Management of intestinal obstruction in malignant disease

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Malignancy may present with intestinal obstruction or it may develop during the course of the disease. Obstruction is any process that prevents the movement of bowel contents distally. The lumen of the bowel may become occluded or there may be a decrease in normal bowel motility preventing normal propulsion of bowel contents along the gastrointestinal (GI) tract. It occurs in approximately 3% of all cancer patients, but in 16% of those with colon cancer and up to 42% of women with ovarian cancer.[1–3] Any site along the GI tract can be affected.

For those unsuitable for surgery, the traditional 'drip and suck' (intravenous hydration and nasogastric suction) will usually fail to control symptoms.[4,5] Medical management will keep most of them free from nausea and pain, allowing them to be managed at home if they wish.[4,6,7]

Pathophysiology

Obstruction may be:

- intraluminal, caused by enlarging primary or secondary tumour
- intramural, caused by infiltration of the bowel wall
- extramural, caused by extrinsic compression from masses, nodes or adhesions
- due to a motility disorder at multiple sites – common in advanced ovarian cancer.[8]

Management

Eight clinical decisions need to be made (Table 1).

1 *Is there any doubt that this is a bowel obstruction?*

The symptoms and signs of intestinal obstruction depend on the level at which it occurs. Malignant obstruction may present acutely with sudden onset of colicky pain, vomiting and constipation, but is more likely to have a gradual onset over weeks or months. Abdominal pain associated with the underlying cancer is present in more than 90% of patients. Vomiting and nausea are common, and about three-quarters will have intestinal colic.[1] Classic tinkling bowel sounds are rare.[9] Symptoms may be intermittent or gradually worsen to become continuous. Obstruction may be complete or partial (subacute), but in practice this is difficult to differentiate. History, examination, observation and radiography will help determine the cause of symptoms. Vomiting tends to be less frequent and develops later in obstructions of the distal ileum and colon. Higher obstructions cause vomiting early, but there is usually little abdominal distension. Other causes of nausea and vomiting, abdominal distension, colic and altered bowel habit should be sought (Table 2).

Table 1. Clinical decisions in bowel obstruction.

1 Is there any doubt that this is a bowel obstruction?
2 Is constipation the sole cause?
3 Is a physical blockage unlikely?
4 Is thirst present?
5 Is surgery possible?
6 Are nausea and vomiting present?
7 Is pain present?
8 Is this a complete or partial obstruction?

2 *Is constipation the sole cause?*

Patients with advanced malignancy will often be less mobile and taking less food and drink. This results in decreased stool frequency and tendency to constipation. Many will also be on at least one drug the side effects of which include constipation. Such drugs include opioids which reduce peristalsis but increase mixing movements, and drugs that reduce all bowel contractions, for example any drug with antimuscarinic effects. Constipation may be accompanied by pain, anorexia and diarrhoea, as well as nausea and vomiting. Examination may reveal abdominal masses which are so hard and fixed that they may be mistaken for tumour. Rectal examination will allow assessment of amount and consistency of faeces in the rectum. 'Overflow diarrhoea' is usually indicated by small amounts of faecal fluid in the presence of an empty rectum due to impaction of faeces distally. Plain abdominal films will show faecal loading in the colon. Treat by clearing the rectum and starting laxatives.

3 *Is a physical blockage unlikely?*

If there is no physical blockage, there may be peristaltic failure, indicated by reduced or absent bowel sounds. This can be caused by tumour infiltration of the gut wall or mesentery, or involvement of the coeliac plexus.[8] Proximal obstructions due to pancreatic carcinoma tend to be due to low motility

Key Points

Intestinal obstruction is common in patients with malignant disease

Surgical intervention should always be considered

Intravenous hydration and nasogastric suction are rarely useful or necessary

Constipation is a common reversible cause of obstruction

Analgesic and antiemetic drugs can be given by continuous subcutaneous infusion

KEY WORDS: colic, constipation, intestinal obstruction, malignancy, nausea, subcutaneous infusion, vomiting

Table 2. Differential diagnosis of symptoms of obstruction.[4]

Nausea and vomiting	• Gastric stasis, distended stomach ('floppy stomach syndrome'), compressed stomach ('squashed stomach syndrome'), gastritis • Chemical causes: drugs, uraemia, hypercalcaemia, bacterial toxins • Constipation • Raised intracranial pressure • Other causes: middle ear infection, tumour at cerebello-pontine angle, vagal stimulation
Abdominal distension	• Organomegaly, especially liver and spleen • Ascites
Colic/abdominal pain	• Colic due to obstruction • Tumour or fibrosis involving coeliac plexus • Drugs (eg contact stimulant laxatives, NSAIDs) • Bowel irritation due to radiotherapy/chemotherapy • Peritonitis • Bile
Altered bowel habit	• Constipation due to reduced intake, drugs, depression or reduced mobility

