Palliative medical management

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Introduction

Bowel obstruction is defined as any process preventing the movement of bowel contents. Cancer patients may develop bowel obstruction at any time in their clinical history; however, patients with advanced disease develop bowel obstruction more frequently.

Malignant bowel obstruction (MBO) is a common complication in patients with abdominal or pelvic cancers, such as those arising from the colon, ovary and stomach. Bowel obstruction occurs in 5–43% of patients with a diagnosis of advanced primary or metastatic intra-abdominal malignancy [1]. The most common primary malignancies are ovarian (5.5–51%) and colorectal cancer where the frequency of bowel obstruction ranges from 10% to 28% according to different authors [2]. MBO has been reported in patients with other advanced cancers, ranging from 3% to 15%. The interval from diagnosis of cancer to onset of MBO is significantly longer in extra-abdominal primary tumours (mean 57.5 months) compared with intra-abdominal (mean 22.4 months) [3–8].

Pancreatic cancer metastasizes to the duodenum or stomach; cancer of the colon metastasizes to the jejunum and ileum; and prostate and bladder cancers metastasize to the rectum [1]. Tumours at the splenic flexure can cause bowel obstruction in 49% of patients, tumours of right and left colon in 25%, and tumours of the rectum and rectosigmoid junction in 6% of patients [9].

Bowel obstruction may be partial or complete, and at single or multiple sites, the small bowel is more commonly involved than the large bowel (61% vs 33%). Both are involved in over 20% of the patients. Even in advanced cancer, the obstruction may be due to benign causes such as adhesions, post-irradiation bowel damage, inflammatory bowel disease, and hernia. Some reports suggest a benign cause is responsible in about 48% of the patients with colorectal cancer. [1,2,10–13].

Pathophysiology

Several pathophysiological mechanisms and causes may be involved in the onset of bowel obstruction and there is variability in both presentation and aetiology (Table 1).

Table 1
Causes of bowel obstruction

Mechanical obstruction is caused by:
(1) extrinsic occlusion of the lumen due to an elargement of the primary tumour or recurrence, mesenteric and omental masses, abdominal or pelvic adhesions (caused either by the tumour or secondary to surgery), postirradiation fibrosis; postirradiation intestinal damage;
(2) intraluminal occlusion of the lumen due to neoplastic mass, polypoidal lesions or annular tumoural dissemination;
(3) intramural occlusion of the lumen due to intestinal linitis plastica.

Functional obstruction (or adynamic ileus) is caused by intestinal motility disorders consequently to:
(1) tumour infiltration of the mesentery or bowel muscle and nerves (carcinomatosis), malignant involvement of the coeliac plexus;
(2) paraneoplastic neuropathy in patients with lung cancer;
(3) chronic intestinal pseudo-obstruction (CIP) mainly due to diabetes mellitus, previous gastric surgery and other neurological disorders;
(4) paraneoplastic pseudo-obstruction.

Other causes such as inflammatory edema, faecal impaction, constipating drugs (such as opioids, anticholinergics,belladonna alkaloids, antidepressants, vinca alcaloyds. etc.), and dehydration, are likely to contribute to the development of intestinal obstruction or to worsen the clinical picture.

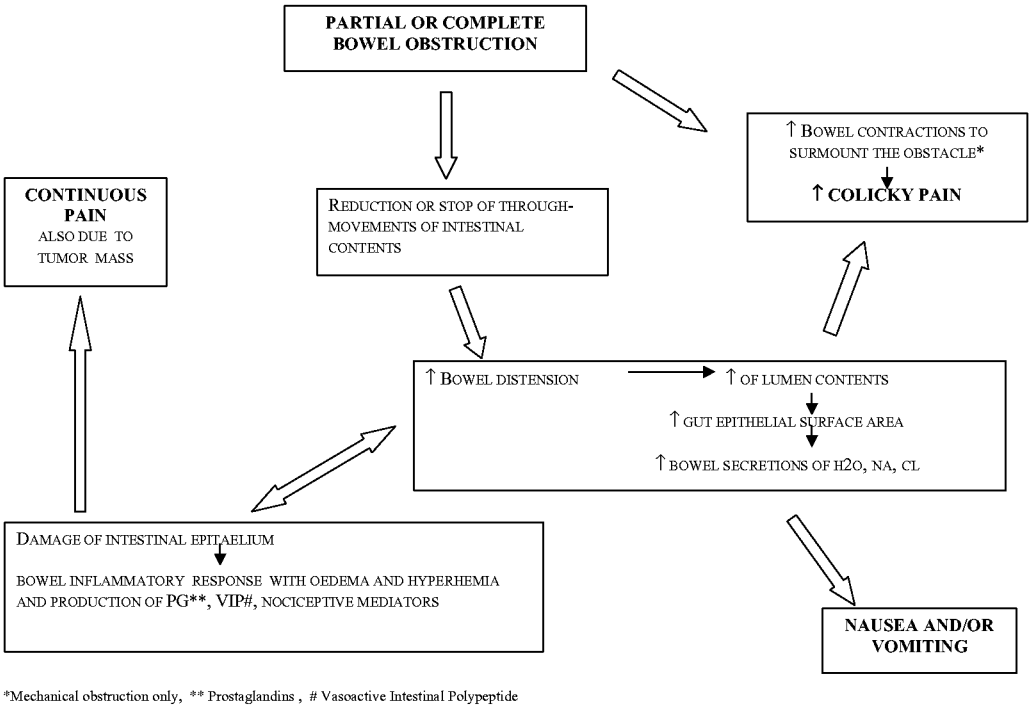

Fig. 1. Pathophysiology of malignant bowel obstruction.

At least three factors occur in bowel obstruction:

- accumulation of gastric, pancreatic, and biliary secretions that are a potent stimulus for further intestinal secretions
- decreased absorption of water and sodium from the intestinal lumen
- increased secretion of water and sodium into the lumen as distension increases.

As a result of the breakdown of the sequence of secretion and reabsorption in the gastrointestinal (GI) tract, there is a loss of fluids and electrolytes. The GI secretions accumulate in the bowel above the obstruction, and the volume of secretions tends to increase following intestinal distension and the consequent increase in surface area, thus producing a vicious circle of secretion–distension–secretion. Depletion of water and salt in the lumen is considered the most important ' toxic factor' in bowel obstruction.

