REVIEW ARTICLE

Drugs 1999 Feb; 57 (2): 133-155
0012-6667/99/0002-0133/$23.00/0

Clinical and Preclinical Modulation of Chemotherapy-Induced Toxicity in Patients with Cancer

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Abstract

Anticancer treatment is generally associated with toxicity to health issues. One of the reasons for this unpleasant association is that anticancer agents have been mostly selected on the basis of an empirically established toxicity towards cancer cell lines and rapidly growing tumours in animal models, and not on the basis of a sophisticated intervention in tumour-specific biology. This strategy of drug development unavoidably produces drugs with toxicity towards normal cells and tissues which also have a high cell turnover and share many characteristics with tumour cells. Therefore it is a continuing challenge to design therapy which is both effective and also has high specificity for the biology of cancer and/or is efficiently targeted to tumour tissue.

This article describes the mechanisms of cytotoxicity of standard chemo- and radiotherapy and discussed the possibilities of currently available cytoprotective agents to reduce or prevent these toxicities. These agents should ideally be selective for normal cells versus cancer cells, be effective in reducing or preventing toxicity, have no negative impact on anticancer therapy and have minimal adverse effects. None of the agents described in this article fulfils these criteria completely and therefore we cannot recommend these agents for standard use in daily anticancer practice. Nevertheless, there are encouraging data concerning the beneficial effects of dexrazoxane for anthracycline-induced cardiomyopathy and amifostine for platinum- and radiotherapy-induced toxicity. These date warrant further studies.

Anticancer therapy is not only cytotoxic towards cancer cells but to healthy cells also. This results in a narrow therapeutic index, with adverse events frequently limiting the administration of optimal anticancer therapy. It is hoped that a better understanding of the essential mechanisms of carcinogenesis will lead to the development of more specific approaches to cancer therapy; however, there is presently a need for strategies to circumvent or reduce healthy tissue toxicity.[1-5]

Approaches to reduce or prevent chemotherapy-induced toxicity include: alternating the duration and route of administration; the use of drug carriers, analogues and prodrugs;[6] the use of growth factors to enhance the recovery of the remaining haematopoietic progenitor/stem cell population; and treatment with rescue agents or cytoprotectants.

Ideally, cytoprotective agents should show selectivity for healthy cells versus cancer cells, prevent or at least substantially reduce the toxicity of chemotherapy, have no negative impact on the distribution and antitumour effect of therapy, be effective against toxicity induced by radiotherapy or chemotherapeutic agents, and have minimal adverse effects of their own.

None of the cytoprotective drugs available fully meet these requirements which means that we are far from an ideal situation. This article will consider present approaches to preventing or modulating the toxicity associated with chemotherapy and

radiotherapy. Treatment for established toxicity, for instance with haematopoietic growth factors or antiemetics, falls beyond the scope of this article.

1. Principles of Radiotherapy-Induced Toxicity

Radiotherapy is especially toxic for cells with a high rate of proliferation. Consequently, radiation of the bone marrow or the mucosa of the orogastrointestinal system may be associated with serious side effects. Radiation causes hydrolysis of intracellular water, and during this process free radicals are generated which cause damage to vital cellular elements, notably DNA.[7-9] Radiation-induced DNA damage includes single- and double-strand breaks and crosslinks between DNA strands and chromosomal proteins. Cells with DNA damage may undergo DNA repair, but as the dosage of radiation increases more cells undergo apoptosis in subsequent cell divisions. Acute radiation toxicity represents the loss of rapidly proliferating cells. Additionally, an inflammation-like response associated with the generation of cytokines and growth factors may be observed.[10] Dermatitis and mucositis are well known adverse effects of acute radiation.

Chronic toxicity is associated with injury to tissue stromal cells and stem cells, resulting in a more or less irreversible deterioration of organ functions. Radiotherapy is particularly damaging to the microcirculation of tissues, thereby causing parenchymal cell death and ultimately tissue fibrosis.[11]

2. Principles of Chemotherapy-Induced Toxicity

There are various mechanisms by which chemotherapy is toxic to specific organs or organ systems. Evidence is growing that most chemotherapeutic agents kill both healthy and cancer cells by causing dysfunction or injury to a specific cellular target. This is interpreted by cells as an instruction to enter a programmed cell death pathway (apoptosis[12]).

Organs with a high cellular turnover are more vulnerable to cytotoxic agents than those with a slower rate of cell growth. Thus, myelotoxicity, gastrointestinal toxicity and hair loss are frequent and early occurring adverse effects of chemotherapy. Toxicity to organs or cells with a reduced rate of proliferation is generally a late event, but is frequently irreversible.

The route of elimination may contribute to toxicity. For example, platinum compounds are largely eliminated by the kidney, and this explains their specific renal toxicity. The detoxicification system of various organs is also important. For example, the inability of heart muscle to remove reactive oxygen species produced during (anthracyclines) therapy may explain the specific cardiac toxicity of these agents. The affinity of some chemotherapeutic drugs for specific cell systems also appears to be important, for instance fluorouracil and the gastrointestinal cell system. A summary of specific organ toxicity of chemotherapeutic agents in common use is shown in table I.

As the toxicity of chemotherapeutic drugs is closely correlated with their local tissue concentration, it can be decreased by reducing the dose. This may be the best option in many circumstances, given that the gradient of the dose-activity curve of many chemotherapeutic agents remains behind that of the dose-toxicity curve.

Nonhaematological toxicity may increasingly become dose-limiting because of the growing practice of giving escalated doses of chemotherapy followed by haematopoietic growth factors, haematopoietic stem cells or bone marrow reinfusion to stimulate recovery of the haematopoiesis.[13]

3. Mechanisms and Manifestations of Chemotherapy-Induced Toxicity

3.1 Myelotoxicity

The demand for newly formed peripheral blood cells is around 4×10^{11} cells/day.[14] This impressive proliferation rate inside the bone marrow implies a high vulnerability to radiation and to agents which are cytotoxic to dividing cells. Bone marrow depression is the dose-limiting side effect for the majority of chemotherapeutic drugs and largely

Table I. Organ toxicity of chemotherapeutic agents in frequent use

Drug	Toxicity for								
	bone marrow	kidney	lung	liver	nerves	CNS	mucosa	heart	hair
Alkylating agents	+++	–	+	–	–	–	+	+	++
Bleomycin	–	–	+++	–	–	–	+	–	+
Cytarabine	+++	–	–	+	–	–	++	–	+
Cytostatic antibiotics (anthracyclines)	+++	–	–	++	–	–	+++	+++	+++
Etoposide	+++	–	–	–	–	–	++	–	+++
Fluorouracil	++	–	+	+	–	–	++	+	–
Ifosfamide	++	++	+	–	–	++	+	+	++
Methotrexate	++	++	+	+	–	–	++	–	–
Nitrosoureas	+++	++	++	++	–	–	++	–	+
Platinum analogues									
carboplatin	+++	+	–	–	+	–	+	–	–
cisplatin	++	+++	–	–	+++	–	+	–	–
Taxanes	+++	–	–	+	+++	–	+	+	+++
Vinca alkaloids	+	–	–	–	+++	–	–	–	–

– = no toxicity; + = low toxicity; ++ = moderate toxicity; +++ = high toxicity.

determines dose and regimen of chemotherapy. The time taken for myelosuppression to develop depends on which type of haematopoietic precursor cell is damaged.[15] Agents that affect cycling cells, such as cytarabine, cyclophosphamide and fluorouracil, will damage more mature progenitor cells and induce acute, but rapidly recovering, myelosuppression. Agents such as busulfan, carmustine and melphalan, which damage the non-cycling primitive stem cells, may result in a permanent loss in repopulating capacity. This may only become apparent when the bone marrow is stressed by new therapy (i.e. chemo- or radiotherapy).

