Cancer Drug Toxicities and Anaesthesia

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INTRODUCTION

Cancer is now overtaking cardiac disease as the most common cause of death in Western societies. Perhaps the main reason for this is increased life expectancy at birth. However, elsewhere, cancer is also rising in incidence, due in no small part to chronic infections such as viral hepatitis. Given improved survival with aggressive and modern treatments, surgery is becoming more important in the management of patients. Patients with cancer present numerous challenges to the anaesthetist. The potential for perioperative incidents and adverse events is increased because of problems related to the *disease process* itself and also because of problems related to the *treatment* of the cancer.

This review will focus on issues related to the use of chemotherapeutic and other agents. Drug development for cancer has changed considerably over the past decade or more, due to better understanding of cancer biology. Up until the late 1990s, the large majority of drugs reaching Phase III registration studies were chemotherapeutic agents. Although the side effect profile of these drugs was better than the previous generation of compounds, the characteristic problems are well known: nausea, alopecia, myelosuppression, fatigue, and other rarer side effects representing end organ damage (pulmonary fibrosis, cardiomyopathy, renal impairment, peripheral neuropathy and the like). Fortunately, with the advent of 5HT3 antagonists and the liberal use of steroids, vomiting is now uncommon. Most patients also receive multi-drug therapy, thereby increasing the complexity of the toxicity profile.

In general, treatment with cytotoxic drugs aims to cure or minimise the progress of a cancer by destroying rapidly dividing cells, ideally with minimal effects on normal cells. Those cells with the highest proliferative capacity are therefore more vulnerable to being affected, though to a lesser degree than malignant cells, thus forming the basis for relative tumour selectivity. Newer anti-cancer compounds however, may not be classical cytotoxics, and therefore have a different spectrum of side effects. These are discussed briefly in the latter sections of this paper. For the purposes of maintaining consistency with other papers, drugs will be classed by their mechanism of action.

An anaesthetic approach to patients with cancer has been recently reviewed in some detail[1,2] and will not be discussed here. Rather, this paper will focus on the toxicities of modern chemotherapeutic agents and their potential impact on anaesthesia.

TUMOUR ANTIBIOTICS

These agents are the most likely to cause pulmonary side-effects. Included in this class of compounds is bleomycin, perhaps the best recognized drug amongst anaesthetists due to its potential for pneumonitis. Bleomycin is given intravenously or intramuscularly, on a weekly schedule, almost always in combination with other drugs. The best known regimen, BEP (bleomycin, etoposide, cisplatin), is used to treat advanced germ cell tumours. Usually three cycles on a 3-weekly basis is administered, and patients generally experience a range of toxicities, given the aggressive intent (to cure) by oncologists. Apart from nausea, vomiting, alopecia and myelosuppression from the combination, the potential for idiosyncratic reactions such as pneumonitis from bleomycin has drawn great interest over many years. Most patients given BEP now have full respiratory function tests performed during treatment, including monitoring of the DLCO. If there is a sufficient fall in DLCO, bleomycin is often omitted from subsequent cycles.

Patients with bleomycin lung toxicity generally present with a hypersensitivity-like syndrome, with fever, tachypnoea, reduced DLCO and basal crackles on physical examination of the chest. Diagnosis of pulmonary toxicity is based on history, examination as well as CXR, lung function tests including DLCO and spirometry.

Chest pain, sometimes pleuritic in nature, may also be present [3]. Risk factors for pneumonitis include increasing age, reduced creatinine clearance, prior lung radiation, route of administration (IV > IM), oxygen exposure and total cumulative dose. [4,5] The risk for pneumonitis has been estimated to be 3% for total doses <450mg (note that the norm for >95% germ cell tumour patients would be a cumulative dose of 270mg after 3 cycles of BEP), and 15% for doses between 450mg and 550mg [6]. Fatalities are fortunately uncommon, but there is no satisfactory treatment. Steroids in high doses are used commonly in affected patients. Other tumour antibiotics (eg mitomycin C, actinomycin D, mithramycin) are infrequently used. Mitomycin C is perhaps the next most commonly used antibiotic, and is typically given intravesically for superficial bladder cancer with minimum side effects) or intravenously for advanced colorectal cancer. Systemic side effects include myelosuppression, prolonged thrombocytopenia, and pulmonary fibrosis. Mithramycin is no longer used for treatment of hypercalcemia.