The vicious circle represented by distension–secretion–motor hyperactivity exacerbates the clinical picture, producing intraluminal hypertension and epithelial damage. Epithelial damage generates an inflammatory response and the release of prostaglandins, potent secretory agents either by a direct effect on enterocytes or enteric nervous reflex. Furthermore, vasoactive intestinal polypeptide (VIP) might be released into the portal and peripheral circulation and mediate local intestinal and systemic pathophysiologic alterations accompanying small intestinal obstruction, such as hyperaemia and oedema of intestinal wall and accumulation of fluid in the lumen due to its stimulating effects [11] (Fig. 1).

Clinical features

Signs and symptoms

In cancer patients, compression of the bowel lumen develops slowly and often remains partial. Gastrointestinal (GI) symptoms such as pain, nausea and vomiting are caused by the sequence of distension–secretion–motor activity of the obstructed bowel (Fig. 1). The symptoms occur in different combinations and intensity depending on the site of obstruction and tend to worsen. Continuous abdominal pain related to an intra-abdominal mass is the most constant feature and is present in about 90% of the patients. Superimposed on this, intestinal segmental activity to attempt to surmount the obstacle in the small or large bowel may cause intermittent colic in about 75% of the patients. With obstructions in the large bowel, the pain is generally less severe, deeper, and occurs at longer intervals. Abdominal distension may be absent in high obstruction, i.e. of the duodenum or proximal jejunum, and when the bowel is ' plastered' down by extensive mesenteric spread. Vomiting develops early and in large amounts in gastric, duodenal and

Table 2
Common symptoms in cancer patients with Malignant Bowel Obstruction

Symptom	Characteristics		
Vomiting	intermittent or continuous	it develops early and in great amounts in gastric, duodenum and small bowel obstruction and develops later in large bowel obstruction	biliary vomiting is almost odourless and indicates an obstruction in the upper part of the abdomen. The presence of bad smelling and fecaloid vomiting can be the first sign of a ileal or colic obstruction
Nausea	intermittent or continuous		
Colicky pain	variable intensity and localization due to distension proximal to the obstruction; secondary to gas and fluid accumulation most of which are produced by the gut	if it is intense, periumbelical and occurring at brief intervals, may be an indication of an obstruction at the jejunum-ileal level. In large bowel obstruction the pain is less intense, deeper, occurring at longer intervals and spreads toward the colon wall	an overall acute pain which begins intensely and becomes stronger, or a pain which is specifically localized, may be a symptom of a perforation or an ileal or colic strangulation. A pain which increases with palpation may be due to peritoneal irritation or the beginning of a perforation
Continuous pain	variable intensity and localization	it is due to abdominal distension, tumour mass and/or hepatomegaly	
Dry mouth		it is due to severe dehydration, metabolic alterations but above all it is due to the use of drugs with anticholinergic properties and poor mouth care	
Constipation	intermittent or complete	in case of complete obstruction there is no evacuation of faeces and no flatus	in case of partial obstruction the symptom is intermittent
Overflow diarrhea		it is the result of bacterial liquefaction of the faecal material	

small bowel obstruction and later in large bowel obstruction [1,10,11] (Table 2).

The patient' s symptoms should be monitored daily. Vomiting can be evaluated in terms of quantity, quality, and number of daily episodes. Other symptoms, such as nausea, pain, dry mouth, drowsiness, dyspnoea, hunger or thirst can be assessed by numerical or verbal scales.

Differential diagnosis

When a cancer patient presents with a suspicion of bowel obstruction, all the possible causes of constipation [14,15] and nausea and vomiting [16] have to be ruled out. The possible metabolic alterations, the type and dosages of drugs taken as well as the state of hydration and nutrition must be assessed. The patient must be investigated regarding a relapse or a disease progression, bowel movements, and the presence of overflow diarrhoea, which could lead to underestimation of the problem. Abdominal examination can show the presence of abdominal cancer or faecal masses, distension of the whole abdomen or only above the obstacle, the eventual presence of ascites as well as painful sites. Rectal exploration can show the absence or presence of faeces in the rectal ampulla.

An abdominal X-ray taken in a supine or standing position is the first investigation in patients with suspected small bowel obstruction to document the dilated loops of bowel, air-fluid interfaces, or both. Contrast radiography can help to evaluate dysmotility, partial obstruction, and to define the site and extent of the obstruction. Retrograde transrectal radiographic contrast studies should be used to rule out or to diagnose isolated or concomitant obstruction of the large bowel. An abdominal computed tomography (CT) scan is useful for evaluating the global extent of disease, to perform staging, and to assist in the choice of surgical, endoscopic, or simple pharmacological palliative intervention for the management of the obstruction [13].

Therapies

The management of patients with malignant bowel obstruction is one of the greatest challenges for physicians who care for cancer patients. In the face of a clearly incurable situation, significant patient discomfort and suffering must be balanced with the need to simplify the care of those patients with a short time to live. The chapter highlights a series of questions that physicians need to consider when faced with terminal cancer patients (patients no longer responsive to specific oncological therapies) with bowel obstruction:

- Is the patient fit for surgery?
- Is there a place for stenting?
- Is it necessary to use a venting nasogastric tube (NGT) in inoperable patients?
- When should a venting gastrostomy be considered?
- What drugs are indicated for symptom control?
- What is the proper route for drug administration?
- Which drugs can be administered in association?
- What is the role of parenteral hydration and total parenteral nutrition?

Surgery

In advanced cancer patients, guidelines for conservative versus surgical treatment are still lacking [13,17]. Unfortunately, survival time is frequently used as the only measure of success. Published data show that, in advanced cancer, the operative mortality is 30–40% and complication rates vary from 27–90% [13]. Not all patients are fit for surgery. According to different authors, the rate of inoperable patients ranges from 6.2% to 50% [1,10,11].

Several authors have emphasized that prognostic criteria are needed to help doctors select patients who are likely to benefit from surgical intervention. The available data suggest that poor prognostic factors include:

- a recent laparotomy, which demonstrated that further corrective surgery was not possible
- previous abdominal surgery which showed diffuse metastatic cancer
- involvement of proximal stomach
- intra-abdominal carcinomatosis demonstrated radiologically with a contrast study revealing a severe motility problem
- diffuse palpable intra-abdominal masses
- massive ascites which rapidly recur after drainage [13].

