and sometimes also for escalations as a way to adapt the regimen to the individual patient.

The number of cycles to be given mostly cannot be defined prior to start of induction therapy. In this setting, the physician in charge of the patient has to closely follow the patient with respect to adverse effects to be able to modify the therapy if too toxic. In the absence of severe toxicity, objective evaluation, mostly by radiology, of the effect on the tumour is often performed every 3rd course and the therapy then continues until a maximum antitumour effect has been achieved or until there is unacceptable toxicity. In the adjuvant setting, the number of courses is stipulated in the treatment protocol and in, e.g. breast and colon cancer, the planned treatment time is often in the range 6–12 months. In the neoadjuvant setting the number of cycles to be given prior to the local treatment is often 3–6, with the option to modify this according to treatment effect and tolerability in the individual patient.

Table 2

Impact of chemotherapy on some malignant tumours in advanced stage. Modified from (7, 8)

Curable by chemotherapy
Acute leukaemia
High grade non-Hodgkin's lymphoma
Hodgkin's disease
Choriocarcinoma
Germ cell tumours
Wilms' tumour
Ewing's sarcoma
Osteosarcoma
Neuroblastoma
Chemotherapy improves survival
Breast cancer
Ovarian cancer
Small cell lung cancer
Bladder cancer
Colorectal cancer
Gastric cancer
Modest survival improvement/Tumour symptomatic response only
Non-small cell lung cancer
Metastatic cancer of unknown primary origin
Endometrial cancer
Soft tissue sarcoma
Carcinoids
Head and neck cancer
Pancreatic cancer
Brain tumours
Mesothelioma
Esophageal cancer
Poorly sensitive to chemotherapy
Prostate cancer
Adrenocortical cancer
Melanoma
Renal cancer
Thyroid cancer

WHY DO CYTOTOXIC DRUGS WORK?

The mechanisms by which cytotoxic drugs act at the cells to induce cell death and/or stop cell growth, have mostly been investigated in the laboratory in continuously growing tumour cell lines, a versatile but perhaps not very appropriate model of human cancer. Given the many differences between these model systems and cancer in patients, there is some uncertainty with respect to how the mechanisms apply in the clinic. The mechanisms summarised first below are the 'classical' ones deriving from these models (10).

There are a few cytotoxic drugs that affect the cells from the outside; asparaginase by breaking down an amino acid necessary for tumour growth and anthracyclines and miltefosine by perturbation of the cell membrane. However, most cytotoxic drugs act inside the cell by interaction with cellular functions necessary for cell growth and survival. The large groups of *alkylators and alkylator-related agents* have the chemical property to bind to various cellular macromolecules, most importantly DNA, thereby precluding the normal function of DNA during cell division and gene expression. The *platinum drugs*, although chemically unrelated to the alkylators, act by mechanisms similar to those of the alkylators.

The *antimetabolites* have several mechanisms of action based on their similarity with normal molecules of importance for the cell. By this similarity, the antimetabolites take the place of the normal molecules in the synthesis of DNA and RNA or inhibit key steps in the synthesis, leading to disturbance of the normal function of the DNA or RNA, which may be incompatible with cell growth and survival. The *topoisomerase inhibitors* act by interaction with the normal function of the nuclear enzymes topoisomerase I and II. These enzymes are of vital importance in the replication, transcription and repair processes of DNA by induction of transient single or double strand breaks. The drug interaction with these enzymes leads to more permanent breaks in the DNA, which precludes the normal function of DNA.

The *microtubule interacting agents* disturb the normal synthesis and break-down of the cellular cytoskeleton, i.e. the microtubule apparatus, which leads to an abnormal deficiency or accumulation of microtubules. Since a well-regulated cytoskeleton is important for, e.g. transport processes, cell adhesion and cell division, the disturbance leads to loss of cell function and growth arrest.

The newly introduced drugs fludarabine and cladribine are mechanistically mostly similar to the antimetabolites but may also act through induction of programmed cell death, apoptosis.

Most of the processes that cytotoxic drugs classically have been found to work through are vividly expressed in proliferating cells. This may explain why the toxic effects of cytotoxic drugs to normal tissues are generally most pronounced in tissues with a rapid turn-over, eg. the bone marrow and gut epithelium. However, there is quite poor correlation between proliferation in various tumour types and their sensitivity to chemotherapy, which points to additional mechanisms for the action of cytotoxic drugs in cancer. In this context, much attention during recent years has focused on the process of apoptosis when discussing the effects of chemo- and radiotherapy. Apoptosis is a morphologically discernable route of cell death that is induced by activation of specific genes, e.g. by metabolic stress or receptor activation.