The haematopoietic system is dependent on a microenvironment that consists of so-called stromal cells (e.g. endothelial cells, fibroblasts, fat cells, macrophages) which maintain haematopoiesis through the secretion of haematopoietic growth factors, and a complex vascular network. Radiotherapy or cytotoxic drugs which cause damage to this system will compromise recovery from future bone marrow injury by reducing the bone marrow reserve. In particular, high dose radiation will induce irreversible damage to the medullary stroma and be associated with permanent marrow aplasia.[16]

3.2 Gastrointestinal Toxicity

Chemotherapy and radiotherapy have both direct and indirect negative effects on the gastrointestinal tract. The direct effects arise from specific mucosal injury induced by these therapies. At any one moment, about 14% of normal intestinal epithelial cells are in the cell division cycle: therefore, this cellular compartment is highly vulnerable to radiotherapy and cytotoxic agents which have proliferating cells as their main target. The acute injury to intestinal mucosa is associated with increased apoptosis of epithelial cells at the villi and crypts, and an insufficient replacement activity at the crypt basis, where the mucosal stem cells are located.[17] Toxicity in the epithelial lining of the orogastrointestinal tract commonly appears as mucositis with an increased risk for bacterial and fungal infections. Diarrhoea and abdominal cramps may be symptoms of damage to the intestinal mucosa. Moreover, when mucositis is accompanied by neutropenia, the risk of systemic infection increases.

The chemotherapeutic drugs which most commonly cause gastrointestinal toxicity are fluorouracil, the anthracyclines and the topoisomerase I inhibitors camptothecin and irinotecan, but at es-

calated doses the majority of cytotoxic drugs have this effect. Therefore, high dose chemotherapy is frequently associated with diarrhoea and stomatitis.[18]

Additional indirect effects of anticancer therapies arise from reduced food intake, which causes a decrease in secretion of enteral hormones, resulting in decreased trophic effects to the mucosa.[19]

3.3 Cardiotoxicity

The mechanisms by which anthracyclines cause cardiotoxicity and antitumour activity are thought to be different. Cardiotoxicity is thought to result from several mechanisms.[20-22] First, the metabolism of this class of drugs is associated with the generation of superoxide radicals, which are highly toxic towards adjacent molecules. Secondly, superoxide radicals may induce the secondary production of even more toxic hydroxyl radicals. Anthracyclines bind to intracellular iron (Fe^{+++}) forming complexes which strongly stimulate the generation of hydroxyl radicals. Furthermore, iron–anthracycline complexes are themselves toxic and have high affinity for cardiolipids, resulting in damage to the internal membranes of the mitochondria and the sarcoplasm.

Thus, the generation of free radicals and the toxicity of iron–anthracycline complexes towards cardiolipids are both thought to be responsible for anthracycline–induced cardiotoxicity.

Heart muscle is a specific target for the toxicity of anthracycline because of the relatively poor antioxidant defence mechanisms of this tissue (low levels of catalase and glutathione peroxidase). Histological assessment of anthracycline-induced cardiotoxicity shows myofibrilar loss and vacuolar degeneration of the sarcoplasmic reticulum[23] and, in the final phase, myocardial fibrosis and hypertrophy of the remaining myocytes. Acute anthracycline–induced toxicity appears generally as nonserious disturbances in cardiac rhythm, but chronic cumulative cardiac toxicity may cause irreversible congestive heart failure, which is fairly resistant to treatment.

The onset of cardiac events usually occurs after a total dose of doxorubicin 450 to 550 mg/m^2 or epirubicin 900 to 1000 mg/m^2 has been administered. In patients with risk factors for cardiac disease (female, age >65 or <4 years, mediastinal radiotherapy, prior cardiopathy, hypertension and diabetes mellitus) cardiac toxicity may arise at lower doses.[24,25] Concomitant administration of other chemotherapeutic drugs (e.g. taxoids[26]) may potentiate the cardiotoxicity of anthracyclines. Of special concern is the late-onset anthracycline-induced cardiotoxicity found in survivors of cancer; this may have a significant impact on their quality of life or even be life-threatening.[27]

The taxoids infrequently induce cardiac disturbances, e.g. hypotension and asymptomatic bradycardia. This may be a manifestation of autonomic neuropathy associated with these drugs, rather than true cardiotoxicity.[28] High dose cyclophosphamide has infrequently been associated with haemorrhagic myocarditis.[29]

3.4 Neurotoxicity

Three classes of chemotherapeutic drugs induce peripheral neurotoxicity: the vinca alkaloids, the taxoids and the platinum compounds. Whereas the vinca alkaloids bind to tubulin and prevent the polymerisation from soluble dimers into microtubules, the taxoids promote the formation of microtubules and prevent their depolymerisation, which results in an abundance of rigid microtubules. Microtubules are essential components of the mitotic spindle and are important for the maintenance of cell shape, a variety of cellular actions and axoplasmic transport. Defective function of microtubules in neurons and axons may be the origin of the neurotoxicity of both families of chemotherapeutic agents.

The vinca alkaloids induce a peripheral sensorimotor polyneuropathy and autonomic neuropathy, which appears to be partially reversible after some months.[30] The taxoids induce primarily a symmetrically distributed sensory distal neuropathy, which is related to both single and cumulative doses of the drug and is possibly dependent on the

regimen.[31] The neurotoxicity of both paclitaxel and docetaxel is presumably caused by microtubule aggregation in neurons, axons and Schwann cells.[32,33] Taxoids are infrequently associated with autonomic neuropathy.[34] At doses of paclitaxel >250 mg/m^2 with granulocyte colony–stimulating factor (G-CSF) rescue of myelotoxicity, neurotoxicity becomes the dose-limiting factor.[35] Taxoids do not accumulate in nervous tissue[36] which explains why, after discontinuation of these drugs, the symptoms of neuropathy gradually disappear.