NSAID = nonsteroidal anti-inflammatory drug.

rather than physical obstruction.[9] It is important to exclude serious but potentially treatable causes of ileus such as peritonitis, septicaemia and recent spinal cord compression. Apparent obstruction may be caused by a medically treatable ileus, for example due to antiperistaltic drugs (eg anti-muscarinics) or autonomic failure. Metoclopramide, a prokinetic agent, can be given as a subcutaneous infusion in a dose of 30–90 mg over 24 hours. Adding a stimulant laxative such as bisacodyl that acts on both the small and large bowel can also be considered.[4]

4 *Is thirst present?*

Fluid is secreted into the bowel lumen in obstruction; if a litre or more is lost in this fashion the patient will feel thirsty. However, most patients will absorb enough fluid from their upper GI tract to prevent symptomatic dehydration and should be allowed to drink and eat a low residue diet. It is kinder to offer cups of tea when wanted than 25 ml of water per hour.

Parenteral feeding is not necessary unless it is a prelude to surgery. Parenteral hydration, either intravenous or subcutaneous, may be needed if patients vomit frequently or have a high obstruction proximal to the mid-duodenum. As patients deteriorate they drink less, but extra hydration is usually not required.[9] Fluids can be given subcutaneously (hypodermoclysis). Up to about two litres in 24 hours can be given in this manner if necessary, and for this reason the intravenous route is rarely used in most palliative care units.[10]

5 *Is surgery possible?*

Surgical treatment should be considered for every patient with malignancy who develops bowel obstruction. Up to 38% of obstructions are due to a benign cause or a new primary tumour.[2] In the presence of existing malignancy, up to 20% of obstructions can be due to adhesions.[11,12] The decision to operate on a patient with advanced malignancy must take into account indicators of poor prognosis:

- poor general condition
- previous surgical findings of advanced intra-abdominal disease
- other indicators of advanced disease, such as ascites or distant metastases
- previous radiotherapy to the abdomen or pelvis, or combination chemotherapy
- small bowel obstruction (higher mortality and morbidity than large bowel obstruction).[3]

The options must be discussed with patient and, if the patient agrees, with the partner and family. Operative mortality is high in bowel obstruction due to advanced malignancy.[13,14] Some will grasp every chance of prolongation of life but others will choose symptomatic treatment.

6 *Are nausea and/or vomiting present?*

Nausea can usually be controlled, though patients may still occasionally vomit. Cyclizine is the first-choice antiemetic. If obstruction is complete and continuous, haloperidol can be added or the cyclizine be replaced by levomepromazine. All three drugs can be given subcutaneously, cyclizine eight-hourly or as a continuous subcutaneous infusion, but haloperidol and levomepromazine have sufficiently long half-lives to allow a single bedtime dose. The amount of gut secretions and therefore volume and frequency of vomit can be reduced by hyoscine butylbromide or octreotide, a somatostatin analogue (Table 3).[15-17] Vomiting may become faeculent when small bowel contents become colonised by bacteria after the obstruction has been present for more than a week. This should be distinguished from faecal vomiting which will occur only when there is a gastrocolic fistula. A nasogastric tube may be necessary for comfort in faeculent vomiting or in patients with a gastric outflow obstruction. An alternative interventional procedure is venting gastrostomy or jejunostomy.[4]

7 *Is pain present?*

The commonest cause of pain is colic, caused by the bowel trying to push against the obstruction. Colic responds poorly to opioids, but responds rapidly to hyoscine butylbromide which is not only effective parentally but also subcutaneously and as a continuous subcutaneous infusion. Other drugs which may be contributing to the colic, such as metoclopramide, should be stopped and hyoscine butylbromide started. Pain due to tumour involvement of the coeliac plexus may respond to gabapentin.[18]

8 *Is this a complete or partial obstruction?*

In partial obstruction it is important to keep the bowel moving with laxatives while avoiding colic. Osmotic (eg lactu-

Table 3. Drugs used in the management of malignant intestinal obstruction.[21]