Relative contraindications include:

- extra-abdominal metastases producing symptoms which are difficult to control (e.g. dyspnoea)
- non-symptomatic extensive extra-abdominal malignant disease (e.g. widespread metastases, pleural effusion)
- poor general performance status
- poor nutritional status (e.g. marked weight loss/cachexia, marked hypo-albuminaemia, low lymphocyte count)
- advanced age in association with cachexia
- previous radiotherapy of the abdomen or pelvis [1, 10–13].

Surgical palliation in advanced cancer patients is a complex issue, and the decision to proceed with surgery must be carefully evaluated for each individual patient [13,17].

Surgery should not be routinely undertaken in patients with very advanced cancer. The overall patient status, including physical, social, psychological, and spiritual domains, is of primary importance [17]. The following questions should be asked if surgery is being considered:

- Is palliative surgery technically feasible?
- Is the patient likely to benefit from surgery?
- What is the likelihood that an operation will be futile, leading only to greater debility, possible complications and earlier death?
- Have medical measures been properly instituted?

In recent years, expandable metallic stents have been used increasingly in the management of obstructions in the gastric outlet, proximal small bowel and colon [11]. Contraindications for the use of self-expanding stents are the presence of multiple stenoses, or peritoneal carcinomatosis located distally in the small bowel that may be undiagnosed at the preprocedural opacification because of the severity of the duodenal stenosis. Failure to relieve the obstruction may be secondary to an inability to cross the stricture, incomplete opening of the stent, or stent malposition that fails to traverse the entire stricture. In this case, it is necessary to apply additional stents across the remaining obstruction. The usefulness of stents in patients with end-stage cancer has not yet been formally evaluated. Further studies are necessary to identify those advanced and terminal cancer patients who may have some benefit in terms of symptom control, complications and quality of life.

Nasogastric suction and intravenous fluids ('Drip & Suck')

Nasogastric suction decompresses the stomach and/or intestine, and corrects fluid and electrolyte imbalance

before surgery, or while a decision is being made. The tube often becomes occluded and requires flushing and/or replacement. During long-term drainage, a nasogastric tube (NGT) can interfere with coughing for clearing pulmonary secretions and may be associated with nasal cartilage erosion, otitis media, aspiration pneumonia, oesophagitis, and bleeding [18]. Both nasogastric suction and intravenous fluid administration can be intrusive, invasive, and distressing for the patient and must be justified on the basis of more benefit than burden to the patient, just like any other medical intervention. Long-term use of a nasogastric tube should only be considered when pharmacological therapy for symptom control is ineffective or when gastrostomy cannot be carried out. Nasogastric suction and intravenous (IV) fluid administration is a temporary measure which:

- allows unhurried evaluation of the patient
- may be therapeutic in some cases
- prepares selected patients for surgery
- reduces gastric distension before the start of symptomatic treatment with drugs.

Gastrostomy

Gastrostomy is a much more acceptable and well-tolerated method for long-term decompression of the obstructed GI tract [19]. Operative or percutaneous endoscopic gastrostomy (PEG) are much more acceptable methods for longer-term decompression of an obstructed GI tract than a NGT [13,20].

Pharmacological treatment

Pharmacological treatment should be used in inoperable patients to:

- relieve continuous abdominal pain and intestinal colic
- reduce vomiting to an acceptable level for the patient (e.g. 1–2 times in 24 hours) without the use of the NGT
- relieve nausea
- achieve hospital discharge
- allow for care at home/hospice if otherwise possible.

The Working Group of the European Association for Palliative Care (EAPC) has recently published recommendations for the management of MBO in patients with end-stage cancer [13].

Drug therapy, comprising analgesics, antisecretory drugs and anti-emetics without the use of a NGT, was first described 20 years ago [21]. Several authors have confirmed the efficacy of this approach, and palliative care centres throughout the world use it successfully in both in-patients and outpatients [13].

The drugs of choice may vary between different countries and different centres, based on clinical experience, drug availability, cost and fashion. Medication should be tailored to each patient with regard to both the drugs to be administered and the route of administration (Fig. 2).

Drugs used for pain management and routes of administration

To control continuous abdominal pain, the administration of analgesics according to the World Health Organization (WHO) guidelines [22] allows adequate pain relief in most patients [13].

Most patients presenting symptoms from bowel obstruction are on strong opioids, usually morphine at the time of diagnosis. The dose of opioids should be titrated against the effect and most usually be administered parenterally. In patients with subsequent episodes of subacute obstruction, which may be worsened by opioids, it may be useful to choose the drug on the basis of presumed selectivity of distribution at the intestinal sites. Morphine tends to accumulate in intestinal tissues, interacting with local opioid receptors. It has been reported that more lipophilic drugs, like methadone and fentanyl, interact less with opioid intestinal receptors [23, 24]. Experimental studies showed a more favourable constipation/analgesia ratio of fentanyl relative to morphine [25]. This is probably a reflection of the lipophilic properties of fentanyl. Some papers seem to indicate that transdermal fentanyl as well as methadone may have less constipating effects or may require lower laxative doses in comparison with morphine [26–28]. Moreover, switching from morphine to methadone improves GI tolerability [29, 30] as well as switching the route of the opioid administration [31–35]. On the other hand, the use of non-steroidal anti-inflammatory drugs (NSAIDs) may allow for a reduction of constipation induced by opioids [36] and may result in improvement in the opioid bowel syndrome [37].

If colics persist despite the use of an opioid, hyoscine butylbromide or hyoscine hydrobromide [21, 38] should also be administered [39–42].

It is well recognized that the oral administration of the opioid drugs is the mainstay of analgesic therapy in cancer patients. Indeed, it is safe, effective, and convenient. Moreover, the oral route for drugs makes home management simpler.

