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Treating the Treatment: Toxicity of Cancer Chemotherapy

SUMMARY

Many cancer chemotherapeutic agents can produce toxicity, even at the usual therapeutic doses. Family physicians are often called upon to treat symptoms of these toxicities and to advise patients about them. This brief discussion may help family physicians to anticipate some of the problems, to avoid some, and to manage others more effectively.
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RÉSUMÉ

Plusieurs agents chimiothérapeutiques contre le cancer peuvent engendrer une toxicité, même aux doses thérapeutiques habituelles. Les médecins de famille sont souvent appelés à traiter les symptômes de telles toxicités et à en aviser les patients. Cette brève discussion peut aider les médecins de famille à anticiper certains de ces problèmes, à les éviter et à les traiter plus efficacement.

Key words: chemotherapy for cancer, family medicine, oncology, pharmacology, toxicity

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ALMOST ALL EFFECTIVE medications have the potential to produce toxicity or side-effects, either at therapeutic dose levels or at levels that exceed the therapeutic dose. Anticancer chemotherapeutic agents (CCAs) are certainly very effective and biologically active when one considers that they are called upon to achieve a task, once thought impossible, of eradicating cancer cells without producing lethal toxicity to the host. Although this goal is achieved in an increasing number of types of cancer, in most instances the treatment falls short in one or the other requirement.

In those types of cancer or situations where, because of extent or distribution of disease, cure is not a reasonable possibility, treatment must be viewed as palliative, intended to relieve or prevent the impending development of symptomatic problems or prolong useful survival. In this circumstance the toxicity expected of treatment must be weighed against the result likely to be achieved, and this must be discussed with the patient. The patient may accept a lower level of toxicity than if he or she anticipates a cure. The aims of treatment must be cure, useful prolongation of life, or enhancement of the quality of life.

The toxicity of CCAs is complicated by the frequent use of combinations of agents rather than single agents and by the fact that many agents share many of the toxicities, which may be additive or more than additive. A number of toxicities also occur well within the therapeutic dose range and are not a result of excessive dose. Fortunately some progress has been made in preventing or managing some of the toxicities.

Common Acute Toxicities

Toxic effects that are common to many CCAs include nausea and vomiting, hair loss, stomatitis, and leukopenia.

Nausea and Vomiting

Nausea and vomiting may be a result of a direct effect of many CCAs or their metabolites on the chemoreceptor trigger zone and the vomiting center located in the medulla. Some agents may have an additional direct effect on the gastrointestinal tract. It must be kept in mind that a number of other situations that are common in cancer patients may be responsible for nausea and vomiting, such as central nervous system, liver, or gastrointestinal tract metastases; bowel obstruction; hypercalcemia; or renal failure.

Although nausea and vomiting can occur with a large number of CCAs, they are likely to be most frequent and severe with cis-platinum, nitrogen mustard, cyclophosphamide, dacarbazine, high-dose cytarabine, and actinomycin D. The nausea and vomiting associated with CCAs usually begin two to several hours after the treatment and can be brief or prolonged but most often disappear within 24 to 48 hours. Anticipatory vomiting is well recognized and may occur before chemotherapy begins. The severity of nausea and vomiting varies widely from patient to patient.

The large number of medications available for the treatment of nausea and vomiting attests to the fact that none are uniformly effective. Drugs that block the chemoreceptor centre include the phenothiazines: prochlorperazine (Ste-

metil), the butyrophenones: haloperidol (Haldol et al.) or droperidol (Inapsine), and the substituted benzamide, metoclopramide (Maxeran, Reglan, et al.). Metoclopramide has additional action on the gastrointestinal tract, increasing motility and gastric emptying.

Tetrahydrocannabinol or the synthetic cannabinoid, nabilone (Cesamet), may be helpful in some patients. Corticosteroids may be useful adjuncts or may by themselves suppress nausea and vomiting. Dexamethasone or methylprednisolone have most frequently been used. Some new agents, including serotonin (5HT3) receptor antagonists, are in the process of clinical testing and may shortly be available for use. Such things as sedatives, relaxation techniques, and hypnosis may be of considerable benefit in some patients and are particularly helpful for anticipatory nausea and vomiting.