Drug	Dose	Mode of action	Comments
Cyclizine	25-50 mg 8 hrly SC or PO or 75-150 mg/24 h by CSCI	ACh_1 and H_1 receptor antagonist Acts on vomiting centres	Antimuscarinic side effects SB occasionally causes irritation
Dexamethasone	8 mg PO or SC once in the morning	Reduces vasogenic oedema around tumour	Can be helpful when short-term improvement is needed
Haloperidol	2.5 mg SC or 1.3-3 mg PO at bedtime	D_2 receptor antagonist Acts on area postrema in the CRTZ	Adverse effects include extra-pyramidal effects, especially increased tone Plasma level approximately halved by carbamazepine
Hyoscine butylbromide	20 mg SC as needed or 60-120 mg/24 h by CSCI	Smooth muscle relaxant (antispasmodic) and antisecretory properties	Does not cross blood-brain barrier so not sedating
Hyoscine hydrobromide	150-300 μg SC or 8 hrly sublingually	Smooth muscle relaxant (antispasmodic) and antisecretory properties	Can cause sedation, hypotension and confusion
Levomepromazine (methotrimeprazine)	2.5-5 mg SC at bedtime	$5HT_2$, D_2, H_1 and ACh_1 receptor antagonist Acts on the vomiting centres	Can cause sedation and hypo-tension at doses above 15 mg/24 h
Metoclopramide	10-20 mg 6 hrly SC or PO or 40-80 mg/24 h by syringe driver	D_2 receptor antagonist $5HT_4$ receptor agonist Acts peripherally on gut as prokinetic In high doses blocks $5HT_3$ receptor	May cause extrapyramidal side effects at higher doses Should not be given concurrently with antimuscarinic drugs which antagonise its action
Octreotide	100-300 μg/24 h by CSCI	Synthetic analogue of somatostatin Gut inhibitory hormone	Adverse effects include nausea, vomiting and abdominal pain Takes 2–3 days to be effective

ACh = anticholinergic (antimuscarinic) receptor; CRTZ = chemoreceptor trigger zone; CSCI = continuous subcutaneous infusion; D = dopamine receptor; H = histamine; 5HT = serotonin receptor; PO = oral route; SC = subcutaneous route.

lose) and contact stimulant laxatives (eg senna, dantron, bisacodyl) should be stopped. Docusate is a mild stimulant and a wetting agent which can be titrated to produce a comfortable stool with less risk of colic. Dexamethasone is of limited benefit but may reduce inflammation around a mass.[19,20] Spontaneous remission is seen in about a third of partially obstructed cancer patients.[21] High roughage foods should be avoided, and patients should be hydrated and fed orally using occasional small snacks.[4] Sublingual hyoscine hydrobromide may be given for intermittent colic, but sparingly to avoid reducing motility too much.

If obstruction is complete and continuous, all laxatives should be stopped as bowel movements have no benefit. Patients can be fed and hydrated orally, and meticulous mouth care will alleviate thirst in most of those whose intake is very poor.

Conclusion

Approximately 3% of patients with malignancy will develop intestinal obstruction, some of whom will be suitable for surgery. For the rest, conservative management can control symptoms without recourse to intravenous therapy or the insertion of a nasogastric tube. Drugs can be given via the subcutaneous route using a syringe driver, allowing patients to spend the rest of their life at home if they wish.

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Recent advances in mesothelioma

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Malignant mesothelioma is a highly aggressive cancer that arises from the surface serosal cells of the pleural, peritoneal and pericardial cavities; it is characterised by a long latency period from initial exposure to the development of disease. Exposure to asbestos fibres is the primary cause. Spread of the tumour is circumferential and longitudinal within the planes of the pleura, into the fissures and interlobular septa, and in places it focally invades the lung parenchyma. Regional lymph nodes can be affected in up to 70% of patients, with spread to the ipsilateral peribronchial and hilar lymph nodes, followed by the mediastinal, contralateral hilar and supraclavicular nodes. Haematogenous metastases are well documented, spreading to the liver, adrenal, bone and brain.

Experimental and epidemiological data support the view that asbestos, particularly amphibole asbestos, causes malignant mesothelioma. However, exposure to asbestos is usually not sufficient for the development of malignant mesothelioma; other factors, including radiation, genetic predisposition and simian virus 40 (SV40) infection, may render some individuals more susceptible to the carcinogenicity of asbestos. SV40 is present in most human malignant mesotheliomas. The virus appears to interfere with key cell cycle regulatory genes and may contribute with asbestos or alone (in nonasbestos-associated tumours) to the development of molecular genetic alterations that ultimately lead to a malignant phenotype. The local and systemic immunosuppressive activity of asbestos may also interfere with the ability of the immune system to attack and destroy cells expressing SV40 antigens, and thus favour tumour progression.[1]

Clinical features

Malignant pleural mesothelioma most commonly develops in the fifth to seventh decade (median age 60 years), typically 20–50 years or longer after the first documented exposure to asbestos. The risk appears to be proportional to both the intensity and duration of exposure. Latency periods between first exposure and diagnosis may vary according to occupation, with shorter latencies for insulators and dock workers and longer intervals for shipyard and maritime workers, as well as domestic exposures.[2] Men outnumber women by

Key Points

- **The management of mesothelioma requires a multidisciplinary and multimodality approach to therapy**
- **Chemotherapy offers an improvement in symptoms and quality of life**
- **Patients with poor performance status require careful assessment**
- **Age should not be a factor when deciding treatment**
- **Much of the research from clinical studies to date is heterogeneous and many of the trials underpowered to detect small differences**
- **Symptomatic benefit from anticancer treatment of mesothelioma is comparable with that of other tumours**

KEY WORDS: asbestos, mesothelioma, pemetrexed, simian virus 40 (SV40)