The mechanisms for induction of apoptosis are not known in detail. However, there are several indications for the role of cell cycle regulating proteins in the process to determine whether a cell will proceed in the cycle, make a stop for DNA repair or go into the process of apoptosis. The tumour suppressor gene p53 seems to have a central role in the regulation of these processes and to which is coupled the expression of various proteins like p21 and cyclin-dependent kinases. These systems seem to interact with various oncogenes and, e.g. bcl-2 and bax proteins that finally govern the further fate of the cell (7). Most cytotoxic drugs have been found to be able to induce apoptosis and for some drugs the normal expression of p53 has been found necessary for a cytoxic effect (11).

The findings in the field of apoptosis provide important additional explanations of how cytotoxic drugs work. Perhaps the above 'classical' findings of changes induced by cytotoxic drugs are just the first signals that, via various routes, induce the cell to undergo apoptosis. The presence in the cell of the machinery necessary for apoptosis would, thus, be the prerequisite for the cytotoxic process. This would explain the pronounced resistance to cytotoxic drugs in some cell types, irrespective of measures taken to increase the cellular uptake of the drug. In the absence of response elements for apoptosis induction by cytotoxic drugs, chemotherapy may be a futile treatment modality unless combined with means to establish the apoptotic machinery in the cell (12, 13).

Although there is often a correlation between objective tumour remission and symptom relief, the former is not necessarily a requisite for the latter. Relief of cancer associated symptoms is frequently observed during chemotherapy also in the absence of (apparent) tumour volume reduction (14–16). It could, thus, be speculated that chemotherapy has additional effects, e.g. by affecting the tumour-induced production of various cytokines from immune cells that probably mediate many of the cancer-related general symptoms (17). These observations may open for new and less toxic pharmacological approaches that would more specifically counteract the mechanisms responsible for cancer-related symptoms.

THE FATE OF THE CYTOTOXIC DRUGS IN THE BODY

Whereas pharmacodynamics defines what the drugs do to the body, pharmacokinetics describes what the body does to the drugs, in terms of uptake, distribution, metabolism and excretion. This knowledge is usually collected by analysis of the concentrations of the drug and/or its metabolites in blood plasma and sometimes also in urine and faeces. Pharmacokinetics has previously received fairly little attention in the field of chemotherapy, which is unfortunate if one considers the very narrow therapeutic index for these drugs.

However, the interest for cytotoxic drug pharmacokinetics has increased considerably during recent years, although the practical clinical consequences of the new knowledge are not yet extensive. Based on computer analysis, only a few blood samples for analysis are necessary to get extensive information on the basic pharmacokinetic aspects of cytotoxic drugs. The most important finding from the recent studies in this field from a clinical point of view is the considerable interpatient variation in the pharmacokinetics of these drugs. This means that the systemic exposure to these drugs, which probably affects the antitumour and adverse effects obtained, varies several-fold, also when adjusting the dose for differences in body surface area (18). In fact, the current way of dose adjustment for body surface area has very little scientific support and does not decrease the inter-patient variation (19).

The several-fold difference in systemic drug exposure after standard dosing could mean that patients with a high clearance of the drugs would risk a too low exposure to the drugs given and, thus, a reduced chance of an antitumour effect. On the other hand, patients with low clearance would risk excessively high drug exposure. This would increase the chance of an antitumour effect but also increase the risk for unacceptable toxic effects. Recently, individualised dosing of chemotherapy was found to significantly improve the long-term outcome of children with acute lymphoblastic leukaemia (20).

It seems reasonable that the dosing of chemotherapy in the future will take into consideration the great inter-individual pharmacokinetic differences. Until more knowledge is at hand on the mechanisms that govern the pharmacokinetics, simplified empirical schedules in which the cytotoxic drug dosing is based on the toxicity from the prior course, as assessed, e.g. by blood cell counts, have already come into use and may allow higher doses and, thus, optimised chances of an antitumour effect without increased toxicity (19, 20).

WHY DO CYTOTOXIC DRUGS FREQUENTLY FAIL TO WORK?

Lack of significant antitumour effect of cytotoxic drugs is unfortunately frequent in chemotherapy of malignant tumours. Many tumour types, e.g. cancer of the lung (non-small cell type), kidney and gastrointestinal tract often show resistance to most cytotoxic drugs already from the beginning. Other tumour types, e.g. cancer of the breast, ovary and haematological malignancies, may respond initially but later appear resistant also to drugs not used earlier (21). Drug resistance may, thus, be acquired during chemotherapy, indicating the emergence, probably at cellular level, of mechanisms that counteract the effect of cytotoxic drugs.

The reasons for clinical drug resistance are probably multi-factorial with a different spectrum for various tumour types and individual patients. Apart from drug resistance at *cellular level*, clinical drug resistance may also be mediated by *increased drug metabolism* leading to an excessively low systemic exposure and, thus, insignificant tumour cell kill, as discussed above (22). Furthermore, parts of solid tumours may be *poorly vascularised*, leaving tumour cells without drug exposure (23). There is also indication of the presence of *cell kinetic resistance* in some tumour types, i.e a lack of drug effect despite tumour cell sensitivity because of rapid tumour regrowth between courses (24).