The antiemetic agents may themselves have significant toxicity. Phenothiazides, butyrophenones, and metoclopramide can all cause extrapyramidal reactions, restlessness, or drowsiness. Extrapyramidal reactions can be prevented or relieved with the use of diphenhydramine (Benadryl et al.) or benztropine (Cogentin et al.) and restlessness relieved with lorazepam sublingually. Nabilone may cause drowsiness, disorientation, or hypotension and be unacceptable to some patients, particularly older patients. Often combinations, such as dexamethasone or methylprednisolone plus diphenhydramine together with a phenothiazide, butyrophenones, or metoclopramide, may be helpful and can be repeated four to six hours after chemotherapy. It may be useful to begin administration, particularly of the corticosteriods, several hours or a day before chemotherapy. Most of these medications can cause drowsiness; patients should be instructed not to drive, and out-patients should preferably be accompanied after using these drugs (Table 1).

Hair Loss

Hair loss may also occur with a number of CCAs, a result of their cytotoxic effect on rapidly proliferating cell populations. Hair loss is a virtual certainty with the anthracycline drugs: doxorubicin (Adriamycin), daunorubicin (Cerubidine) and epirubicin (Pharmorubicin), as well as etoposide (Vepesid). Hair loss is less constant with others but a possibility with many, particularly combinations. Scalp cooling or the use of a scalp tourniquet have occasionally been of some benefit but are unreliable and not commonly used. Patients should be aware of the possibility or likelihood of hair loss, but can be assured that the alopecia is temporary and hair will regrow after treatment is discontinued. Meanwhile an attractive wig may be required.

Mucositis

Stomatitis and irritation or ulceration of other mucous membranes is also common because these tissues, too, are proliferating. Methotrexate, fluorouracil, doxorubicin, and other anthracyclines are frequent offenders. Prior radiation treatment and poor oral hygiene may contribute to the problem. Conversely, good oral hygiene and prevention of trauma to mucous membranes by hot, sharp, or spicy foods or by tooth brushing will reduce the likelihood of problems. A water pick or swishing of tepid baking soda solution will keep the mouth clean. Viscous 2% lidocaine (Xylocaine Viscous) or benzydamine (Tantum) mixed 1:1 with warm water can be swished or gargled to produce a local anesthetic effect three or four times daily.

The mucous membranes should be examined regularly for evidence of the creamy white plaques or spots of moniliasis (*Candida albicans*). If these lesions appear, nystatin (preferably as the oral suspension 100 000 U/mL) should be used to swish and swallow, 1 to 2 mL every four waking hours. One millilitre three times daily can help to prevent recurrence. Deep, painful mucosal ulceration from herpes simplex may occur if the patient is receiving continuous corticosteroid therapy. Oral acyclovir for five to seven days is usually effective.

Bone Marrow Toxicity

Leukopenia or, in some cases, pancytopenia may occur with the use of many CCAs. This, again, is the result of the cytotoxic effect of these agents on proliferating cell populations. Although most CCAs can produce leukopenia, a few are relatively marrow sparing, such as vincristine, bleomycin, and cis-platinum. The use of most CCAs results in a drop in granulocytes maximal between seven to 14 days, with subsequent recovery during the third week. The nitrosoureas (carmustine, or BCNU, or lomustine, or CCNU), busulfan, and mitomycin C cause a more delayed and prolonged reduction in the granulocytes.Mitomycin C and carboplatin tend to produce more thrombocytopenia than other agents. Care must be taken in calculating and