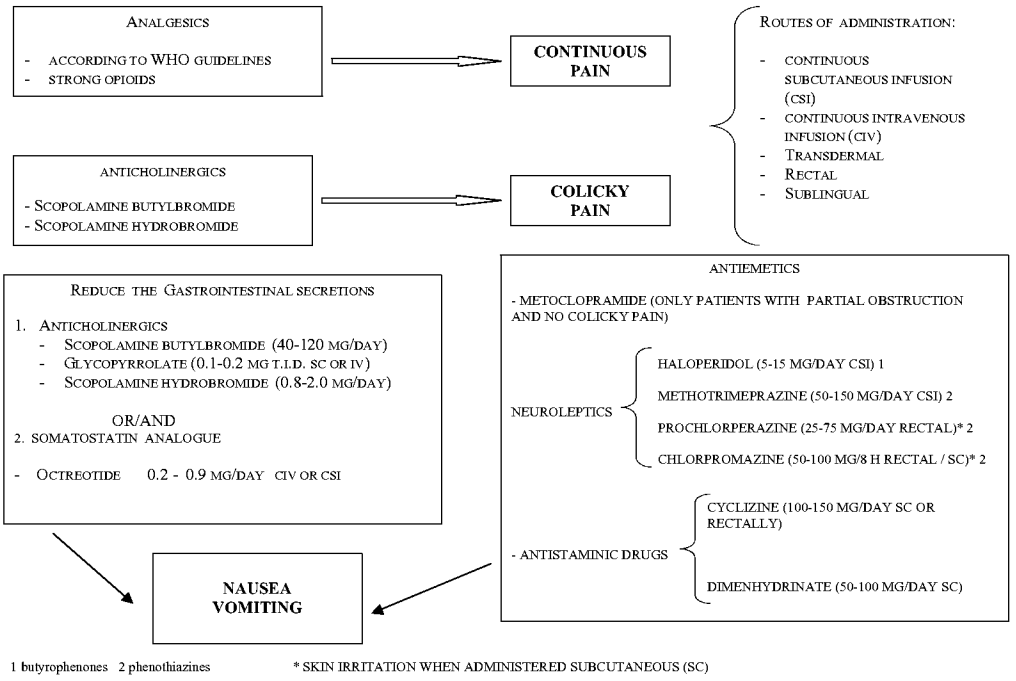

Fig. 2. Symptomatic pharmacological approach.

Table 3
Potential applications of alternative routes for systemic opioid administration

Symptoms	Route[a]					
	sublingual	rectal	CSI[b]	IV	transdermal (fentanyl, buprenorphine)	transmucosal (fentanyl)
vomiting	++	++	++	++	++	—
bowel obstruction	++	++	++	++	++	—
dysphagia	++	++	++	++	++	—
cognitive failure	–	+	++	++	++	—
diarrhea	++	–	++	++	++	
hemorrhoids, anal fissures	++	–	++	++	++	—
coagulation disorders	++	++	–	++	++	—
severe immunosuppression	++	++	–	+	++	—
generalized edema	++	++	–	++	–	—
frequent dose changes	++	–	++[c]	++[c]	–	—
titration	++	+	++[c]	++	+/–[c]	– —
breakthrough pain	++	++	++[c]	++[c]	–	++

[a] + = may be indicated, ++ = indicated, – = contraindicated, — = not indicated.
[b] Continuous Subcutaneous Infusion.
[c] Patient Controlled Analgesia, PCA.

However, in some clinical situations such as severe vomiting, bowel obstruction, severe dysphagia or severe confusion, and in situations where rapid dose escalation is necessary, oral administration of opioids is impossible and an alternative route has to be implemented. In the last few years, a number of modes for opioid administration have been explored. Table 3 shows the potential clinical applications of these alternative routes of opioid administration. Table 4 reports the EAPC recommendations

Table 4
Opioid administration according to the EAPC recommendations

- A small proportion of patients develop intolerable adverse effects with oral morphine (in conjunction with a non-opioid and adjuvant analgesic as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid or a change in the route of administration should be considered.
- If patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful.
- The average relative potency ratio of oral morphine to subcutaneous morphine is between 1:2 and 1:3 (i.e. 20–30 mg of morphine by mouth is equianalgesic to 10 mg by s.c. injection).
- In patients requiring continuous parenteral morphine, the preferred method of administration is by subcutaneous infusion.
- Intravenous infusion of morphine may be preferred in patients:
  (a) who already have an indwelling intravenous line;
  (b) with generalized oedema;
  (c) who develop erythema, soreness or sterile abscesses with subcutaneous administration;
  (d) with coagulation disorders;
  (e) with poor peripheral circulation
- The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3.
- Rectal administration may be preferred by some patients. The equianalgesic dose by oral and rectal routes is about 1:1.
- The buccal, sublingual and nebulized routes of administration of morphine are not recommended because at the present time there is no evidence of clinical advantage over the conventional routes.
- Oral transmucosal fentanyl citrate (OTFC) is an effective treatment for ' breakthrough pain' in patients stabilized on regular oral morphine or an alternative step 3 opioid.
- Transdermal fentanyl is an effective alternative to oral morphine but is best reserved for patients whose opioid requirements are stable. It may have particular advantages for such patients if they are unable to take oral morphine, as an alternative to subcutaneous infusion.
- Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia or suffer intolerable adverse effects despite the optimal use of systemic opioids and non-opioids.

[a] Reference [43]. EAPC, European Association for Palliative Care.

regarding the different routes of opioid administration [43].

Subcutaneous and intravenous routes are the most frequently used in patients with symptoms due to inoperable bowel obstruction. Transdermal, rectal and sublingual medications are useful alternatives, particularly for patients being cared for at home.

Subcutaneous route

The main factors determining the subcutaneous absorption are the solubility of the drug, the site of injection, the surface exposed, the patient' s blood pressure, and the presence of cutaneous vasoconstriction, oedema or inflammatory processes.

Subcutaneous (SC) opioid administration can be performed both intermittently and continuously. Intermittent injection may represent a valid option in some circumstances. However, it can be associated with a ' bolus effect' characterized by acute toxicity and a brief analgesic effect. Moreover, because of the short duration of action of most opioids, injections need to be repeated frequently, usually at intervals of four hours or less. In palliative medicine, this method is undesirable because it is painful for the patient, time-consuming for the caregivers, and difficult to maintain in the home setting. Therefore, continuous subcutaneous infusion (CSI) is recommended [44].

Patient-controlled analgesia (PCA) devices permit the patient to choose an intermittent (demand) bolus, continuous infusion, or both intermittent and continuous modes of administration. A continuous infusion with an intermittent bolus dose allows patients to maintain a baseline level of opioid administration with additional doses for breakthrough pain. The device can be used to deliver the drug through continuous intravenous, subcutaneous or epidural infusions. Many different portable pumps or non-portable devices are available for CSI, including a syringe pump, disposable plastic cylinder, and battery-operated computer-driven pumps. It is important to select the most suitable solution for each patient. In general, it is recommended to perform infusion by using a 25- or 27-gauge butterfly needle inserted in the abdomen.

