

# Oncology

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## Acute non-myelosuppressive complications of systemic anticancer therapy

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*Clin Med* 2008;8:439–42

Systemic cancer treatments are being used with increasing frequency, and treatment options are expanding with new drugs and new indications. Both these increases, coupled with the stated aims of the Cancer Reform Strategy to deliver treatments close to home, will inevitably result in more involvement of non-specialist clinicians in the acute management of cancer treatment complications. The most recent therapeutic newcomers to oncology are targeted therapies with more specific modes of action than conventional cytotoxic agents. This article will review the acute non-myelosuppressive complications of current and emerging cancer therapies, focusing mainly on toxicities that non-specialists are likely to encounter where active intervention is required.

### Hypersensitivity and acute drug reactions

Hypersensitivity and allergic reactions to intravenous (iv) anticancer agents are common, but mostly mild or moderate.<sup>1</sup> The presentation is similar to other drug reactions such as those seen with antibiotics and are treated in a similar way. Mild hypersensitivity reactions without hypotension or significant bronchospasm can be managed by discontin-

uation of the drug and administration of hydrocortisone and chlorpheniramine. Such reactions often settle rapidly, in which case drug infusion can be restarted under careful observation with a prolonged administration schedule. More severe anaphylactic reactions should be managed by immediate cessation of drug, and standard management for anaphylactic shock initiated with intensive therapy unit management where patients fail to respond to treatment.

### Special cases

*Paclitaxel* is notorious for inducing hypersensitivity, but the culprit is usually cremophor added as a solubilising agent in the formulation of the drug. Routine premedication with H1 and H2 receptor antagonists and high-dose dexamethasone should be given.

*Irinotecan* is associated with an acute cholinergic syndrome where patients may report sweating, diarrhoea, tachycardia and palpitations. These adverse events respond to subcutaneous atropine, often given prophylactically.

*Oxaliplatin* can provoke acute neurological symptoms, ranging from perioral dysaesthesiae, cold-related dysaesthesiae, muscle contractions and acute pseudolaryngospasm where patients experience a frightening sensation of being unable to breathe but stridor, wheezing and hypoxia are absent. The acute neuropathy improves spontaneously after cessation of drug

infusion and may be attenuated by prolongation of the infusion. Both acute and late onset oxaliplatin neuropathy have been linked to chelation of calcium and magnesium by oxaliplatin and its metabolites. Severe oxaliplatin induced pseudolaryngospasm should be treated with iv calcium and magnesium. However, they are not generally used as routine prophylaxis because both may reduce anticancer efficacy.

### Extravasation

Fortunately, serious extravasation is uncommon with well trained, experienced chemotherapy teams. All chemotherapy units will have an extravasation policy which should be readily available. Attempts should be made to aspirate back any extravasated drug through the original cannula. In the absence of drug specific treatment, ice packs should be applied to the affected area and steroid creams applied to reduce inflammation. Locally injected thiosulphate, hyaluronidase, dimethylsulfoxide or local heat packs are advocated for certain situations, but should not be used without specific input from an oncology team. Dexrazoxane is now licensed for the treatment of extravasation. However, it needs to be given within six hours and access to this expensive agent within such a short time frame may be limited.

### Tumour lysis syndrome

Tumour lysis syndrome presents as a characteristic set of metabolic derangements, arising as a consequence of rapid and massive lysis of tumours.<sup>2</sup> It manifests clinically as muscle weakness, cramps, paraesthesiae, paralysis in association with hypocalcaemia, and as arrhythmias including asystolic arrest, ventricular or atrial tachycardia.

Tumour lysis syndrome is a well recognised complication of the treatment of acute leukaemia and high-grade lymphoma. In both these diseases preventive measures, monitoring and active management usually ensure that the massive lysis does not adversely affect the patient's health. Less commonly, tumour lysis is seen in the treatment of solid

malignancies. There have been a number of published reports of tumour lysis associated with biological agents such as sunitinib.

The critical abnormalities in tumour lysis syndrome are the development of hyperuricaemia in association with hyperkalaemia, hyperphosphataemia and hypocalcaemia. Hyperuricaemia and hyperphosphataemia result in renal impairment or failure through urate and calcium phosphate crystal formation.