Out of these 4, principally different, mechanisms for resistance to chemotherapy, there is reason to believe that the major decisive factor for the outcome of treatment with cytotoxic drugs is the lack of sensitivity of the tumour cells despite optimal exposure to the drugs (11). A major argument for this conclusion is the finding that the clinical pattern of drug response is mimicked in the laboratory when testing tumour cells from patients with different tumour types (25). In this setting, all other factors acting at the organism level have been removed, leaving cellular drug sensitivity alone to be decisive for drug sensitivity.

Knowledge of the mechanisms for drug resistance at cellular level is, therefore, of importance for understanding the failure of chemotherapy in patients. These mechanisms have been extensively studied in cell lines, often by comparing the properties of a parent cell line with those of a subline made drug-resistant in vitro by continuous exposure to increasing concentrations of a cytotoxic drug (26).

A phenomenon observed in the cell lines is that acquired resistance to one cytotoxic drug frequently also confers resistance to other chemically and mechanistically unrelated drugs (27). This has been termed multidrug resistance (MDR) and indicates the presence of a general defense mechanism. MDR has been associated with increased expression of a membrane 170 kD membrane protein, P-glycoprotein (Pgp), supposed to mediate resistance by acting as an ATP-dependent drug exporter, thereby decreasing cellular drug accumulation (11, 27).

Other membrane proteins, e.g. the MDR associated membrane protein, MRP, have also been found to confer drug resistance by decreased drug accumulation much like Pgp (28). Furthermore, for drugs mediating their cytotoxic effect through defined enzymes, decreased levels of the target enzymes or mutations leading to altered interaction have been found to lead to drug resistance (11).

For the vinca alkaloids and probably also the newly introduced taxanes, mediating their cytotoxic effect through interaction with microtubule assembly or disruption, non-Pgp associated drug resistance has been suggested to be mediated by a decreased interaction between the drugs and the tubuline target (29).

Many cytotoxic drugs are dependent on metabolic activation in the target cell to become active. For such drugs, a decrease in this metabolism or an increased inactivation through enzyme mediated conjugation with glutathione have been associated with drug resistance (30).

As indicated above, recent observations have linked together altered expression of oncogenes or tumour suppressor genes and apoptosis. Drug resistance may, thus, be mediated by, e.g. abnormal expression of the bcl-2 and p53 proteins (11, 31). Such expression, on the other hand, is probably linked to the induction of apoptosis. Considering the emerging support for the induction by cytotoxic drugs of apoptosis, a major reason for drug resistance might be the absence in the cell of response elements connecting the biochemical effects induced by the cytotoxic drugs to apoptosis (12, 13).

It should be observed that the above theories for cytotoxic drug resistance are mainly based on observations in experimental models, the clinical relevance of which might be questioned. There are reasons to believe that the interaction between the tumour cells and the normal cells and stroma is important for the biologic properties of the tumour cells, which may also include therapeutic effects.

OPTIMISATION OF THE USE OF CURRENTLY AVAILABLE CYTOTOXIC DRUGS

While awaiting the possible clinical exploitation of emerging new knowledge in cancer biology, it seems reasonable to try to optimise the treatment options already available. In the field of chemotherapy, the application of the following principles would perhaps lead to better treatment outcome.

Given the considerable variation in the metabolic handling of cytotoxic drugs between patients, the classical dosing according to body surface area seems obsolete (19). Expanding knowledge in the field of pharmacokinetics, including the principles of limited sampling and Baysean

forecasting (32), makes *individualised dosing* feasible already now. Such an approach would reasonably mean that the chance of an antitumour effect at acceptable toxicity is increased, as clearly indicated by the study in acute lymphoblastic leukaemia (20).

Given the frequent problem of lack of selectivity of the cytototoxic drug for tumour vs normal cells, the *formulation of cytotoxic drugs* in, e.g. liposomes may confer an improved therapeutic index for some tumour types. Furthermore, the use of *prodrugs being activated by enzymes located specifically at the tumour cells* by tumour specific antibodies may accomplish a better therapeutic index (33). There are also indications for the importance of *the timing of cytotoxic drug administration* for the antitumour effect and normal cell toxicity (34). Increased knowledge in the chronobiology of cytotoxic drugs and the application of this knowledge in clinical practice could be a way for treatment optimisation.