Cisplatin induces a peripheral sensory axonal neuropathy, affecting large-diameter and, to a lesser extent, small-diameter sensory fibres. Paraesthesias and impaired propriocepsis, leading to ataxia, are the most common symptoms.[37-40] Histological examination of peripheral neural tissue affected by cisplatin showed axonal degeneration, gradually progressing from the periphery to the cell body and secondary myelin breakdown.[41] Cisplatin accumulates in and damages the dorsal root ganglia, axonal changes being secondary to neuronal damage.[37,39]

The incidence of cisplatin-induced neuropathy depends largely on the cumulative dose, the onset of symptoms being seen at a total dose of cisplatin 300 to 400 mg/m^2. Cisplatin binds tightly and irreversibly to nerve tissue, which explains the deterioration of neurological condition which sometimes occurs after cessation of cisplatin therapy.[42]

Toxicity of the CNS is an infrequent event, primarily because of the inability of many chemotherapeutic agents to cross the blood-brain barrier. Patients treated with ifosfamide, however, may experience symptoms such as somnolence and hallucinations. This reversible encephalopathy is dose- and regimen-dependent and thought to be caused by the generation of lipophilic neurotoxic metabolites such as acrolein and chloroacetic aldehyde.[43,44]

3.5 Ototoxicity

The most frequently used anticancer agent which induces ototoxicity is cisplatin. The association of other chemotherapeutic drugs with ototoxicity is both sporadic and inconsistently evaluated.[45,46] Cisplatin ototoxicity is characterised by tinnitus and a symmetrical high frequency hearing loss which is both dose and regimen dependent.[47] Younger patients tend to be more susceptible, whereas prior exposure to cranial irradiation increases the severity of hearing loss caused by this drug.[48]

The mechanisms by which the platinum compounds induce ototoxicity have not been completely elucidated. Temporal bone biopsies from 4 patients with documented cisplatin ototoxicity revealed loss of inner and outer hair cells in the basal half of the cochlea (which sense the higher frequency sounds), degeneration of the stria vascularis and a decrease in spiral ganglion cells as the most striking histopathological changes.[49] Animal studies showed that the level of glutathione was reduced in the cochlea after cisplatin treatment[50] and suggested that the production of reactive oxygen species in the cochlea might contribute to the ototoxicity of this agent. It remains questionable whether the disturbances in the ion transport in the stria vascularis (differences in the concentration of sodium and potassium between the endo- and perilymph), which have been described after platinum therapy,[45,46] are the cause or a consequence of cochlear damage.

The first manifestation of cisplatin-induced ototoxicity occurs at a cumulative dose of cisplatin 200 mg/m^2 or higher, and appears as a shift in auditory brainstem response threshold at the higher frequencies tested, followed by clinical hearing loss. It is an irreversible process. Carboplatin induces very little ototoxicity when given at conventional doses (300 to 400 mg/m^2). However, at much higher dosages it may also cause damage to the inner ear.[51]

3.6 Renal and Bladder Toxicity

The kidneys are the main route of elimination of many chemotherapeutic agents, but notably of platinum compounds. At high local concentrations, cisplatin induces proximal and distal tubular damage. Necrosis, interstitial oedema and tubular dilatation are seen microscopically.[52,53] Clinically, this

may appear as a decrease in creatinine clearance and renal magnesium wasting. Cisplatin-induced renal toxicity is related to both the acute and cumulative dose given and is for the greater part irreversible.[54]

Methotrexate and its metabolites are also mainly excreted in the urine. The nephrotoxicity of high doses of methotrexate is probably caused by the limited solubility of that drug in urine at acid pH, resulting in crystallisation in renal tubules and parenchymal damage.

The alkylating agents cyclophosphamide (at high doses) and ifosfamide can induce haemorrhagic cystitis, probably through the generation of urotoxic metabolites, e.g. acrolein. Ifosfamide at high dosages may also cause renal impairment by the generation of nephrotoxic metabolites. Pretreatment with cisplatin is a risk factor for ifosfamide-induced renal toxicity.[55] High-dose chemotherapy regimens frequently include carboplatin and ifosfamide; this may result in nephrotoxicity, which is associated with greater transfusion requirements and a longer hospital stay.[56]

3.7 Pulmonary Toxicity

Bleomycin-associated pulmonary damage is initiated by inflammation and followed by interstitial fibrosis. It has been associated with the (local) generation of tumour necrosis factor-α (TNFα).[57] The fibrous tissue that accumulates in the alveoli causes damage to alveolar epithelial lining cells, particularly type I cells.[58,59] It is thought that bleomycin-Fe^{+++} complexes catalyse the generation of superoxide and hydroxyl radicals, which are toxic for both DNA and intracellular membranes. Low levels of bleomycin hydrolase, a bleomycin-inactivating enzyme, may be responsible for the sensitivity of the lung for this drug.

Pulmonary toxicity has also been described following therapy with busulfan, cyclophosphamide, mitomycin C and carmustine.[60,61] Mitomycin C, when used at high cumulative doses (>30 mg/m^2), may induce chronic and progressive lung toxicity, despite high doses of corticosteroids.[62] The use of carmustine in high-dose chemotherapy programmes may induce substantial pulmonary toxicity, which usually appears some weeks after treatment.[61,63] Pulmonary function tests after treatment with high doses of these agents revealed restrictive lung disease with reduced diffusion capacity, and lung biopsies showed fibrosis and endothelial cell injury. Enhanced pretreatment plasma levels of transforming growth factor β (TGFβ), a growth factor involved in the fibrotic response to tissue injury, seem to predict the risk of lung toxicity due to carmustine.[64]

Pulmonary toxicity has also been reported with gemcitabine, a new deoxycytidine analogue used mainly for pancreatic and lung cancer. This toxicity is usually mild and self-limiting, but toxic deaths due to respiratory distress syndrome have also been described.[65]

3.8 Liver Toxicity

Direct damage to liver cells is an infrequent event during chemotherapy. This may be related to the unique detoxifying potency of these cells or any damage may remain unnoticed due to the large reserve of liver tissue and/or the absence of easy and sensitive markers of liver toxicity.[66] Veno-occlusive disease of the liver (VOD), which is characterised by weight gain, hepatomegaly, ascites and hyperbilirubinaemia, may occur after treatment with high dose chemotherapy followed by bone marrow or stem cell reinfusion. Busulfan, mitomycin C and carmustine are commonly associated with this disorder.[67] Injury of the hepatic vascular endothelium, ultimately resulting in fibrosis, is the postulated mechanism of VOD. The pretreatment plasma level of TGFβ before therapy is positively correlated with its occurrence.[64]

3.9 Gonadal Toxicity

The testes and ovaries are tissues with a high cell turnover. Menstrual irregularities and deficient spermatogenesis are therefore common findings in young patients treated with chemotherapy; infertility may be the definitive outcome of intensive treatment.[68] The degree of gonadal dysfunction depends on the age of the patient and the type and

cumulative dose of the cytotoxic drugs used. Cyclophosphamide, a drug commonly used in chemotherapy programmes for breast cancer, is a major cause of amenorrhoea due to primary ovarian failure. However, in women aged <35 years, pregnancy following adjuvant chemotherapy is possible.[69] Of special concern is the effect of platinum-based therapy on spermatogenesis in young men treated for germ cell tumours. Differentiating spermatogonia are the most sensitive to killing by cytotoxic agents, resulting in short term azoospermia. Sperm production may gradually recover from surviving stem cells, but this is related to the degree of stem cell killing.[70] Some patients with oligospermia will slowly recover while others have reproductive capacity despite continued oligospermia.[71] The prechemotherapy sperm count largely predicts the recovery of spermatogenesis following treatment.[72]