### Treatment

Allopurinol inhibits xanthine oxidase conversion of xanthine to urate and should be initiated if allopurinol was not used as prophylaxis. Rasburicase is a recombinant urate oxidase and converts uric acid into allantoin which is readily excreted. It should be considered in established tumour lysis syndrome to eliminate existing uric acid. High fluid loads should be used to increase urinary throughput. Haemodialysis is required if renal impairment is severe. Hypocalcaemia should be corrected only if symptomatic, to prevent worsening of the calcium phosphate deposition.

### Emesis

Failure to control emesis is common with first-line anti-emetic protocols.<sup>3</sup> A more aggressive anti-emetic regimen should be used where standard anti-emetics for a particular regimen have failed. If emesis is uncontrolled and

where inadequate oral intake is maintained, iv fluid and electrolytes are required while attempts are made to control the emesis. The most hazardous situation is where cisplatin has been administered and patients' urine output drops because of poor oral intake as this will magnify the renal toxicity of this agent. Cisplatin is increasingly used as a day-case treatment; prompt readmission is required in patients who are vomiting during the few days after administration.

Moderately or highly emetogenic regimens require premedication with high-dose steroids and 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) antagonists, with follow-on oral steroids in combination with further oral anti-emetics such as domperidone or additional 5-HT<sub>3</sub> antagonists. If these agents fail, addition of the NK-1 inhibitor aprepitant or longer acting 5-HT<sub>3</sub> antagonists such as palonosetron should be considered. Anxiety plays an important role in acute emesis and benzodiazepines can be used to good effect in reducing this.

### Renal toxicity

Although several anticancer agents are recognised as potentially nephrotoxic, cisplatin is the most common agent associated with renal toxicity.<sup>4</sup> Cisplatin is actively transported into renal tubular cells where a complex mechanism of direct and indirect cytotoxicity results in tubular necrosis leading to a magnesium- and potassium-losing nephropathy. Renal damage is largely reversible

in most patients but permanent renal impairment or renal failure is possible in severe nephrotoxicity.

Pre- and posthydration is a mandatory component of safe cisplatin treatment. After discharge, high fluid intake is required to maintain urinary flow to limit renal damage. Administration of magnesium is thought to limit renal toxicity. Reduced hydration status from dysphagia or emesis is hazardous and compounds renal toxicity. Management of established renal toxicity comprises careful attention to fluid balance, replacement of potassium and magnesium, and allowing tubular regeneration.

### Gastrointestinal tract toxicity

The gastrointestinal (GI) tract is second only to bone marrow in sensitivity to standard cytotoxic agents. Certain drugs have a propensity to cause GI damage preferentially, often schedule dependent. GI toxicity is dose-limiting in high-dose chemotherapy where bone marrow support or transplantation is used. The mechanism of damage is probably similar throughout the GI tract, but symptomatic presentation depends on the predominant site of damage.

#### Upper gastrointestinal tract

Oral mucositis or stomatitis commences about 5–10 days after starting chemotherapy, initially as erythematous inflammation of the oral mucosa, followed when severe by ulceration. Without treatment, secondary infection ensues, primarily candidiasis but colonisation or active infection with other organisms is common and delays healing. The condition is painful and interferes with, first solid nutritional intake and then liquids, or completely prevents, liquid intake. This necessitates parenteral fluid replacement and, when severe and protracted, parenteral feeding. Oesophageal and gastric GI toxicity manifests as dysphagia, dyspepsia and nausea.

*Pathogenesis.* Chemotherapy-induced mucositis is increasingly recognised as a complex process causing damage and reaction in epithelial and submucosal

## Key Points

**Specialist advice should be sought in the management of severe acute side effects from anticancer treatment**

**Moderately severe acute non-myelosuppressive side effects from chemotherapy are common, mostly self-limiting and responding to supportive care measures**

**Infusion reactions are common, occasionally severe, but respond well to appropriate management**

**Uncontrolled chemotherapy-induced emesis is a particular concern in patients treated with cisplatin**

**Severe oropharyngeal mucositis requires parenteral rehydration, treatment of superadded infection, mucosal protection and adequate analgesia**

**KEY WORDS:** supportive care, anticancer treatment, complications, Mucositis

elements.<sup>5</sup> On exposure to chemotherapy, direct DNA damage accounts for a modest degree of rapid cell death, followed by a complex activation of multiple cascades mediated through generation of reactive oxygen species. These include activation of NF- $\kappa$ B which mediates further tissue injury and production of pro-inflammatory cytokines. The resultant ulceration, usually covered by a fibrinous exudate or pseudomembrane, carries a rich bacterial flora which further promotes an inflammatory response in the submucosa. Healing proceeds through migration of epithelial cells from less damaged borders of ulcers to repopulate the ulcer base and rebuild the integrity of the mucosa.