MECHANISM OF OXYGEN-ENHANCED BLEOMYCIN TOXICITY

The mechanism of oxygen-enhanced bleomycin toxicity is unknown, but may be related to the phenomenon of chemotaxis-induced polymorphonuclear infiltration and subsequent superoxide anion generation due to some insult, or possibly due to direct effects of oxygen on fibroblasts and alveoli. Under conditions of hyperoxia, one could conceive of free radicals overwhelming antioxidant enzymes with subsequent apoptosis or injury to alveolar cells susceptible to injury in this way[7,8]. Since oxygen in normal concentrations does not injure alveolar cells, the mechanism for pulmonary toxicity may lie in a combination of factors, one of which could be DNA-strand instability induced by bleomycin. This is plausible because bleomycin hydrolase inactivates bleomycin, and is found only in low concentrations in alveolar cells. Given that activation of bleomycin - DNA intercalation is dependent on the presence of iron and oxygen, it is feasible that appropriate concentrations of oxygen and bleomycin in the alveolar cell could lead to fibrosis. The mechanism by which this occurs is unknown, but may involve inflammation and subsequent deposition of collagen[9]. Prolonged exposure to oxygen concentrations > FiO_2 0.3 (especially in patients with preexisting bleomycin lung injury, or those with bleomycin exposure within the past 1 to 2 months) can exacerbate bleomycin pneumonitis.

ANTHRACYCLINES

Also sometimes classified as antibiotics, this group of compounds (doxorubicin, daunorubicin, epirubicin, mitoxantrone and others) forms the mainstay of many treatment regimens (Table 3). Their proposed mechanism of action involves topoisomerase II dependent DNA cleavage and subsequent intercalation with double stranded DNA. Although myelosuppression is universal with this group of compounds, it is their potential for cardiotoxicity that sets them apart. Acute effects include ECG changes (sinus tachycardia, nonspecific S-T wave changes, ectopic beats, low voltage QRS complexes), whereas chronic use causes dose-dependent cardiomyopathy. Retrospective analyses have suggested hypothetical totals for the following drugs, beyond which the incidence of cardiomyopathy steeply rises: $450mg/m^2$, $600mg/m^2$, and $100mg/m^2$ cumulative total doses for doxorubicin, daunorubicin, and mitoxantrone, respectively. However, even in patients with normal resting cardiac function, prior anthracycline exposure may enhance the myocardial depressive effects of anaesthetics[10]. Known risk factors for doxorubicin - induced cardiomyopathy include prior/ current mediastinal radiotherapy, preexisting heart disease, concurrent cyclophosphamide or mitomycin use and the very young and very old patient. For daunorubicin the risk is increased in the elderly and the young. For mitoxantrone, mediastinal radiotherapy and prior doxorubicin use increase the risk of developing cardiomyopathy. Assessment for potential cardiotoxicity includes a history of cumulative dose, ECG and left ventricular ejection fraction estimation including wall motion abnormalities.

ALKYLATING AGENTS

These are a diverse set of drugs that can interact with nucleic acids, proteins and other intracellular molecules by forming charged compounds that bind with electron rich areas of other molecules. Their cytotoxicity probably relates to their ability to alkylate DNA and interfere with mitosis. If used on rapidly-growing tumours, tumour-lysis syndrome may result, leading to hyperkalaemia, hyperphosphataemia, hypocalcaemia and uric-acid nephropathy. Cyclophosphamide is perhaps the best known drug of this group. It inhibits pseudocholinesterase activity, exerts an ADH-like effect on the kidney, may cause interstitial pneumonitis (especially when given concurrently with bleomycin or carmustine) and may cause haemorrhagic cystitis. Ifosamide may cause haemorrhagic cystitis and renal tubular damage. Mesna, given concurrently with cyclophosphamide or ifosfamide, can protect against haemorrhagic cystitis.

Busulphan, chlorambucil and melphalan may cause interstitial pneumonitis. Radiotherapy to the chest enhances the risk. Nitrosureas (carmustine, lomustine, semustine and streptozocin) can all cause mild to moderate myelosuppression. Carmustine may cause interstitial pneumonitis, and the risk is increased with cumulative doses $>1000mg/m^2$, in smokers and when used in conjunction with radiotherapy or cyclophosphamide. Streptozocin, now used rarely, may cause hypoglycaemia acutely, but hyperglycaemia in the long term.