4. Currently Used Cytoprotective Agents

4.1 Amifostine

Amifostine (S-2-[3-aminopropylamino] ethylphosphorothioic acid, WR-2721) is a prodrug which is converted into the active, cell-permeable, dephosphorylated metabolite WR-1065 by cell membrane–bound alkaline phosphatase.[73]

Cytoprotection by amifostine occurs via scavenging of free radicals,[74] deactivation of reactive cytotoxic agents, prevention of cisplatin-DNA adduct formation[75] and facilitation of DNA repair.[76,77] The effect of amifostine on DNA platination was studied by incubating salmon sperm DNA with cisplatin.[75] WR-1065, and to a lesser extent amifostine, prevented platinated-DNA (Pt-DNA) adduct formation. It only slightly reduced preexisting Pt-DNA adducts. This suggests that prevention and not rescue is the most probable mechanism of protection by WR-1065 and, at the same time, it suggests that the optimal time to administer amifostine is shortly before administration of platinum compounds. This has been confirmed by *in vivo* studies for cisplatin[78] and carboplatin.[79]

The selectivity of amifostine for healthy tissue is thought to be related to the presence of high alkaline phosphatase concentrations in healthy tissue capillaries[80] and at the brush border of renal tubules.[81] It is thought that the enzyme activity is higher in healthy tissues than in tumours because they have a normal local pH. Tumour cells often have a lower pH because of their tendency to anaerobic metabolism. Due to these pH differences, WR-1065 is also more avidly taken up by healthy cells.[82,83]

In vitro, amifostine and WR-1065 are less reactive with cisplatin and carboplatin than thiosulfate or diethyl-dithiocarbamate.[75,84] Administration of amifostine shortly before platinum compounds does not jeopardise their antitumour activity.[78,79] However, amifostine influences the pharmacokinetics of carboplatin. An increase in the area under the plasma concentration-time curve (AUC) of platinum in plasma ultrafiltrate, kidney, liver and tumour has been observed in tumour-bearing nude mice.[85] In patients, a significant increase in the terminal elimination half-life of ultrafilterable platinum has been observed after pretreatment with amifostine, resulting in a slight increase in AUC.[86] Amifostine most probably decreases the renal clearance of carboplatin by influencing kidney function. Serum creatinine levels were found to be increased 24 hours after treatment.

Similar observations, but to a lesser extent, have been made for patients treated with cisplatin in combination with a single dose of amifostine.[87] Together, these results suggest that there will be increased exposure to platinum compounds in the presence of amifostine.

4.2 Dexrazoxane

Dexrazoxane (ICRF-187) is the *d*-isomer of the racemic compound razoxane (ICRF-159), a lipophilic derivative of the chelating agent ethylenediaminetetraacetic acid (edetic acid, EDTA). Dexrazoxane readily penetrates cell membranes. It has been shown to reduce the cardiotoxicity of doxorubicin (one of the anthracyclines). This effect results from its intracellular hydrolysis to ICRF-198

which chelates intracellular iron, producing a reduction of the Fe^{+++}-(doxorubicin)$_3$ complexes, thus preventing free radical formation.[88,89]

Dexrazoxane also has a cytotoxic effect via inhibition of topoisomerase II,[90] and may potentiate[91] or antagonise[92] the cytotoxicity of some antitumour agents in experimental models. Its adverse effects are myelotoxicity and phlebitis at the site of injection.[93]

4.3 Glutathione

Reduced glutathione (γ-Glu-Cys-Gly, GSH), a tripeptide with a free sulfhydryl (SH) group, is the principal intracellular thiol in mammalian cells. It exerts its cytoprotective effects in several ways. First, it maintains the active form of glutathione peroxidase to scavenge toxic peroxides. Secondly, it forms intracellular complexes with cisplatin, for instance, which reduces the toxicity of this agent, whereas the reactivity with DNA is maintained.[94,95] Thirdly, glutathione regulates the kinetics of several ion channels, which are of great importance for the biological integrity of the cell.[96]

Various chemotherapeutic agents reduce the circulatory and cellular levels of glutathione.[97,98] Exogenously administered glutathione accumulates in the kidney, and thus protects against cisplatin-induced nephrotoxicity.[99] The glutathione system has also been associated with chemotherapy resistance. Altered glutathione metabolism is thought to be one of the mechanisms of this,[100] and the expression of the enzyme glutathione *S*-transferase, which catalyses the conjugation of glutathione with several cytotoxic drugs, correlates with the antitumour response to these agents.[101]

The selectivity of the cytoprotection by glutathione may be related to a higher activity of this endogenous detoxification system in healthy tissues and a limited uptake of exogenously administered glutathione by tumour tissues, due to reduced levels of γ-glutamyl transpeptidase in the membrane of tumour cells.[102]

4.4 Sodium Thiosulfate

Sodium thiosulfate (STS) neutralises platinum compounds by converting them into nontoxic species.[103,104] Since sodium thiosulfate is limited to the extracellular space, it does not interact with intracellular platinum. The molar ratio of sodium thiosulfate to platinum determines the extent and rate of neutralisation. About a 400-fold excess of sodium thiosulfate is necessary for an adequate inactivation of cisplatin. Clinically, sodium thiosulfate is still in use for residual ovarian cancer in the abdomen, when cisplatin is given intraperitoneally with systemic sodium thiosulfate protection.[105] The rapid accumulation of sodium thiosulfate in the kidneys and high concentration in the urine explains its specific protection against the renal toxicity of cisplatin.[106]

4.5 Mesna

Mesna binds with and inactivates the alkylators phosphoramide mustard and acrolein, which are toxic metabolites of cyclophosphamide and ifosfamide.[107,108] In the circulation, mesna is converted into the inactive disulphide dimesna, but during transport in the urothelial tract it is reconverted into mesna by glutathione reductase. In the bladder, free sulfhydryl groups neutralise acrolein, the agent which is responsible for urothelial toxicity. This toxicity consists of haemorrhagic cystitis, bladder fibrosis and an increased risk of bladder cancer. The peak urinary mesna concentration after intravenous or oral administration occurs after 1 or 3 hours, respectively.[109] In order to maintain the optimal urothelial protection, mesna should be given continuously before, during and after ifosfamide administration.