Table 1
Antiemetic Medications

Drugs	Dose	Administration
Prochlorperazine	5–10 mg PO or IV	q 4–6h
(Stemetil)	10-mg suppository	q 4–6h
OR		
Metoclopramide	10–20 mg PO	q 4–6h
(Maxeran, Reglan, Emex)	1–2 mg/kg IV	q 4–6h
OR		
Haloperidol	1–2 mg PO or IM	t.i.d.
OR		
Droperidol (Inapsine)	0.5–2 mg IV	q 4–6h
Dexamethasone	4–8 mg PO	q 4–6h
	10 mg IV	q 4–6h
OR		
Methylprednisolone	250–500 mg IV	q 4–6h
Nabilone (Cesamet)	1–2 mg	q 8–12h
Diphenhydramine (Benadryl et al.)	25–50 g PO or IV	q 4–6h

giving correct doses of CCAs, and doses may have to be modified or delayed based on the nadir blood counts or the counts done before each treatment. Patients should be aware of the possibility of infections, particularly near the time of nadir counts, and the signs to watch for, such as fever, chills, cough, or urinary symptoms. Any infection or suspected infection should be treated vigorously with appropriate cultures and antibiotic treatment. If there is significant leukopenia (granulocytes less than $1.0 \cdot 10^9$) in a febrile patient, wide-spectrum intravenous antibiotic coverage should be started without awaiting report of cultures. Severe leukopenia may be anticipated in patients who have had extensive radiation, chemotherapy, or infiltration of the marrow by tumour.

Toxicities and Specific Agents

Cardiac Toxicity

Cardiomyopathy is an uncommon toxicity associated with the use of the anthracycline group of agents: doxorubicin, daunorubicin, and to perhaps a lesser degree, epirubicin and the anthracenedione, mitoxantrone. Some other agents also produce similar toxicity less frequently. These agents are best avoided in patients with a history of severe hypertension, cardiomegaly, any pre-existing cardiomyopathy, or congestive failure.

If used in patients with a history of cardiac disease or if the cumulative doses are to exceed 400 to 450 mg/m^2 for doxorubicin or daunorubicin, 900 mg/m^2 for epirubicin, or 150 mg/m^2 for mitoxantrone, cardiac assessment should be done, including serial measurement of cardiac ejection fraction and possibly endomyocardial biopsies. The use of any of these agents will have cumulative toxicity, which is additive to the toxicity of other agents in the group; radiation that includes myocardium will reduce the level at which cardiotoxicity may occur. If cardiac failure or incipient failure develops, it should be treated in the usual way and all cardiotoxic drugs stopped permanently.

Lung Toxicity

Lung toxicity can similarly be seen with a number of CCAs, but bleomycin is the most frequent offender. The toxicity is to some extent dose related, but lung irradiation and high oxygen concentration will increase the risk and severity. Other CCAs that could produce interstitial reaction and fibrosis include busulfan, methotrexate, mitomycin C, nitrosoureas, and cyclophosphamide. Treatment with adrenal corticosteriods may be of some benefit, but therapeutic oxygen may worsen the situation. Pulmonary toxicity is dangerous, and severe toxicity may develop quite abruptly despite care and frequent monitoring of lung function.

Renal Toxicity

Renal toxicity may occur with some of the CCAs, and impairment of renal function may increase the systemic toxicity of others. Cis-platinum is the agent most frequently responsible for renal failure; others less frequently implicated are the nitrosoureas and high-dose methotrexate. Care should be taken to maintain a good urine output when these agents are given. Mannitol may be given to improve the diuresis, sometimes in combination with furosemide. Drugs known to have the potential for renal toxicity, such as aminoglycoside antibiotics, should be avoided. Hypomagnesemia from impaired renal tubular function may occur with the use of cis-platinum. This may be asymptomatic or may be severe enough to result in tetany.

Neurotoxicity

Peripheral neuropathy may occur with vincristine and, to a lesser extent, vinblastine. It is partially recoverable when the medication is discontinued. Consideration must be given to discontinuing the drug when paresthesias of fingers and toes occur and deep tendon reflexes are reduced or absent in the lower extremities. Continuing with the medication will result in foot drop and more severe neurologic impairment. An acute visceral neuropathy may occur with a single dose of dimeric alkaloids derived from *Vinca rosacea* with ileus, abdominal distention, and constipation. This may be mistaken for bowel obstruction if not recognized.