**Treatment.** Until recently treatment has been purely supportive using antiseptic and analgesic mouth washes. Active treatment of associated infection with topical and systemic antifungals or antibiotics together with aspirin mouth washes is important in minimising the inflammatory process and facilitating healing. Protection of the damaged mucosa with sucralfate orabase or proprietary products such as gelclair eases symptoms further and protects the mucosa. When required, systemic analgesia may involve strong opiates. If fluid intake is restricted, iv fluids are mandatory. In very severe cases, predominantly associated with high-dose chemotherapy, temporary parenteral nutrition may be required. Mucositis associated with bolus 5-fluorouracil therapy can be reduced by sucking ice chips to reduce drug delivery to the oral mucosa.

**Keratinocyte growth factors.** Keratinocyte growth factor-1 (KGF-1), a member of the fibroblast growth factor family, is now available as a recombinant therapeutic agent (palifermin). It has recently shown a significant reduction in severe mucositis when used prophylactically in patients undergoing stem cell transplants where mucositis is particularly severe. In addition to encouraging more rapid re-epithelialisation, there is evidence that KGF species can reduce mucosal injury by suppression of apoptosis and limiting damage effects of reactive oxygen species

through upregulation of Nrf-2. Current use of palifermin is low, primarily because of cost.

#### **Lower gastrointestinal tract**

The primary presentation of lower GI toxicity is diarrhoea. This can become profuse, causing severe dehydration and electrolyte imbalance and there may be associated abdominal pain. The mechanism of damage to the lower GI tract is similar to that described for mucositis. Recovery is achieved through regrowth of an intact columnar epithelium.

Management of chemotherapy-induced diarrhoea is supportive. For modest cases, loperamide can suppress the symptoms. For severe cases, inpatient management with iv fluids and electrolyte replacement is usually sufficient, but in very severe protracted cases parenteral nutrition should be considered because protein loss from the GI tract can be significant and absorption of nutrition impaired. Secondary infection can prolong the episode. Faecal testing for pathogenic organisms and *Clostridium difficile* enterotoxin should be repeated during prolonged episodes.

#### **Dermatological toxicity**

Skin rashes are common with chemotherapeutic drugs. A non-specific dermatitis is often seen which can vary in severity from a mild itchy rash to a severe skin eruption that necessitates discontinuation of the offending agent. Two specific skin syndromes are well recognised:

- palmar-plantar erythrodysesthesia (PPE) or hand-foot syndrome
- interference with epidermal growth factor receptor (EGFR) function.

#### **Palmar-plantar erythrodysesthesia**

PPE is common with fluoropyrimidines, particularly the oral agent capecitabine, but is also seen with liposomal anthracyclines and some of the newer biological agents such as sunitinib. Characterised by palmoplantar erythema, the condition can progress to painful desquamation of the affected areas. Treatment comprises protection of the skin by emollient creams and avoiding friction.

There is some data supporting use of pyridoxine to reduce severity of PPE but usually treatment interruption and dose modification are needed to prevent worsening of the condition and to achieve recovery.

#### **Epidermal growth factor receptor antagonism**

The second skin toxicity of interest is associated with agents that interfere with EGFR function. This appears as an acneiform rash predominantly affecting the trunk and face. Licensed agents such as cetuximab (a monoclonal anti-EGFR antibody), erlotinib and lapatinib (inhibitors of the intracellular tyrosine kinase activation region of EGFR) are recognised as provoking this reaction which can be florid in presentation. However, the current use of these agents is somewhat limited. The rash often settles with time and perseverance is recommended since its appearance is associated with a higher probability of clinical benefit. Management is with a combination of moisturising and masking creams, with antibiotics in severe cases. An oatmeal based face cream appears to improve the rash and is widely used.