4.6 Ditiocarb Sodium

Ditiocarb sodium (diethyldithiocarbamate, DDTC) is a heavy-metal chelating agent, which is used as an antidote for acute nickel and cadmium poisoning. In animal studies, ditiocarb sodium reduced the cytotoxicity of platinum compounds by interaction with these drugs in the circulation and by inhibition of cisplatin-DNA adduct formation.[110] Clinical studies were discontinued, however, because of ditiocarb sodium–related autonomic hyperactivity, consisting of hypertension and flushing in the absence

of a substantial reduction of platinum-induced toxicities.[111,112] In a recent study, using a regimen of ditiocarb sodium with low toxicity, there was no evidence of cytoprotection. In fact, the patients in the control arm tolerated cisplatin treatment better than those in the ditiocarb sodium arm.[113]

4.7 Flavonoids

Flavonoids are ubiquitous in photosynthesising cells and are therefore present in various plants. They possess iron-chelating,[114] oxygen[115] and nitric oxide[116] radical–scavenging capacity and have a favourable toxicity profile, even at high concentrations. Monohydroxyethylrutoside (monoHer), a semisynthetic flavonoid, is a promising compound for protection against doxorubicin-induced cardiotoxicity, without influencing the antitumour activity of that drug *in vitro* and *in vivo*.[117]

4.8 ORG-2766

Melanocorticoids [corticotropin (ACTH) and α-melanocyte–stimulating hormone–like peptides] affect the function of nervous tissue in animals[118,119] and humans. It is hypothesised that melanocorticoids mimic an endogenous peptide, which stimulates the recovery of damaged neurons. ORG-2766, a synthetic corticotropin (4-9) analogue is without corticotropic or melanotropic activity and has mainly been studied as a means of preventing or improving the recovery of neuropathy induced by cisplatin,[120-122] vinca alkaloids[123] and paclitaxel.[124]

5. Prevention of Chemotherapy-Induced Toxicities

5.1 Cardiotoxicity

The problem of anthracylcine–associated cardiotoxicity has been addressed with various strategies:[125] reducing the dose, adjusting the dose to individual risk factors, prolonging infusion duration, administration of moderate doses of doxorubicin on a weekly basis, development of less cardiotoxic analogues of doxorubicin (e.g. epirubicin), use of liposomes as carriers of doxorubicin,[126,127] and the introduction of cardioprotective agents.

5.1.1 Dexrazoxane

A number of clinical trials found that dexrazoxane significantly reduced cardiotoxicity in women with breast cancer and children with soft tissue sarcomas receiving an anthracycline–containing therapy (see table II).[128-132] All except one of the trials in breast cancer patients employed standard-dose doxorubicin. Clinical congestive heart failure (CHF), measurements of heart contractility by echocardiography or left ventricular ejection fraction (LVEF) and endomyocardial biopsies were used as parameters of cardiotoxicity in these studies. By all of these criteria, dexrazoxane, at a dexrazoxane/ doxorubicin ratio of 20 : 1 or 10 : 1, has consistently been demonstrated to reduce cardiotoxicity.[128-132] The risk of developing any cardiac event during these studies was 2 to 3 times lower and the risk of CHF was 8 to 10 times lower in patients treated with dexrazoxane than in controls.

Patients receiving dexrazoxane were able to tolerate higher cumulative doses of doxorubicin.[128] The resting LVEF showed a gradually progressive fall, starting from a dose level of doxorubicin 300 mg/m^2, but the rate of decline was significantly less in the dexrazoxane group. Moreover, when dexrazoxane was started after a cumulative dose of doxorubicin 300 mg/m^2, there was still a cardioprotective effect observed with a 3.5 times reduced risk of experiencing a cardiac event.[135] This observation has led to the recommendation that dexrazoxane be started after a cumulative dose of doxorubicin 300 mg/m^2 in responding patients for whom further treatment is indicated. Cardiac protection has also been shown in combination with high dose epirubicin, using a 10 : 1 dexrazoxane/ epirubicin ratio.[133] Finally, it has been shown that dexrazoxane is also beneficial for children treated with doxorubicin-containing chemotherapy.[134]

While these data show that dexrazoxane is a safe, effective cardioprotective agent, in our opinion 3 issues remain to be clarified before it can be recommended for standard use in patients treated with anthracyclines.

Firstly, large, randomised studies with a long term follow-up are needed to determine whether

Table II. Randomised studies using anthracycline with and without dexrazoxane (Dex)

Reference	Drug	Anthracycline dose (mg/m^2)	Ratio Dex : anthracycline	No. of patients
Speyer[128]	F, D, C	50	20	150[a]
Rosenfeld[129]	F, D, C	50	10	349[a]
Weisberg[130]	F, D, C	50	20	121[a]
Maillard[131]	F, D, C	50	10	185[a]
Swain[132]	F, D, C	50	10	534[a]
Venturini[133]	FEC *or* E	60 *or* 120	10	162[a]
Wexler[134]	VDC/Et	50-70	20	33[b]

a Adult women with advanced breast cancer.

b Children with a sarcoma.

C = cyclophosphamide; **D** = doxorubicin; **Dex** = dexrazoxane; **E** = epirubicin; **Et** = etoposide; **F** = fluorouracil; **I** = ifosfamide; **V** = vincristine.

dexrazoxane will prevent or reduce chronic, late-onset cardiotoxicity. This issue is of special importance as >50% of survivors of childhood cancer have been treated with anthrcyclines and are candidates to develop late-onset cardiotoxicity.[136,137]

Secondly, there is evidence that dexrazoxane influences the pharmacokinetics of anthracyclines. This has been demonstrated for doxorubicin[138] and for epirubicin[139] at doses of dexrazoxane >900 mg/m^2, but not at the presently recommended 10 : 1 ratio of dexrazoxane/doxorubicin dose. Higher doses of dexrazoxane increased the systemic clearance of these anthracylines, resulting in a decrease in the AUC. This decrease in exposure to anthracyclines may have an impact on both toxicity and the antitumour effect of these agents. However, only 1 study in breast cancer patients[131] has shown a reduced response rate in patients given doxorubicin plus dexrazoxane than that in patients given doxorubicin plus placebo. However, there was no effect on survival. In all other studies the response rate to the anthracycline was not compromised by dexrazoxane.

Thirdly, dexrazoxane has its own toxicity and may also have antitumour activity.[91] It is able to induce a moderate myelotoxicity at dosages of >1000 mg/m^2, and a chemical phlebitis. There is a lack of information about long term adverse effects.

The avoidance of anthracyclines in high dose chemotherapy programmes has made cardiotoxicity an infrequent complication of this strategy.[140] However, other drugs which are commonly included in these protocols, such as alkylating agents and mitoxantrone, an anthraquinone structurally related to doxorubicin, can also induce cardiotoxicity.[20,29] No data are available concerning the use of dexrazoxane in these high dose chemotherapy protocols.

5.1.2 Other Agents

Other agents of potential interest as cardioprotectants are amifostine and some flavonoids. Amifostine accumulates rapidly in heart tissue[141] and, by virtue of its potential to scavenge oxygen radicals, it reduces doxorubicin-associated cardiotoxicity, as has been shown in cultured neonatal rat heart myocytes[142] and in mice.[143] In addition, contrary to dexrazoxane, amifostine does not reduce the systemic exposure to anthracyclines but may even increase their steady-state plasma concentrations and their AUC.[138] These findings suggest that the cardioprotective effect of amifostine is worth investigating in patients treated with (high dose) anthracyclines.

Monohydroxyethylrutoside has been studied *in vitro* [144] and in mice treated with doxorubicin.[114] Cardiotoxicity, as measured by ST interval and histological investigations, was reduced to a level similar to that achieved with dexrazoxane.[144,145] Monohydroxyethylrutoside did not compromise the antitumour activity of doxorubicin,[117] and animals given high doses of the former showed no toxicity. Evaluation of the cardioprotective effects of this agent in patients receiving anthracycline therapy is warranted.