Extravasations

Many CCAs are highly irritating to the tissues and may cause local pain or thrombosis of the vein proximal to the site of injection. Extravasation of some agents may cause an extensive slough of the surrounding tissues. Particular care must be taken with doxorubicin, daunorubicin, mitomycin C, actinomycin, and nitrogen mustard. The vinca alkaloids are extremely painful if extravasated but less likely to result in a slough.

Avoidance is by far the best treatment, but if an extravasation occurs an attempt should be made to aspirate as much as possible before removing the needle and the area cooled with ice packs for 24 to 48 hours. Injecting "antidotes" is usually unwise, and topical application (except possibly dimethyl sulfoxide, or DMSO) unhelpful. If a tissue slough appears imminent, the expertise of a plastic surgeon should be sought.

Special Precautions

A number of CCAs or their metabolites are excreted largely by the kidney, and they must be avoided or their doses reduced if renal clearance is impaired. These agents include methotrexate, cis-platinum, cyclophosphamide, bleomycin, and streptozotocin.

Anticancer chemotherapeutic agents that depend to a significant degree on hepatic clearance include doxorubicin, daunorubicin, etoposide, vincristine, and vinblastin. Their doses should be reduced in the presence of hyperbilirubinemia.

Methotrexate becomes distributed throughout the extracellular fluid, including any third space fluid. In the presence of pleural effusion, ascites, or significant edema, it will be slowly released back into the circulation, which may result in severe toxicity. Methotrexate is best avoided if fluid has accumulated in the third space. Blood levels may be monitored and folinic acid given to bypass the metabolic block and prevent toxicity until serum levels are below $5 \cdot 10^{-7}$ M.

Late Effects

Sterility may occur following the administration of CCAs because of their effect on the rapidly proliferating cells associated with spermatogenesis in men and oogenesis in women. The degree and permanence of sterility depend on the drugs used and doses given. Alkylating agents (nitrogen mustard, melphalan, cyclophosphamide, chlorambucil, and busulfan) appear to be most likely to produce sterility, but a number of others, particularly combinations, may be implicated. Patients must be aware of this possibility if it is relevant. In males, sperm banking may be considered.

The risks of secondary malignancies may be increased after CCAs are used. The risk has been appreciated since the cure or long-term survival of some

patients with lymphomas and some other malignancies. The most common secondary malignancies are leukemias, most often appearing two to four years after chemotherapy. The alkylating agents are again most frequently implicated. The combination of CCAs, particularly alkylating agents, and radiation treatment appears to significantly increase the risk.

The risk of second malignant tumours is small in comparison with the potential benefits of CCAs (perhaps with radiation treatment) in highly treatable or curable tumours. When CCAs are used in palliative situations, the duration of patient survival often makes the risk of second malignancies irrelevant. ■

Appendix 1

Generic and Proprietary Names of Anticancer Chemotherapeutic Agents

Alkylating agents
Nitrogen mustard (mechlorethamine, Mustargen)
Cyclophosphamide (Cytoxan, Procytox)
Melphalan (L-PAM, Alkeran)
Chlorambucil (Leukeran)
Busulfan (Myleran)
Thiotepa
Nitrosoureas
BCNU (Carmustine, BiCNU)
CCNU (Lomustine, CeeNu)
Streptozotocin (Zanosar)
Cis-platinum (Platinol)
Carboplatin (Paraplatin)
Anthracyclines
Doxorubicin (Adriamycin)
Daunorubicin (Cerubidine)
Epirubicin (Pharmorubicin)
Vinca alkaloids
Vincristine (Oncovin)
Vinblastine (Velbe)
Antimetabolites
5-Fluorouracil (Adrucil, Efudex)
Methotrexate
Cytosine arabinoside (cytarabine, Ara C, Cytosar)
Others
VP16 (etoposide, Vepesid)
Mitomycin C (Mutamycin)
Bleomycin (Blenoxane)
Actinomycin D (dactinomycin, Cosmegen)
Dacarbazine (DTIC)
Mitoxantrone (Novantrone)

Davis continued from 1824

be thoroughly investigated to exclude the presence of neoplasm. In addition to hypothyroidism, levothyroxine therapy is indicated in the euthyroid CLT patient. ■

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