Metal salts such as *cis*-platinum, carboplatin and oxaliplatin are among the most widely used agents in oncology. These compounds cause intra-strand and inter-strand cross links in DNA ("adducts") which are thought to be their primary cytotoxic mechanism of action. In general, they can uncommonly cause nephrotoxicity, myelosuppression and neurotoxicity (especially ototoxicity and peripheral neuropathy). However, there is marked variation in the degree of these side effects depending on the compound and also the intent with which they are used. When used in potentially highly curable diseases such as metastatic germ cell tumour, the risk of peripheral neuropathy is low, but outweighed by the benefits of cisplatin, for example.

ANTIMETABOLITES

These agents have structural similarities to metabolites involved in nucleic acid synthesis, and result in either critical enzyme inhibition or incorporation of the wrong DNA code during cell synthesis. As a group (folic acid, pyrimidine and purine analogues), they can cause myelosuppression and gastrointestinal side effects.

Methotrexate is the most widely used drug in the folic acid class, although others such as pemetrexed have been recently developed for use in mesothelioma and non – small cell lung cancer. Mostly well tolerated, they may cause renal impairment, hypersensitivity pneumonitis and hepatic impairment. Nitrous oxide may potentiate methotrexate toxicity.

5-fluorouracil (5FU) was rationally designed in the late 1950s, and is still commonly used for diseases such as colorectal cancer, oesophageal cancer and head and neck cancer, most commonly in combination with other drugs. Adverse events also partly depend on the drug schedule; weekly 5FU is well tolerated, and causes proportionally more mucositis and diarrhoea than infusional 5FU, which is associated with more frequent myelosuppression and hand – foot syndrome. Capecitabine is an orally available pro-drug of 5FU, and has a similar side effect profile to infusional 5FU. Cardiotoxicity is often raised as an issue with this class of drugs, but in the main, studies investigating this toxicity are retrospective, and vary as to their definition of cardiotoxicity. Nevertheless, infusion-associated angina is thought occur in 1% to 4% of patients, possibly secondary to vasospasm.

MITOTIC INHIBITORS

Vincristine, vinblastine, and their semi – synthetic derivatives vindesine and vinorelbine act by inhibiting the formation of microtubule complexes within the cytoplasm, thereby arresting cell growth in metaphase. Neurotoxicity is the best known side effect of vinblastine and vincristine, particularly in the form of peripheral neuropathy. Inadvertent administration of vincristine into the CSF (intrathecally) is invariably fatal. Vincristine may potentiate ADH release, and constipation is also a feature of this group of compounds. Due to its relative lack of myelosuppression, vincristine can be incorporated in full dose with other drugs, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for Non – Hodgkin's lymphoma.

MITOTIC STABILISERS

Otherwise known as taxanes (docetaxel, paclitaxel), this class of compounds has a wide range of activity across various cancer types. Unlike mitotic inhibitors, taxanes stabilize the microtubule assembly once it has formed, thus preventing mitosis from proceeding. Newer, non – taxane microtubule stabilizers such as epothilones are also being developed. Typical adverse events include myelosuppression, peripheral neuropathy and occasionally, hypersensitivity reactions that are sometimes severe. Dexamethasone, antihistamines and H2 antagonists are often employed as premedication for paclitaxel in particular.

TOPOISOMERASE INHIBITORS

Topoisomerase enzymes are critical for unwinding of DNA during replication. Topoisomerase II inhibitors (etoposide, teniposide) are semi-synthetic podophyllotoxin derivatives from the May apple plant. Side effects include myelosuppression.

Topoisomerase I inhibitors such as irinotecan and topotecan contain lactone rings that are converted to their less active carboxylate moiety in the presence of blood. Irinotecan has activity in colorectal cancer, whereas topotecan is approved for use in ovarian cancer. Both drugs cause myelosuppression, anorexia and nausea. Acute and delayed onset diarrhoea is common with irinotecan.