5.2 Neurotoxicity

5.2.1 Corticotropin Analogue

The analogue of corticotropin (ACTH 4-9; ORG-2766) has been shown to prevent cisplatin-[118] and paclitaxel[124]-induced peripheral neuropathy in rats. In humans, ORG-2766 has been used at different doses (usually 2mg or 2 mg/m^2, administered subcutaneously) before and after cisplatin or vinca alkaloid therapy. A small study suggested a protective effect of ORG-2766 on vinca alkaloid neuropathy in lymphoma patients.[123] No studies have been done combining paclitaxel and ORG-2766. Two randomised studies showed that this drug reduced neurotoxicity in cisplatin-treated patients with ovarian or testicular cancer.[120,121] In these trials, the ORG-2766 group of patients showed a more limited reduction in vibration perception threshold (VPT) and fewer paraesthesias. However, these results could not be reproduced in 2 subsequent randomised studies of larger numbers of ovarian cancer patients treated with a similar cisplatin regimen.[146,147] Because of the negative findings in the last 2 trials, further clinical development of ORG-2766 was terminated.

5.2.2 Glutathione

In a rat model, glutathione prevented cisplatin-induced neuropathy, as measured by the sensory nerve conduction velocity.[102]

In 3 recent randomised studies, patients with advanced gastric[97] or ovarian cancer[148,149] received cisplatin-based chemotherapy with or without glutathione. Glutathione 1.5 mg/m^2 was administered immediately before cisplatin in all trials and it was repeated over 4 days in one study.[148] In all studies, this drug gave significant neuroprotection as measured by clinical symptoms, sensory nerve conduction and VPT. Although glutathione reduced neurotoxicity, it did not completely prevent it. It did not reduce the antitumour response to cisplatin in these studies.

5.2.3 Amifostine

Two laboratory studies, using the ganglia of the CNS of the pond snail *Lymnaea stagnalis*[150] or dorsal root ganglion cells in culture,[151] demonstrated prevention of cisplatin-induced neuropathy by amifostine. These findings have been confirmed in 2 randomised studies in patients. In the first, ovarian cancer patients were treated with 6 cycles of cisplatin 100 mg/m^2 plus cyclophosphamide 1000 mg/m^2 with or without amifostine 910 mg/m^2. Neuropathy, defined as the occurrence of symptoms of peripheral neuropathy or a decrease in neurological function, was significantly reduced from cycle 5 onwards in the amifostine arm.[152] In the second, head and neck cancer patients were treated with weekly cisplatin 70 mg/m^2 for 6 cycles with or without amifostine 740 mg/m^2.[153] In this study, the protection was evident only from the VPT assessments, not from clinical signs or symptoms. In a phase II study using doses of paclitaxel >310 mg/m^2 preceded by amifostine 910 mg/m^2, the neurotoxicity was less than expected,[154] which suggested protection by amifostine against taxoid-induced neurotoxicity. Because cisplatin and paclitaxel are often used in combination, further investigation into the use of amifostine for this indication is warranted.

5.2.4 Other Agents

Preclinical data suggest that nerve growth factor (NGF) prevents neurotoxicity induced by cisplatin, vinca alkaloids and taxoids.[155,156] Thus, clinical investigation of NGF seems also to be warranted.

A recent report suggested that methylthioninium chloride (methylene blue) may be used both for prophylaxis and for reversal of ifosfamide-induced encephalopathy.[157] This interesting observation remains to be investigated further.

5.3 Ototoxicity

5.3.1 Sodium Thiosulfate

Animal studies have shown that the administration of sodium thiosulfate or ditiocarb sodium reduced the ototoxicity induced by cisplatin or carboplatin.[158]

Sodium thiosulfate, given 2 hours after carboplatin, substantially prevented carboplatin-induced ototoxicity in patients with malignant brain tumours.[51] However, in a large, randomised clinical study using high dose cisplatin in combination with

ditiocarb sodium or alone, hearing loss was equivalent in both treatment arms.[113]

5.3.2 Amifostine

In 2 randomised clinical studies the effect of pretreatment with amifostine on cisplatin-induced ototoxicity was investigated. Kemp et al.[152] obtained only baseline audiograms, which were repeated if clinical hearing problems developed. With this approach a 43% reduction in the incidence of cisplatin-induced ototoxicity was documented in patients given amifostine. In the study by Planting et al.,[153] ototoxicity assessed by serial audiograms was similar in both treatment arms. There seems to be a good case for further studies of the effect of sodium thiosulfate and amifostine on cisplatin-induced ototoxicity, using systematically applied measurements.

5.4 Nephrotoxicity

Hyperhydration is a useful general approach to reducing or preventing chemotherapy-induced nephrotoxicity. In the case of methotrexate, additional urinary alkalinisation helps to prevent precipitation of the drug in the renal tubules. The use of mesna to inactivate reactive metabolites of ifosfamide and cyclophosphamide in the renal system is a common and successful practice.

Several preclinical studies indicate that amifostine also offers protection against cisplatin-induced nephrotoxicity. In rats and mice, amifostine given at a dose of 200 mg/kg intraperitoneally, 30 minutes before cisplatin, protected against nephrotoxicity (determined by measuring blood urea nitrogen levels and histological examination).[159] The time dependence of modulating cisplatin-induced nephrotoxicity was demonstrated in Balb/c mice in which amifostine was given 30 or 5 minutes before or 30 minutes after cisplatin.[78] Only those mice given amifostine before cisplatin were protected against cisplatin-induced nephrotoxicity. Those treated with amifostine also tolerated a larger dose of cisplatin, resulting in an improved antitumour effect.

The protective effect of amifostine on nephrotoxicity induced by cisplatin has been confirmed in phase I and II studies.[160] Further evidence comes from 2 randomised trials in ovarian and head and neck cancer patients.[152,153] In the large ovarian cancer trial, a >40% decrease in creatinine clearance occurred in 30% of the control patients, compared with 13% in the amifostine arm. 5% of control patients discontinued treatment because of nephrotoxicity (serum creatinine level above 1.5 mg/dl 5 weeks after a chemotherapy cycle), compared with none in the amifostine arm. In the head and neck cancer study, no significant differences were observed in serum creatinine levels, but renal magnesium wasting was significantly reduced in the amifostine group.

5.5 Myelotoxicity

A large number of studies have shown the efficacy of haematopoietic growth factors on the recovery of peripheral blood cells after chemotherapy. However, protection of the bone marrow from toxicity has been studied less frequently.

5.5.1 Amifostine

A number of animal studies have demonstrated a myeloprotective effect of amifostine for haematopoietic progenitors or stem cells. Bone marrow function was studied in Balb/c mice treated with carboplatin with or without amifostine,[79] (given 30 or 5 minutes before or 30 minutes after the administration of carboplatin). After 24 hours, the *in vitro* proliferation of whole bone marrow (WBM) and 3-day nonadherent cells (NACs), and the clonogenic capacity, were evaluated. Optimal protection of WBM cells and NACs was achieved when amifostine was given 5 minutes before carboplatin, but the loss of clonogenic capacity was similar with and without the cytoprotective drug. In further animal studies, protection of haematopoietic stem cells by amifostine was observed for melphalan,[161] chlormethine (nitrogen mustard),[162] cisplatin, cyclophosphamide and fluorouracil.[163] Myelotoxocity was reduced 1.5 to 4.6 times in the presence of amifostine.