The SC route, with special reference to CSI, should be considered as the standard alternative route for systemic opioid delivery in the setting of palliative care. CSI of drugs allows a parenteral administration of different drug combinations, produces minimal discomfort for the patient and is easy to use in a home setting.

Intravenous route

Intravenous (IV) administration of opioids permits complete systemic absorption, and produces rapid analgesia that is correlated to lipidic solubility (10–15 minutes for morphine, 2–5 minutes for methadone) but of short duration. This makes it necessary to repeat infusions at least every 4 hours.

Bolus administration can be substituted by continuous intravenous infusion (CIVI) using a pump. This is very frequent in the cancer population during hospitalisation, above all in those with central venous catheters. PCA is also possible by the intravenous route [45].

Although morphine is the drug of choice, clinical experience has shown that other drugs, such as methadone, hydromorphone and fentanyl can also be used successfully [31,32,46].

The choice of a drug for CIVI depends on the previous analgesic treatment and on the pharmacokinetic profile of the drug employed. If the patient refers a good analgesia with a particular opioid but presents adverse effects to a bolus administration (plasmatic peak toxicity or pain during the reduction of the plasmatic concentration) this is a suitable candidate for CIVI with the same drug. On the other hand, if the patient presents adverse effects at plasmatic peak and refers poor or absence of analgesia, the CIVI must be initiated with a different opioid. The opioid dosage at the beginning of treatment depends on the patient' s pharmacological intake. Patients being treated with repeated parenteral doses can switch to CIVI with the same drug using the same daily dosage, whereas the administration of a different opioid would require a dosage reduction of half to two-thirds.

Continuous parenteral (subcutaneous or intravenous) opioids improved analgesia and tolerability in 71% of cancer patients previously treated with oral opioids (codeine, tramadol, morphine, methadone) or with transdermal fentanyl. Parenteral opioids may be considered a good alternative to spinal opioids [47].

CIVI of opioids used in cancer-related pain are specifically indicated in cases of generalized oedema, coagulation disorders, increased frequency of subcutaneous local site infections, reduced peripheric circulation, when frequent intramuscular (IM) or IV injections are required to maintain pain control, in the presence of prominent ' bolus effects' on repetitive injection and when rapid titration of drug doses is required to produce rapid pain relief.

Opioid administration through CIVI can be carried out via central venous catheters. However, these catheters are expensive, need to be surgically implanted and require considerable nursing expertise and care/education. For these reasons CIVI should be considered for patients who already have an implanted catheter and for patients, who present bleeding diathesis or diminished muscle mass, or who develop intractable vomiting, bowel obstruction or malabsorption.

Transdermal route

Among opioids, the potent synthetic drug fentanyl citrate is particularly suitable for transdermal administration, and its utility in pain therapy has been extensively evaluated. Transdermal fentanyl systems (TTS) are available in four release profiles of 25, 50, 75, 100 μg/h depending on the patch size. The drug is released continuously for three days. When the TTS is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot. However, opioid withdrawal symptoms may occur after discontinuation of TTS administration, as well as after conversion from other opioids to TTS [48,49]. Moreover, withdrawal symptoms were reported during chronic TTS administration and were managed with oral methadone [50].

Published data show that application intervals had to be shortened in approximately 25% of patients [51] at 48–60 hours because on the 3rd day of each patch period, the need to use rescue doses of short release oral morphine increased in respect to 1st and 2nd day [51,52]. In 11–43% of patients, the patch had to be changed every 48 h during long-term treatment [53].

In stable, chronic cancer pain this formulation offers an interesting alternative to oral morphine [52,54]. Of course, this formulation is contraindicated during the titration phase, or to control breakthrough pain.

The permeability coefficient for fentanyl is affected by temperature. A rise in body temperature to 40°C may increase the absorption rate by about one-third [55]. Acute toxicity related to increased absorption secondary to high temperature has been reported [56]. A recent study in volunteers demonstrated that the application of local heat to the transdermal patch significantly increased systemic delivery of fentanyl [57].

The partial agonist buprenorphine is another ideal candidate for delivery via a transdermal patch [58]. In the currently available formulation (buprenorphine transdermal delivery system, TDS) this drug is incorporated in a polymer adhesive matrix from which it is released through the skin. Transdermal buprenorphine has a bioavailability of about 50%, which is comparable to that observed after sublingual administration [59]. Buprenorphine patches are available in three dosage strengths. The patches are loaded with 20, 30 or 40 mg of buprenorphine and are designed to release the opioid at a controlled rate of 35, 52.5 and 70 μg/h, corresponding to a daily dose of 0.8, 1.2 and 1.6 mg, respectively. All of the patches are designed for a 72-hour application period. They should be applied to a flat and hairless area of non-inflamed skin, preferably on the upper back,

subclavicular region or chest. Following their removal, buprenorphine plasma levels slowly decrease. The manufacturers suggest that additional opioids should not be administered within 24 hours of patch removal. Buprenorphine TDS has been used and investigated less extensively than fentanyl TTS.

Rectal route

Rectal drug vehicles may be liquid or solid. The absorption of aqueous and alcoholic solutions may occur very rapidly but the absorption of suppositories is generally slower and very much dependent on the nature of the suppository base, the use of surfactants, and other factors such as the presence/absence/quantity of faecal mass and the total volume content inside the rectum. Davis et al. [60] reviewed the clinical pharmacology and therapeutic role of suppositories and rectal suspension of opioids and other analgesics. The analgesic efficacy and the tolerability of following opioids have been proven: morphine, methadone, oxycodone pectinate, and tramadol [60].

Rectal administration of drugs can be used to produce local or systemic effects. In some countries, preparations of opioids in the form of suppositories are not commercially available. To overcome this, micro-enemas made up of liquid opioid (the same used for parenteral administration) are prepared and then given rectally as a bolus using a insulin-type syringe without needle. This has the advantage of rapid absorption [61,62].

The rectal route of drug administration may present some disadvantages when used chronically and when faeces or diarrhoea are present. This alternative route can be administered successfully in patients with breakthrough pain (defined as transient flares of severe or excruciating pain in patients already managed with analgesics) and in some clinical situations (Table 3). The colostomy administration route of opioids is not recommended [63].

With respect to subcutaneous (SC) and IV routes, the rectal route has the advantage of not requiring needles to be inserted or pumps to be carried. On the negative side, chronic and frequent rectal administration can lead to discomfort, and the presence of faeces in the rectum, diarrhoea or normal peristalsis can reduce absorption. There are several barriers to the development of rectally-administered drugs. Sometimes physicians, caregivers and patients find this route unappealing.