Hormonal Agents

These agents modify the hormonal environment and have diverse mechanisms of action, not all of which are understood. Included are direct effects such as lysis of lymphoma cells caused by corticosteroids. In general, this group of drugs are well tolerated, though there is increasing appreciation of subtle and more long term side effects such as cognitive impairment and fatigue for example, in women undergoing adjuvant anti-oestrogen therapy. Similarly, men being treated with LHRH analogues for prostate cancer report changes in mood and personality, fatigue, congnitive changes and osteoporosis. Vascular events (both venous and arterial) are somewhat increased in some patients on hormonal treatment such as tamoxifen. Very little in the way of gastrointestinal, cardiological, neurological, renal or hematological side effects however, are experienced. Newer classes of drugs such as aromatase inhibitors (anastrazole, letrozole, exemestane) are very well tolerated on the whole but may cause musculoskeletal pain and osteoporosis.

NEW CLASSES OF AGENTS
Antibodies

A number of antibodies are now registered by the TGA for use in a variety of cancer patients. Perhaps the most commonly encountered agent is trastuzumab ("Herceptin"), a so-called targeted treatment to HER2 receptors. These are overexpressed on breast cancer cells in about 20% of women, and represent a poor prognostic factor. Women with HER2+ breast cancer in general have more aggressive cancers and poorer outcomes. Landmark studies[11] have now shown that the addition of trastuzumab to chemotherapy can improve response rates and survival for women with metastatic disease. Further, adjuvant treatment for up to 12 months with trastuzumab is standard for women with early HER2+ disease. The antibody may also be given as a single agent. Adverse effects are minimal for the drug alone, although an important side effect is cardiomyopathy. When combined with anthracyclines, the incidence of cardiomyopathy rises significantly (>10%), but even as a single agent in the adjuvant setting, some 14% of women required cessation of drug due to falls in left ventricular ejection fraction[12].

Rituximab is in common use for the treatment of Non-Hodgkin's lymphoma, but also in increasing demand for non – malignant diseases, including rheumatoid arthritis. It is well tolerated generally, other than flu – like side effects, and is not associated with cardiomyopathy. Bevacizumab is registered in Australia for advanced colorectal cancer, but is not commonly used because of cost issues. It has an infrequent though important side effect: major bleeding (pulmonary and GIT haemorrhage, <2% patients).

Other antibodies such as cetuximab (colorectal and head and neck cancer), panitumumab (colorectal cancer), TRAIL receptor agonists (to enhance apoptosis in a variety of cancer types) are either completing registration studies or in development.

Tyrosine kinase inhibitors

One of the gratifying developments in recent years for the treatment of cancers has been the advent of tyrosine kinase inhibitors. Many cell signaling pathways are initiated by ligand interaction with the appropriate cell surface receptor, and almost all of these have intracytoplasmic domains that contain a tyrosine kinase function that allows transduction of extracellular signals into cytoplasmic events. Blocking tyrosine kinase function can be achieved through antibodies (trastuzumab for HER2+ breast cancer, above) or small molecules such as imatinib ("Glivec") for the Philadelphia chromosome translocation in chronic myeloid leukaemia. Cancer cells exploit tyrosine kinase functions to increase or permanently switch on cell survival and proliferation pathways so that targeting these pathways in a cancer cell that is "addicted' to constitutive stimulation may result in increased apoptosis. Imatinib initially, followed by others such as erlotinib (Epidermal Growth Factor Receptor in non – small cell lung cancer, pancreatic cancer), sunitinib (Vascular Endothelial Growth Factor Receptor and other targets in renal cell cancer) and sorafenib (Raf – kinase in renal cancer, hepatocellular carcinoma) have provided strong proof-of-concept success in a wide variety of cancers.

Tyrosine kinase inhibitors have similar, but not identical side effect profiles. Typically, varying degrees of hypertension (especially for angiogenesis inhibitors), skin rash, GIT (diarrhoea, constipation, nausea), palmar – plantar syndrome, mild myelosuppression and liver function abnormalities may be encountered.

Drug interactions

Interactions between chemotherapy agents and anaesthesia drugs are not well studied. However, there are reports of significant interactions for some commonly used agents[13, 14]. Whilst some antibodies have prolonged half – lives (in the order of weeks), fortunately most small molecules used for cancer treatment have usually been eliminated by the time a patient requires surgery.

CONCLUSION

The prevalence of patients with cancer is increasing in Australia, due perhaps to unproved longevity. Together with the array of chemotherapeutic agents now available for the treatment of cancer, there is increasing likelihood that a substantial proportion of patients with cancer will require surgery and anaesthesia at some point in their disease course. The range of toxicities of cancer therapies is now very broad, and as many treatments are not cytotoxics, particularly the newer agents, the traditional classification of cancer drugs by mechanisms of action requires revision and better understanding. Although nausea and myelosuppression are still very common side effects of chemotherapy treatments, and the risk for pulmonary and cardiac complications fortunately uncommon, the sheer variety of adverse events and the potential for drug interactions now poses an escalating challenge to anaesthetists.