The growth of primitive haematopoietic progenitors, harvested from healthy human donors, was studied *in vitro* in the presence of a broad spec-

trum of antineoplastic agents with or without amifostine or its dephosphorylated metabolite WR-1065.[164] A significant degree of cytoprotection was demonstrable for 5 of the 7 chemotherapeutic agents used, with a magnitude of 1.35- to 65-fold. These indications of cytoprotection by amifostine for multilineage haematopoietic progenitors have been further confirmed in bone marrow purging studies.

Purging of bone marrow with hydroperoxycyclophosphamide in the presence of amifostine resulted in a significant decrease in time to marrow engraftment *in vitro*,[165] need for platelet transfusions, need for antibacterials and duration of hospital stay.[166]

Taken together, these data show that amifostine offers substantial cytoprotection for haematopoietic progenitor cells. These haematoprotective effects have been confirmed in animal studies using peripheral blood counts as parameters, and using different antineoplastic agents, including platinum compounds and fluorouracil,[167,168] and cyclophosphamide.[169] Haematoprotection, however, was mostly found in the thrombopoietic lineage and the gain, in terms of the maximum tolerated dose of the chemotherapeutic agent used, was moderate.[170] These animal studies have been followed by a series of human phase II studies which confirmed their findings. In these studies cisplatin,[160] carboplatin,[170] cyclophosphamide[171] and mitomycin C[172] were used.

In a large randomised ovarian cancer trial,[152] pretreatment with amifostine reduced the incidence of grade 4 neutropenia (associated with fever and/or infections) by 53%, and significantly reduced the number of days on antibacterial therapy and the number of days in hospital. The duration of neutropenia was longer in the control arm (i.e. without amifostine), which became more pronounced with multiple cycles of chemotherapy. Moreover, there was less need for transfusions of platelets and erythrocytes in the amifostine group. Withdrawal from chemotherapy because of haematological toxicity occurred significantly more in the control group.

In a head and neck cancer trial,[153] treatment delay because of bone marrow toxicity was also significantly reduced in the amifostine group. In addition, a small randomised trial of carboplatin with or without amifostine in patients with advanced solid tumours showed the protective effect of the latter drug on the thrombocyte cell lineage.[173]

Further large, randomised clinical studies using various chemotherapeutic agents are necessary in order to define the importance of amifostine for bone marrow protection, and to answer the question whether we really need amifostine for this purpose in view of the established stimulatory effects of haematopoietic growth factors on the recovery of blood cells.

From the data available, it appears that amifostine protects multilineage progenitors. This is different from the lineage-specific stimulatory effects of the commonly used colony-stimulating growth factors. Therefore, theoretically, amifostine given before and haematopoietic growth factors given after chemotherapy could provide complementary benefits to the haematopoietic status after cytotoxic therapies. In fact, this has been observed in preclinical models,[174-176] and should be investigated clinically.

5.6 Gastrointestinal Toxicity

Different procedures have been used to protect the oral mucosa against chemotherapy-induced damage. Vigorous mouth washes with disinfectants or saline solution have a limited effect on the occurrence of stomatitis, but should not be omitted.[177]

Mouthwashes containing epidermal growth factor[178] or α-tocopherol (vitamin E),[179] 2 substances which are thought to be important for the integrity of the gastrointestinal mucosa, have been used with some success in reducing or preventing chemotherapy-induced mucositis. The same is true for oral cryotherapy used for the prevention of stomatitis associated with fluorouracil.[180]

The use of a bowel decontamination regimen is a generally accepted procedure in high dose chemotherapy programmes, in order to prevent

fungal and Gram-negative invasion of the orogastrointestinal mucosa. In a recent clinical trial,[181] prolonged inhibition of gastric acid production by omeprazole was shown to be effective in preventing chemotherapy-induced gastroduodenal mucosal injury.

Another agent of interest is interleukin-11. In mice treated with fluorouracil in combination with radiotherapy, interleukin-11 prevented apoptosis of intestinal crypt cells and stimulated their proliferation, resulting in a reduction of intestinal toxicity.[182,183] Amifostine has been shown to protect against melphalan-induced gastrointestinal toxicity in mice.[161] The amino acid glutamine seems to be important for the maintenance of the intestinal structure in both healthy and stressed states. Animal studies have shown that exogenous glutamine reduced the intestinal toxicity induced by abdominal radiotherapy or intravenous fluorouracil.[184] Administration of glutamine to cancer patients treated with chemotherapy alone,[185] or with total body irradiation and high dose chemotherapy,[186] significantly reduced mucositis and other intestinal complications in these patients. Further clinical trials, using sensitive evaluations of mucosal injury throughout the gastrointestinal tract, should demonstrate the relevance of these observations.

5.7 Hepatotoxicity

The high uptake of amifostine by the liver,[187] together with its effective hydrolysis by hepatocytes,[188] makes this a promising drug for the prevention of chemotherapy-induced liver toxicity. Studies addressing this possibility and using sensitive markers of liver toxicity are sparse. Recently, a study was published in which amifostine was given via the hepatic artery preceding intra-arterially administered chemoembolisation; this treatment was well tolerated and seemed to be associated with less liver toxicity.[189] However, further investigation is warranted.

5.8 Pulmonary Toxicity

In vitro studies have shown that dexrazoxane has the capacity to remove iron from the iron-bleomycin complex, which is thought to be responsible for lung toxicity. Mice pretreated with dexrazoxane showed a significantly reduced severity of bleomycin-induced lung damage, in particular less fibrosis.[190] Amifostine has also shown a protective effect on lung damage induced by cyclophosphamide in mice.[191] In another study *in vitro*, it protected lung fibroblasts, but not non–small-cell lung cancer cells, from paclitaxel-induced cytotoxicity.[192] Recently, the protective effect of keratinocyte growth factor on bleomycin-induced lung fibrosis has been described in the rat.[193]

Finally, as lung toxicity may be associated with high-dose chemotherapy programmes containing cyclophosphamide and carmustine, early diagnosis by a noninvasive scoring system followed by early treatment with prednisone may ameliorate the outcome of lung toxicity.[194]

5.9 Gonadal Toxicity

Until now, there has been no established means of protecting gonadal function against chemotherapy-induced damage. At most, the sperm of germ cell cancer patients may be frozen for later use. Animal studies showed that a luteinising hormone–releasing hormone (LHRH) agonist could protect spermatogenesis against toxicity induced by doxorubicin.[195] Clinical trials using this strategy may be expected.

6. Prevention of Radiotherapy-Induced Toxicity

Reduction of radiation-induced toxicity to healthy tissues is a matter of technology in the first instance. The aim being to reduce the exposure of healthy tissues to radiation as much as possible without compromising tumour control. A second strategy involves the use of radioprotective agents which should decrease the radiosensitivity of healthy tissues without affecting the antitumour activity.