In the case of a too low antitumour effect of the cytotoxic drugs, it seems logical to increase the dose with the hope that there might be a dose-response relationship for the antitumour effect. This is the bearing idea behind *high-dose chemotherapy* which makes it necessary to support the patient by, e.g. bone marrow stem cells, to counteract otherwise lethal toxicity. This approach to overcome drug resistance has been studied for many years in several tumour types, unfortunately mostly in uncontrolled studies. High-dose chemotherapy has shown some promise in, e.g. breast and testicular cancer and haematological malignancies and has become a standard treatment in some settings (35). However, this approach only seems fruitful for tumour types and patients in which a positive dose-response relationship is present. A better selection of drugs, which is now empirical, for the high-dose procedure may perhaps lead to improvement for the high dose approach. The use of growth factors to stimulate bone marrow recovery after chemotherapy is another way to increase the dose-intensity and, thereby, the antitumour effect in drug sensitive tumour types.

The selection of drugs for the individual patient has so far been based on experience from clinical studies defining the average treatment effect in a large patient population. Drug selection based on the knowledge of the specific characteristics of the tumour cells of the individual patient could reasonably lead to a better treatment outcome. Methods for such *tailor-made drug selection* have been available for many years but have, based on technical and conceptual progress, become more expedient during recent years. The basic principle is to prepare tumour cells from a tumour sample from an individual patient, followed by short-term exposure of these cells to cytotoxic drugs during culture in the laboratory. Drug selection is then based on measurement at the end of the culture of cell viability after incubation with the different drugs. It is quite clear that these techniques at least would make it possible to exclude drugs that the patient's tumour would not respond to, and that would only add to toxicity and perhaps also increase the response rate (7, 36).

During the last decade a number of drugs have been found to counteract cytotoxic drug resistance at cellular level and several have been used in clinical trials, among them calcium channel blockers, cyclosporine A and its analog PSC 833 (37). Although the concept of *pharmacological drug resistance modulation* seems to become less fruitful in the clinic than what might be expected from the basic research, it may certainly prove beneficial in some tumour types, probably in those already being drug sensitive (38).

Finally, expanding knowledge in the molecular biology of the tumour cell apoptosis might lead to *transfer to the tumour cells of genes necessary for induction by cytotoxic drugs of apoptosis* (39).

NEW DRUG DEVELOPMENT

It is quite clear from the above that there is a need for new and more active drugs in cancer chemotherapy. The strategies used so far for the development of cytotoxic drugs have been based on empirical observations, rational drug design based on suitable targets as evident from research in cellular biochemistry, synthesis of analogs to already known active drugs and the use of laboratory systems for screening of cytotoxic properties among chemicals available (40). Drug development has relied on the testing of the drug against various tumour cell lines in the laboratory followed by evaluation in tumour-bearing mice. Following this preclinical development, the new drugs are tested at increasing doses in cancer patients with the aim to define the optimal dose to be used in larger clinical studies to define the antitumour activity.

A bearing principle in the development process for new cytotoxic drugs is the hope that there may perhaps be targets in tumour cells that are not present in normal cells and the exploitation of which may confer a more advantageous therapeutic index for cytotoxic drugs. The finding of such targets may well be related to the research on the mechanisms regulating apoptosis and cell cycle progression. However, there are also several other putative targets for new drugs. Among these are tumour-specific properties in the cell signal transmission system, cell membrane composition, angiogenesis, telomerase and matrix interaction (7, 11, 33).

With respect to the process of drug development there is reason to believe that it will become more efficient. By the addition of laboratory testing systems with good correlation to activity in the patients, the preclinical part of new drug development may become more rapid and efficient than so far. Besides rational drug design, there will probably also be space in the future for progress in drug development based on analog-synthesis, unprejudiced drug screening and exploitation of serendipitous findings.

CHEMOTHERAPY AND LABOUR PROTECTION

By their mode of action, most cytotoxic drugs bear the risk of induction of secondary malignancies (see specific chapter on adverse effects). This could pose an employee-protection problem if the handling in the clinic is associated with repeated exposure to these drugs. In fact, mutagenic activity was observed in the urine from nurses involved in the preparation of cytotoxic drugs (41). However, these nurses used neither a safety-box nor individual safety routines. All preparation of patient doses of cytotoxic drugs is now performed in a safety-box and all patient-associated handling of these drugs is now detailed with respect to safety measures with the aim to minimise labour exposure (41).

After implementation of these routines, labour exposure has been claimed to be insignificant (42). However, more recently performed analyses of labour exposure to cytotoxic drugs using more sensitive analytical techniques indicate systemic exposure despite adherence to current protective measures (43). Furthermore, this exposure might be associated with increased chromosomal changes in peripheral blood lymphocytes (44). The relevance of these observations for Swedish conditions, with even stricter protection rules, might be questioned but they still seem to argue in favour of centralised preparation of patient doses of cytotoxic drugs and/or the use of closed systems for reconstitution and dilution of these drugs.

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