Table 1. Common chemotherapy agents and selected, featured toxicities
See Skeel[15] for more detail.

	Neuro	CVS	Resp	Haem	GIT	Renal	Other
anastrazole							musculoskeletal pain, osteoporosis
bleomycin			pneumonitis and pulmonary fibrosis				rashes, nail changes
capecitabine		cardiotoxicity (rare)			diarrhoea, increased bilirubin		hand – foot syndrome, fatigue
carboplatin				myelosuppression, thrombocytopenia	nausea		dosed according to GFR
cisplatin	peripheral neuropathy, ototoxicity				nausea, vomiting	increased creatinine	requires fluid loading
cyclophosphamide				myelosuppression	nausea	haemorrhagic cystitis	
docetaxel				myelosuppression		fluid retention	rashes
doxorubicin		cardiomyopathy, total-dose dependent		myelosuppression	nausea, vomiting, stomatitis		
epirubicin		cardiomyopathy, total-dose dependent		myelosuppression	nausea, stomatitis		
etoposide				myelosuppression			
5FU		cardiomyopathy, idiosyncratic			mucositis, diarrhoea		dihydropyrmidine deficiency may be associated with severe toxicity
gemcitabine			shortness of breath	myelosuppression, thrombocytopenia			rashes
ifosfamide	somnolence, confusion			myelosuppression		haemorrhagic cystitis	
imatinib				myelosuppression		fluid retention	rashes
interferon	headaches, dizziness				anorexia		asthenia, fatigue
irinotecan				myelosuppression	diarrhea		
letrozole							osteoporosis

LHRH analogues						fluid retention	fatigue, hot flushes
methotrexate			pneumonitis	myelosuppression	stomatitis		
mitoxantrone		cardiomyopathy, total-dose dependent		myelosuppression			
oxaliplatin	peripheral neuropathy				nausea		
paclitaxel	peripheral neuropathy			myelosuppression			musculoskeletal pain, hypersensitivity
rituximab				lymphopenia			hypersensitivity, myalgia
tamoxifen				venous thromboses		fluid retention	uterine cancer
temozolamide	dizziness, insomnia			myelosuppression	nausea		
trastuzumab		cardiomyopathy					fever, chills
vincristine	peripheral neuropathy				constipation		
vinorelbine				myelosuppression			
zoledronic acid						increased creatinine	fever, chills, osteonecrosis

Table 2. <u>Significant toxicities and their estimated drug class frequency</u>

The estimate of frequency is necessarily arbitrary because many toxicities are dose related. A significant proportion of patients on clinical trials and on clinical practice have treatment delays or dose reduction due to toxicities, and this can clearly alter the ultimate frequency with which a given toxicity occurs. Also, patients can be treated with varying degrees of aggressiveness, depending on their risk / benefit profile, so some patients may be expected to have more, or less toxicity. Finally, the frequency with which a toxicity occurs is not necessarily related to the severity. For instance, patients treated with anthracyclines may experience a 10-15% decline in their ejection fractions without experiencing any clinical sequelae.

	+ (<5% patients)	++ (5-10% patients)	+++ (>10% patients)
cardiomyopathy	miitoxantrone, doxorubicin, epirubicin		trastuzumab
	5FU, capecitabine		
	cyclophosphamide		
CNS toxicity	Ifosfamide, temozolamide		
creatinine	cisplatin, carboplatin, oxaliplatin		
	cyclophosphamide, ifosfamide		
fatigue			interfeon alpha
			platins
			anthracyclines
			taxanes
gonadal failure or dysfunction			anthracyclines, cyclophosphamide, ifosfamide

lymphopaenia		rituximab	fludaribine, temozolamide
severe myelosuppression (neutrophils < 0.5×10^9/L)	vincristine, vinblastine	carboplatin	anthracyclines
			taxanes (docetaxel > paclitaxel)
			gemcitabine, vinorelbine
			irinotecan, topotecan
			cyclophosphamide
			etoposide
pneumonitis / pulmonary fibrosis	methotrexate		bleomycin
	gemcitabine		
	nitrosureas		
	methotrexate		
	cyclophosphamide		
peripheral neuropathy	cisplatin	vincristine, paclitaxel	oxaliplatin
thrombocytopenia platelets < 50 x 10^9/L)			gemcitabine
			carboplatin