Amifostine has been applied extensively for this indication. Originally developed during extensive screening of sulfhydryl-containing compounds, it proved to be the most potent protector

against radiation-induced injury. Preclinical studies, indeed, showed convincingly that amifostine preferentially increased the radioresistance of healthy tissues.[7,196] In these studies, radiation was applied to cultured cells[197] and to animals, in which amifostine afforded protection against irradiation to intestinal crypts and the intestinal mucosa,[198] lung tissue[199] and the parotid gland.[200,201] Furthermore, amifostine proved to be responsible for the improved survival of mice after whole-body irradiation.[176]

It became clear that this drug should be administered shortly before radiation because of its rapid uptake in healthy tissues and the almost immediate generation of cellular damage by ionising radiation. Furthermore, it appeared that radioprotection by amifostine was dose-dependent, with a greater effect at higher doses.[196]

Human phase II/III studies of radioprotection by amifostine have concentrated on the toxicity of radiotherapy to the pelvis,[202-205] and head and neck.[206-210]

One of the first randomised trials included patients with advanced or recurrent rectal cancer treated with radiotherapy of the pelvis with or without amifostine.[202] Patients treated with intravenous amifostine 340 mg/m^2 before each radiation session showed a significant reduction of grades 2 and 3 late toxicities to the skin, bladder and bowel. However, in 2 other phase II studies,[203,204] amifostine did not protect against acute toxicities induced by radiation of the pelvis, but the drug doses used were somewhat low. In a phase I study of patients with cervical cancer who received amifostine with cisplatin and concurrent pelvic radiation, fewer late mucosal toxicities were seen compared with historical control patients.[205]

The benefit of amifostine in patients treated with radiotherapy for head and neck cancer may be of particular interest. Three studies have shown that amifostine protects the salivary gland from radiation damage, leading to a lower incidence of xerostomia.[206-209] This will be of even more importance for patients treated with a combination of radiotherapy and chemotherapy. In the study by Büntzel and colleagues,[209] amifostine significantly reduced the incidence and severity of stomatitis and xerostomia induced by simultaneous treatment with radiotherapy and carboplatin. Giglio et al.,[210] however, found that amifostine did not reduce the mucositis induced by an alternating regimen of radiotherapy and cisplatin plus fluorouracil.

Tannehill et al.[211] showed that pretreatment with amifostine could reduce the oesophageal toxicity caused by sequential cisplatin-based chemotherapy followed by radiotherapy for patients with lung cancer.

We conclude that amifostine has some potential to reduce early and late radiation-related toxicities, but that further studies are warranted in order to optimise its radioprotective effects and to establish the true benefit of this agent.[212]

7. Conclusions and Recommendations

In summary, cytoprotective agents should have the following properties: selectivity for healthy cells, ability to prevent or substantially reduce toxicity from chemotherapy and/or radiotherapy, have no effect on pharmacokinetics or antitumour activity of therapy, be well tolerated.

Comparing the various cytoprotectants (fig. 1) we come to the following conclusions:

Several cytoprotective agents have shown promising results in reducing toxicity from chemotherapy including amifostine, dexrazoxane, glutathione, sodium thiosulfate, ditiocarb sodium and mesna.

Amifostine is a broad-spectrum cytoprotective agent which at present has the largest preclinical and clinical database. Several of the other agents are either in a preliminary stage of investigation, or have a more restricted indication (e.g. flavonoids or mesna).

Glutathione is part of an important endogenous cytoprotective system. Administration of exogenous glutathione results in preferential support of healthy tissue detoxification over tumour tissue. Further investigation of the properties of this agent in various tissues is warranted.

Amifostine $NH_2–(CH_2)_3–NH–CH_2–CH_2–S–PO_3H_2$

WR-1065 $NH_2–(CH_2)_3–NH–CH_2–CH_2–SH$

Glutathione γ–Glu–Cys–Gly (SH)

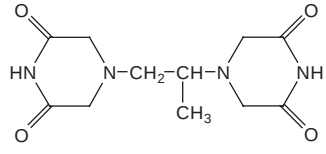
Sodium thiosulfate $Na_2S_2O_3$

Ditiocarb sodium $Na^+S^-–C–N(C_2H_5)_2$

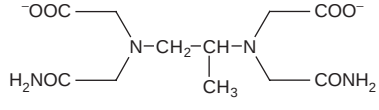
Mesna $H^+S–C–C–SO_3^-Na^+$

Dexrazoxane

Parent compound



ICRF-198



Monohydroxyethylrutoside

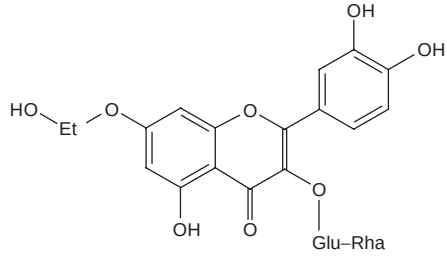


Fig. 1. Chemical structure/structural formulae of various cytoprotective agents for healthy tissues.

Some cytoprotectants inactivate anticancer agents in the circulation including sodium thiosulfate and ditiocarb sodium, and thus reduce the exposure to these chemotherapeutic agents. In the case of sodium thiosulfate, it is used systemically as a rescue agent in combination with high dose intraperitoneal cisplatin.

Pharmacological interactions between the different cytoprotective agents and various anticancer agents have been insufficiently investigated and need further attention before the cytoprotectors can be used routinely.

Some cytoprotectors, e.g. ditiocarb sodium, have serious adverse effects which prohibit their use. Others (e.g. amifostine) have less serious but nevertheless troublesome side effects, the cause of which needs to be further understood in order to make optimal use of the drug.

Combination therapy with amifostine with haematopoietic growth factors is worthy of consider-

ation given their different mechanisms of action. This might be of great value in patients undergoing high dose chemotherapy.

An accurate assessment of the kidney and liver functions of the cancer patient should be used to determine the optimal dose of chemotherapy. Evaluation of kidney function (e.g. by monitoring creatinine clearance) is important when using drugs which are largely metabolised or excreted by that organ. Indeed, many anticancer agents are metabolised by the liver, thus, impaired liver function, whatever the cause, can strongly influence their pharmacological behaviour. An easy and reliable test of liver function is, however, not as yet available.

The development of reliable and sensitive assessments of acute and late haematological and nonhaematological toxicities of anticancer therapy is, in our opinion, a neglected area in oncology which deserves more attention, especially in view of the tendency to use higher dose anticancer therapies.

In conclusion, none of the available drugs fulfil all the criteria of an ideal cytoprotective agent. The goal of future therapy should be to develop agents which are both specific for the biology of cancer and are able to be delivered preferentially in cancer tissue. Besides using chemo- and radioprotectants, the targeting of cytotoxic drugs by taking advantage of the expression of specific antigens by tumour endothelium[213] may be an important step in the direction of a more effective and less toxic anticancer therapy.

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