Sublingual route

There are very few reports on the long-term efficacy and tolerability of sublingual opioids. Lipophilic drugs such as buprenorphine, fentanyl and methadone are better absorbed than polar ones [64]. Buprenorphine is the only commercial opioid available as a sublingual formulation. Single dose crossover studies have shown sublingual buprenorphine to be 15 times more potent than morphine in terms of total analgesic effect [65]. A dose of 0.4 mg sublingually gives similar analgesia to 0.2 to 0.3 mg IM, with an onset of analgesia within 30–60 min of administration and a duration of 6–9 hours [66].

De Conno et al. [67] found that patients previously treated with sublingual or IM buprenorphine required a dose of morphine significantly higher than those treated with other opioids (codeine, oxycodone, dextropropoxyphene, pentazocine) to obtain the same pain relief. Like the mixed agonist–antagonists, buprenorphine may precipitate withdrawal in patients who have received repeated doses of a morphine-like agonist and developed physical dependence. Naloxone is relatively ineffective in reversing serious respiratory depression caused by buprenorphine [68].

Drugs used for the management of nausea and/or vomiting

Nausea and vomiting can be managed using two different pharmacological approaches:

- administration of drugs that reduce GI secretions such as anticholinergics (hyoscine hydrobromide, hyoscine butylbromide, glycopyrrolate) and/or somatostatin analogues (octreotide)
- administration of anti-emetics acting on the central nervous system, alone or in association with drugs to reduce GI secretions.

There are no comparative studies on the efficacy of these different approaches. Generally, physicians are guided by drug availability and costs. Figure 2 describes the drugs used to control nausea and vomiting, their possible association and the doses reported to be effective [21,39,42,69–78].

Anticholinergic drugs, such as hyoscine butylbromide and glycopyrrolate, may reduce vomiting by virtue of their antisecretory effects.

Scopolamine butylbromide is frequently used for both vomiting and colicky pain by some palliative care centres [21,39,40]. Its anti-cholinergic activity decreases the tonus and peristalsis in smooth muscle both by competitive inhibition of muscarinic receptors at the smooth muscle level and by impairment of

ganglionic neural transmission in the bowel wall. Muscarinic cholinergic receptors have also been observed on mucosal cells of the intestinal lumen and in human salivary glands [79], which explains its analgesic effect on the colicky pain while reducing intestinal secretion.

This drug differs from both atropine and scopolamine hydrobromide in having a low lipid solubility. It does not penetrate the blood-brain barrier as well as these other drugs and, consequently, may produce fewer side effects, such as somnolence and hallucinations when administered in combination with opioids. Dry mouth is reported as the most significant side effect, but the patients tolerated it by sucking ice cubes and drinking small sips of water.

Many open studies have demonstrated that this class of drugs may be effective in controlling GI symptoms in inoperable malignant bowel obstruction, alone or in combination with other drugs [38,40,42,77,78].

Glycopyrrolate is a quaternary ammonium anticholinergic, with little central nervous system penetration. Davies et al. [2] found it to be an effective agent in the management of mechanical bowel obstruction.

Octreotide is a synthetic analogue of somatostatin and it has also been used to manage the symptoms of bowel obstruction in pre-clinical [80] and clinical studies [81]. The efficacy of long-acting octreotide is under investigation [82].

Somatostatin and octreotide act by binding to specific receptors situated on the cellular membranes of almost all body tissues. In humans, five subtypes of somatostatin receptors that are able to bind to different effector systems have been identified [83]. Octreotide has been shown to have the same biological effects as somatostatin, but it has greater specificity and potency in inhibiting the release of certain hormones [80,84] and a longer duration of action (half-life, 90–120 minutes), with a peak at 2 hours and an overall duration of 12 hours [80]. Octreotide can be administered by continuous subcutaneous or intravenous infusion or by bolus parenteral injection.

Octreotide has been shown to inhibit the release and activity of gastrointestinal hormones, modulate GI function by reducing gastric acid secretion, slow intestinal motility, decrease bile flow, increase mucous production, and reduce splanchnic blood flow. It reduces GI contents and increases absorption of water and electrolytes at intracellular level. These effects may be due to the inhibition of vasoactive intestinal polypeptide (VIP), which has been shown to be increased in experimental bowel obstruction, and is known to have unfavourable effects on intestinal secretion, splanchnic flow, and peristalsis [85–87].

Thus, the inhibitory effect of octreotide on GI secretions appears to break the vicious circle of secretion, distension, and contractile hyperactivity.

The inhibitory activity of octreotide on GI motility and secretions seems to offer an advantage in both the perioperative management of bowel obstruction, and the medical management of inoperable malignant bowel obstruction, as well as the reversal of intestinal transit. Table 5 summarized the case reports [70,72, 88] and prospective studies [71,73,75] showing the efficacy of octreotide in the control of GI symptoms due to bowel obstruction.

The percutaneous endoscopically placed gastrostomy (PEG) tube, initially developed for enteral feeding, recently has been used effectively for intractable vomiting due to obstruction of the upper GI tract [89]. In the presence of marked and diffuse bowel distension, the administration of octreotide may reduce GI secretions sufficiently to allow appropriate PEG placement [90].

These studies, although uncontrolled, support the use of octreotide in the management of GI symptoms due to inoperable malignant bowel obstruction. Reported effective doses range from 0.1 to 0.6 mg/day, given either as a continuous parenteral infusion or as intermittent subcutaneous or intravenous boluses. Octreotide, administered in association with either morphine or hyoscine butylbromide or haloperidol (0.5–1.2 mg/mL) does not show visual precipitation when mixed in the syringe [40].

Two randomised prospective studies were carried out to compare the antisecretory effects of octreotide (0.3 mg/day) and scopolamine butylbromide (60 mg/day), administered by continuous subcutaneous infusion for 3 days in 17 patients with inoperable bowel obstruction and a nasogastric tube in place [77] and in 15 similar patients who did not have a nasogastric tube [78]. In both studies, half of the patients were cared for at home, and the other half were hospitalised in surgical wards. In both studies, the hospitalised patients received significantly more parenteral hydration (2000 mL vs 500 mL daily) than the patients cared for at home.