Table 3. Common malignancies and selected chemotherapy drugs and regimens

Malignancy	Common regimens and drugs	Notes
Non Hodgkin's Lymphoma	CHOP	cyclophosphamide, vincristine, doxorubicin, prednisone. Probably the most commonly used regimen for NHL.
	CNOP	As above, with mitoxantrone (an anthracenedione, also associated with cardiomyopathy) substituted for doxorubicin.
	R-CHOP	rituximab added to CHOP
	fludaribine	May cause significant lymphopenia.
	etoposide	Causes myelosuppresion. Most commonly used in combination
Hodgkin's Disease	ABVD	adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine. The most commonly used regimen for HD.
	MOPP	nitrogen mustard, vinblastine, procarbazine, prednisone
Bladder cancer	GC	gemcitabine alone or in combination with either cisplatin or carboplatin
	MVAC	methotrexate, vinblastine, adriamycin, cisplatin
Breast cancer	AC	adriamycin, cyclophosphamide
	FEC	5-fluorouracil, epirubicin, cyclophosphamide
	CMF	cyclophosphamide, methotrexate, 5-fluorouracil
	docetaxel, paclitaxel	taxanes commonly used as part of adjuvant treatment for early breast cancer, usually follows AC, but may be given in combination
	vinorelbine	vinca alkaloid, toxicities include myelosuppression and peripheral neuropathy
	capecitabine	oral 5FU pro-drug

	trastuzumab	Antibody to HER2 receptor. May cause cardiomyopathy, more frequently when used concurrently with doxorubicin.
Colorectal cancer	5-fluorouracil	Well tolerated generally. Uncommonly (<5%) associated with a variety of cardiac symptoms. Can cause severe toxicity in patients with dihydropyrimidine dehydrogenase deficiency (<1% population)
	FOLFOX	oxaliplatin, 5FU, Folinic Acid
	FOLFIRI	irinotecan, 5FU, Folinic Acid
	capecitabine	
	cetuximab	Antibody to Epidermal Growth Factor Receptor
	bevacizumab	Antibody to Vascular endothelial growth factor. Anti-angiogenic agent. Uncommon (1-3%) risk of major bleeding.
Gastric cancer	ECF	epirubicin, cisplatin, 5FU
	docetaxel	
Germ cell tumour	BEP	The most commonly used regimen. bleomycin, etoposide, cisplatin
	paclitaxel	
	ifosfamide	Can cause CNS toxicity
Head and Neck cancer	methotrexate	
	docetaxel	Recently approved by the TGA for head and neck cancer
	cisplatin, 5FU	
Lung cancer – non small cell	carboplatin or cisplatin	Usually used in combination with one of the "newer generation" of cytotoxics listed below
	gemcitabine	
	vinorelbine	
	paclitaxel	
	docetaxel	
	erlotinib	Oral Epidermal Growth Factor Receptor antagonist, usually used in second or third line treatment.
Lung cancer – small cell	carboplatin, etoposide	The most commonly used regimen for small cell lung cancer.
	OCA	vincristine, cyclophosphamide, adriamycin (doxorubicin)
	topotecan	topoisomerase I inhibitor
Melanoma	dacarbazine	
	fotemustine	Usually used for cerebral metastases.
Oesophageal cancer	cisplatin, 5FU	5FU usually given as a continuous infusion over 4-5 days in this regimen.
	ECF	
Ovarian cancer	carboplatin, paclitaxel	The most commonly used regimen for ovarian cancer.
	liposomal doxorubicin	
	docetaxel	
	gemcitabine	
	topotecan	
Pancreatic cancer	gemcitabine	The most commonly used drug for pancreatic cancer, sometimes in combination with other drugs. Thrombocytopenia is the most common toxicity.
	5FU	
Sarcomas	doxorubicin, ifosfamide	
	methotrexate	Sometimes used in combination or in very high dose.
	cyclophosphamide	Tends to be used in paediatric sarcoma populations (e.g. Ewing's sarcoma)
	etoposide	Paediatric sarcomas
	vincristine	Paediatric sarcomas

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