#### **Cardiotoxicity**

Anthracyclines have long been recognised as cardiotoxic agents, inducing direct and cumulative myocardial damage. With the current availability of many new cytotoxic agents the number of patients treated close to the recognised threshold for maximum anthracycline exposure is now small. In addition, less cardiotoxic anthracyclines are in common usage. Cardiac damage presents clinically as a dilated cardiomyopathy with reduced ejection fraction and frequently refractory to treatment.<sup>6</sup>

#### **Trastusumab**

Trastusumab is a monoclonal antibody that targets the cell surface signalling molecule HER-2 which is overexpressed in some breast and other cancers and contributes to the aggressive nature of these

cancers. HER-2 is also important in cardiac development and in the response to cardiac injury. Trastusumab, as monotherapy or in combination with other cytotoxic agents, still produces a cardiotoxic effect in a minority of patients. Therefore, cardiac monitoring, with serial measurement of cardiac ejection fraction by echocardiography or multiple gated acquisition scans, is recommended. If there is significant decline in ejection fraction, trastusumab therapy should be suspended; if it has declined below normal, patients should be treated with angiotensin-converting enzyme inhibitors or other drugs to reduce afterload.

**Tyrosine kinase inhibitors**

A number of the new tyrosine kinase inhibitors are in development for the treatment of a wide range of cancers. Lapatinib, an inhibitor of both HER-1 and HER-2, appears to have a relatively safe cardiac toxicity profile. Other tyrosine kinase inhibitors that target a variety of oncogenic signalling pathways (often multiple) need to be monitored carefully as many induce prolongation of the QTc interval and have the potential to induce cardiac arrhythmia.

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**Contemporary management of hepatocellular carcinoma**

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*Clin Med* 2008;8:442–7

The liver is the organ most frequently involved in cancer, usually by metastases. Primary liver cancer (hepatocellular carcinoma (HCC)) is a major public health problem in developing countries, responsible for over 500,000 deaths per year. In the West its incidence is rising, in part due to the increasing prevalence of chronic hepatitis C virus (HCV) infection.<sup>1</sup> A variety of treatment options exist but these are generally limited to carefully selected patients. Until recently there was no good systemic therapy, but an increased understanding of the molecular pathogenesis of HCC and the advent of novel targeted agents have seen the emergence of active therapies in this setting.

**Epidemiology and aetiology**

HCC is one of the commonest malignancies worldwide but with wide geographical variation (Table 1). It occurs almost

exclusively on a background of chronic liver disease (Table 2), usually at the stage of cirrhosis. This has a significant impact on the mode of presentation, complicates diagnosis and limits therapeutic options. Knowledge of aetiological factors provides the opportunity for preventive strategies. A hepatitis B virus vaccination programme of inoculating neonates, initiated in Taiwan in the early 1980s, has resulted in a clear reduction in the incidence of childhood HCC.<sup>2</sup> An effect on the incidence in adults may take a further 20 years to become apparent. There is also evidence to suggest that antiviral therapy in patients with chronic hepatitis B may reduce the incidence of HCC.<sup>3</sup> There is no vaccine against HCV, but antiviral drugs probably also reduce the incidence of HCC in that situation.

**Diagnosis**

The functional reserve of the liver is such that tumours can reach a considerable size before causing symptoms or signs, typically right upper quadrant pain, hepatomegaly and weight loss. Decompensation of chronic liver disease (variceal haemorrhage, ascites, encephalopathy) is also a frequent presentation. Less commonly, a tumour may rupture, resulting in severe abdominal

**Table 1. Geographical incidence of hepatocellular carcinoma per 100,000 population.**

Incidence	Country	Men	Women
Low	UK	1.6	0.8
	USA (white)	2	1
	Australia	1.1	0.5
	Germany	4	1.2
	Denmark	3.6	2.3
Intermediate	Italy	7.5	3.5
	Spain	7.5	4
	Romania	11.8	7.9
	Argentina	8	5
High	Japan	20	5
	Hong Kong	32	7
	Zimbabwe	65	25
	Senegal	25	9
	Taiwan	85	–