In the first study performed by Ripamonti et al. [77], octreotide was shown to significantly reduce the volume of GI secretions on the second ($P = 0.016$) and third day ($P = 0.020$) sufficiently that the nasogastric tube could be removed in all 10 home-care patients and in three hospitalised patients without changing the dosage of the drug. In two patients, it was possible to remove the nasogastric tube when the octreotide was added to scopolamine butylbromide or when the scopolamine butylbromide dose was

Table 5
Role of octreotide in malignant bowel obstruction[a]

Author	Number of patients	Site of cancers/sSite of obstruction	Symptoms	Octreotide dose/route and other drugs	Outcomes
Mercadante et al. [70]	2	Intra-abdominal/small and/or large bowel and carcinomatosis	Abdominal pain and vomiting (1°)	0.2–0.3 mg/day + 0.9 mg buprenorphine via CSI	Pain and vomiting disappeared within 24 hours. NGT was removed; no adverse effects were reported. NGT secretions decreased from 2,600 mL/day to 350 mL/day and vomiting disappeared within 24 hours.
			Colic pain and vomiting despite the use of NGT and haloperidol (2°)	0.9 mg/day + 3 mg haloperidol	NGT was removed; **no** further need for analgesics or intravenous fluids. No adverse effects were reported.
Khoo et al. [72]	5	Various intra-abdominal sites/small bowel	Intractable vomiting, unresponsive to conventional therapy	0.1–0.5 mg/day via SCB to start, then CSI	Vomiting stopped within 1 hour of start of treatment. The only patient with a NGT presented a reduction in aspirate from 2,000 mL/day to < 300 mL/day. No important toxicity was reported.
Steadman et al. [88]	1	pancreas/small bowel	Vomiting and drowsiness with diamorphine, cyclizine, and hyoscine	0.2 mg/day + diamorphine	Switching to octreotide produced good symptom relief without causing unwanted uncomfortable drowsiness. NGT was removed.
Mercadante et al. [71]	14	Various intra-abdominal sites/small and/or large bowel	Nausea, vomiting unresponsive to haloperidol or chlorpromazine	0.3–0.6 mg/day via SCB or CSI + haloperidol + analgesics	Vomiting was controlled in 12 patients and reduced in 2 patients. In 2 of 3 patients NGT was removed and symptoms were controlled. No important toxicity was reported.
Riley et al. [73]	24	Various intra-abdominal sites/small and/or large bowel	Intractable vomiting not responsive to a combination of antiemetics, steroids and/or NGT drainage for 24 hours	0.1–1.2 mg/day via SCB or CSI	Fourteen patients had no further vomiting, and 4 pts showed some improvements on 0.1–0.6 mg/day of octreotide. Aspirate was reduced in all 5 pts with a NGT. Six patients did not respond, despite dosages of 0.6–1.2 mg/day. No adverse effects were reported, even at higher doses.
Mangili et al. [75]	13	Ovary/small and/or large bowel	Vomiting not responsive to metoclopramide and haloperidol	0.3–0.6 mg/day via SCB or CSI ± analgesics	Vomiting was controlled in all cases within 3 days (range, 1–6 days). In eight patients with a NGT there was a significant reduction of secretions and the NGT was removed. No adverse effects were reported.

[a] CSI: continuous subcutaneous infusion; NGT: nasogastric tube; SCB: subcutaneous bolus.

doubled and parenteral hydration was reduced. In these patients, octreotide tended to be more effective than scopolamine butylbromide. In the hospitalised patients, removal of the nasogastric tube was less likely in patients who were receiving greater amounts of parenteral hydration.

In the second study [78], octreotide induced a more rapid reduction in the number of daily episodes of vomiting and alleviated nausea better than scopolamine butylbromide. When one of these drugs is ineffective by itself, combining the two may reduce GI secretions and alleviate vomiting [77].

In a recent study of 68 terminally ill cancer patients with various malignancies who were randomly assigned to receive continuous subcutaneous administration of chlorpromazine (15–25 mg/day) plus hyoscine butylbromide (60–80 mg/day) or octreotide (0.6–0.8 mg/day), relief of vomiting, nausea, fatigue, and anorexia was significantly better in the patients receiving octreotide [91]. Opioid analgesics were also available to all patients in both groups and pain relief was obtained.

Octreotide also may be effective in relieving partial bowel obstruction because it can reduce the hypertensive state in the lumen that causes the distension–secretion–distention cycle, which can lead to total obstruction if not treated [92,93]. Such obstruction can often be avoided if aggressive treatment is initiated early, before faecal impaction and oedema render obstruction irreversible. Early and intensive pharmacologic treatment may not only alleviate GI symptoms but also reverse malignant bowel obstruction [93]. In one recent study of patients with advanced cancer, octreotide combined with metoclopramide, dexamethasone, and an initial bolus of amidotrizoate allowed the recovery of intestinal transit within 1–5 days and prevented bowel obstruction until death in most of the patients studied [94].

The perioperative use of octreotide in bowel obstruction with intravenous replacement of fluids and electrolytes, placement of a nasogastric tube, and use of antibiotics is indicated to improve the obstructed patient' s condition [92,95].

Anti-emetic drugs

Metoclopramide is an anti-emetic drug that increases gastric motility. It acts centrally in the chemoreceptor trigger zone (CTZ) and peripherally as gastroduodenal prokinetic. Most authors [13] do not recommend this drug in the presence of complete bowel obstruction because it tends to increase nausea, vomiting and colicky pain symptoms. Isbister et al. [69] successfully used parenteral metoclopramide with a mean dose of 6.9 mg/h to control nausea and vomiting in patients not having an upper GI obstruction, presumably by encouraging the stomach to evacuate its contents into the paralysed reservoir of the bowel. According to Fainsinger et al. [39], metoclopramide (a parenteral dose of 10 mg every 4 hours) was the drug of choice in patients with incomplete bowel obstruction. Metoclopramide, given parenterally, can be considered the drug of choice in patients with mainly functional bowel obstruction.

If metoclopramide fails to relieve vomiting or associated colics, other anti-emetics to consider are the butyrophenones, antihistaminic-anti-emetic and phenothiazine [13]. There are no studies comparing these anti-emetics in patients with inoperable bowel obstruction. The drugs indicated in Fig. 2 refer to clinical practice at palliative care centres in different countries.

Cyclizine is the drug more frequently used in palliative care centres in the UK. It can be added to prochlorperazine suppositories and to haloperidol subcutaneously. Crystallization may occur at higher doses or in association with other drugs [1].

Haloperidol, a dopamine antagonist and a potent suppressor of the CTZ, is considered to be the anti-emetic drug of first choice in complete obstruction by many palliative care specialists [21,40,70]. It causes less sedation and has less anticholinergic effects than phenothiazines. Parkinsonian side effects may occur with doses higher than 15 mg/day. It can be administered subcutaneously as a bolus or as a continuous infusion and may be combined with scopolamine butylbromide and opioid analgesic in the same syringe.

Among the phenothiazines, methotrimeprazine (levomepromazine), chlorpromazine and prochlorperazine [21], are all used and effective. Chlorpromazine and prochlorperazine are not recommended for continuous subcutaneous infusions because they cause skin irritation [21,96]. A combination of anti-emetics with different sites of action may be more effective than a single agent [97].

Several authors recommend the use of corticosteroids for the symptoms due to bowel obstruction because they can reduce peri-tumoural inflammatory oedema, thus improving intestinal motility. Corticosteroids are potent anti-emetics. They act possibly by reducing the permeability of the area postrema and the blood-brain barrier to emetogenic substances and by reducing the neuronal content of gamma-aminobutyric acid (GABA), an inhibitory amine, in the

brain stem. Steroids have been shown to increase water and salt absorption, thus reducing the net balance of water and electrolytes in the intestinal content. For this reason, this class of drugs can be considered as antisecretory agents. Steroids have been found to be effective in MBO in a series of studies [98, 99]. Apparent benefit must be differentiated from spontaneous remission seen in about one third of partially obstructed cancer patients. A recent meta-analysis of these studies showed a trend towards resolution of bowel obstruction using dexamethasone in doses ranging from 6 to 16 mg/day intravenously with minimal morbidity, although this result did not achieve statistical significance [100].

Drug associations

Most of the recommended drugs for pain management and for treating vomiting can be administered in combination in a single syringe, thereby facilitating administration [101]. However, drug incompatibility may lead to drug crystallization, resulting in blockage of the cannula. Some authors report the results of stability and/or compatibility testing for interactions between the recommended drugs [102–105]. The administration of haloperidol (2 mg/ml) has no detrimental effect on the stability of the diamorphine/cyclizine combinations, but appears to stabilize the mixture [105]. Morphine administered in association with hyoscine butylbromide or octreotide and haloperidol (0.5–1.2 mg/ml) does not show visual precipitation when mixed in the same syringe [40,106, 107]. Laxatives, which increase small bowel content (e.g. magnesium salts and non-absorbable sugars) should not be used in obstructed patients. In patients with a colon obstruction, peristaltic stimulants should also be avoided. A faecal softener can be used (e.g. docusate sodium) in obstructed patients to prevent secondary faecal impaction.

Total parenteral nutrition and hydration

The main goal of parenteral nutrition is to maintain or restore the patient' s nutritional status and to correct or prevent malnutrition and its related symptoms [108]. The role of parenteral nutrition in the management of patients with inoperable bowel obstruction should be carefully considered based on several factors. It is predicated on the expectation of demonstrable benefit for the patients [109]. The efficacy depends on whether it improves quality of life and does not simply lengthen survival. Parenteral nutrition may prolong survival but can also lead to complications, add further suffering and make prolonged hospitalisation necessary [110].

In some circumstances in which bowel obstruction is temporary and can spontaneously resolve, it is of value in maintaining an appropriate nutrient intake until a therapeutic action has an effect. However, in most cases this practice is unnecessary and may worsen the patient' s burden. It is often practiced as a psychological measure at the insistence of relatives. In most cases, parenteral nutrition is interrupted after appropriate information about the short prognosis and the evidence of no benefit [111]. Therefore, routine use should be avoided simply for the form of prolongation of life. Parenteral nutrition should not be started without a full discussion with the patient and family members. Only those patients who strongly support this decision after a clear explanation should be offered this approach. A home care program for such patients requires active participation of the patient' s caregiver and the involvement of skilled nurses, pharmacists and physicians [112]. Total parenteral nutrition should only be used in selected patients.

Most patients with bowel obstruction are dehydrated due to an accumulation of water and electrolytes in the intestines and poor oral intake of fluids. The correction of this status does not have an effect on dry mouth and thirst, as the intensity of these symptoms seems to be independent of the amounts of fluids administered either by oral or parenteral route [13,77,113]. High level of hydration may result in more bowel secretions [77]. On the other hand, the intensity of nausea was significantly lower in patients treated with moderate amounts of water (>500 mL/day), probably due to the prevention of metabolic derangement associated with severe dehydration and reduction of stimulation of the chemoreceptor trigger zone [77,78]. Administration of 1–1.5 litre/day of solution containing electrolytes and glucose may be useful in preventing symptoms due to metabolic derangement. Hypodermoclysis is a valid alternative to intravenous administration of fluids for patients with poor venous availability of without a central venous catheter [114]. Providing sips of fluids orally, frequent mouth care and sucking ice cubes are of paramount importance for relieving dry mouth, commonly associated with the use of anticholinergics [13,115].

Artificial hydration is indicated only to correct dehydration-related symptoms. Hypodermoclysis has many potential advantages over the IV route for patients who have not a previously inserted central venous catheter.

Inoperable patients managed by drug therapy should be encouraged to drink and eat small amounts of their

favourite beverages and food. Some patients find that they can manage food best in the first half of the day. Most patients managed in this way do not need artificial hydration.

Conclusions

The optimal treatment of bowel obstruction in patients with advanced cancer is still an open and widely debated issue. Patient are usually considered suitable candidates for surgery when survival is expected be more than two months. Studies of prognostic indicators of survival in advanced cancer patients are necessary to assist doctors in making appropriate therapeutic decisions, together with the patient and family members. Medical treatment by continuous subcutaneous or intravenous administration of opioids, corticosteroids, anticholinergic drugs, octreotide, and anti-emetic drugs can be an effective approach for controlling pain, nausea and vomiting in patients with inoperable GI obstruction. Nasogastric suction or percutaneous gastrostomy may be considered for patients with refractory symptoms and/or upper bowel obstruction who do not respond satisfactorily to pharmacological measures alone. The efforts of the doctor/nurse team must be aimed at both symptom control and other aspects of the patient' s suffering, including psychological distress and spiritual concerns.

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