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The Rationale for a Multimodal Approach in the Management of Breakthrough Cancer Pain: A Review

Luiz Guilherme Soares, MD, and Vincent W. Chan, MD, FRCPC

Breakthrough pain has been described differently in various countries, and not surprisingly, recommendations for its management vary according to the institution. Usually when breakthrough pain occurs, the patient's pain has already been managed according to the World Health Organization 3-step ladder for cancer pain. After this point, the treatment choice is usually based on clinical judgment, the physician's personal experience with interventional procedures, and local resources available. Opioids remain the mainstay of the management of breakthrough cancer pain. However, the combination of radio-oncology, adjuvant drugs, and interventional pain procedures can improve pain relief. This review addresses those questions and proposes a multimodal approach to manage breakthrough cancer pain.

Keywords: cancer pain; breakthrough pain; cancer pain management

Proper use of World Health Organization (WHO) guidelines can control cancer pain in 80% to 90% of patients. Unfortunately, pain is refractory in the remaining 10% to 20%.[1,2] Many cancer patients with refractory pain suffer from intermittent pain episodes or breakthrough pain, which is defined as a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving continuous opioid therapy.[3] Breakthrough pain is usually related to functional impairment, psychologic distress, poor prognosis, reduced likelihood for adequate pain control, and increased associated background pain.[4-6] Since its description by Portenoy and Hagen[3] more than 15 years ago, breakthrough pain has been studied by different investigators. Controversies over the definition, prevalence, and treatment still persist, however.

Prevalence

Although a number of studies have evaluated breakthrough pain, differences in definition, diagnosis, and sampling between clinicians and researchers resulted in inaccurate estimates of its prevalence. An international survey of cancer pain characteristics indicated that the breakthrough pain definition varied from country to country.[7] Furthermore, "breakthrough pain" is an English term with no literal translation in many languages, including Spanish, Italian, and Portuguese, among others. Despite the semantic and sampling controversies, evidence shows that breakthrough pain is a prevalent syndrome,[8,9] with an incidence rate as high as 89%, depending on the setting.[10]

Etiology and Assessment

A thorough breakthrough pain evaluation is the most important step in choosing the best therapeutic approach. Breakthrough pain must be characterized according to its temporal patterns, etiology, and precipitating factors. Breakthrough pain usually occurs at the same site as the background pain.[3,7] Breakthrough pain episodes are typically abrupt and severe, with peak intensity within 5 minutes and lasting 15 to 30 minutes. It occurs daily, and many patients experience more than 3 episodes per day.[3,7,10]

Pain exacerbation related to activity or a specific event is known as "incident pain." Most commonly, these episodes of pain exacerbation occur during

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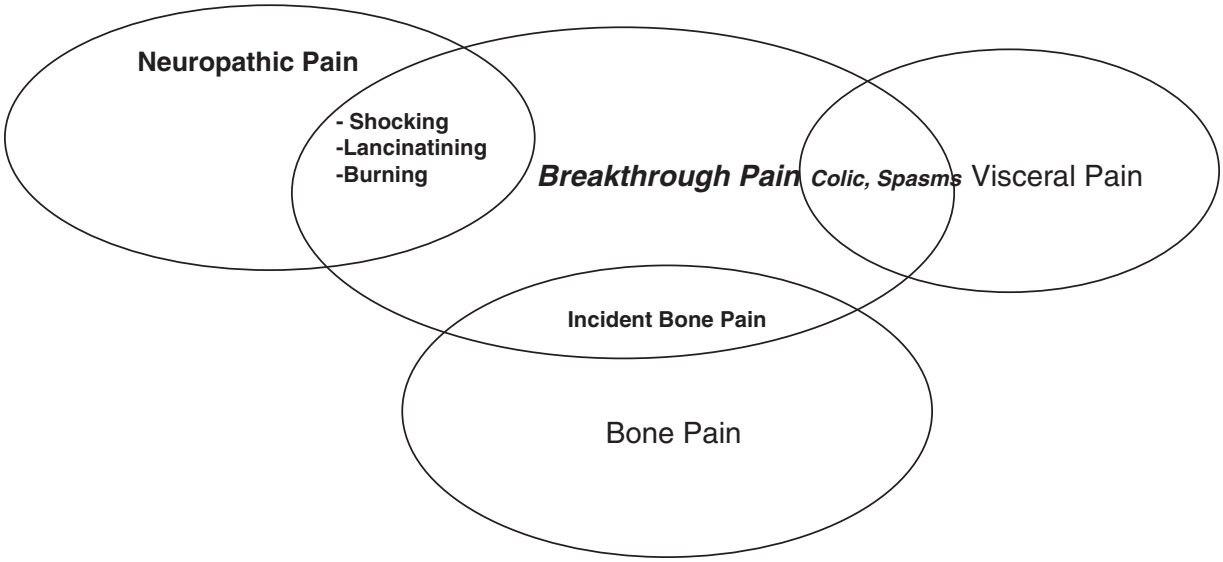

Figure 1. Common clinical presentations of breakthrough cancer pain.

routine daily activities such as walking, sitting, coughing, and moving in bed. The predictable course of pain imposes additional suffering, functional limitation, and anxiety.[4] Incident pain due to movement is the most common form of breakthrough pain and is usually related to bone metastases.[11] Vertebral, pelvic, and long bone lesions are the most prevalent syndromes associated with breakthrough pain. Elimination of pain in motion is a difficult goal to achieve in these patients.[12]

Spontaneous pain is usually related to tumor invasion into nerve roots or visceral organs. Stimulus-independent breakthrough pain can be the result of spontaneous ectopic activity in afferent nerve fibers that have a "new" lowered threshold.[13] Nerve injury could also be related to cancer treatment, such as chemotherapy, radiotherapy, and surgery.[14] Cancer patients with neuropathic syndromes usually complain of sudden onset of burning, lancinating, or electrical pain.

Abdominal visceral pain is a common presentation in patients with pancreatic, intestinal, or genitourinary tract cancer. Patients with intestinal obstruction refer to pain as a colic sensation, usually due to hollow, viscus contraction.

Frequently, inadequate analgesic dose or intervals result in end-of-dose pain. End-of-dose pain has been defined as a pain flare that occurs before a scheduled dose of an around-the-clock analgesic.[15] In these cases, pain usually reflects inadequate analgesia or inappropriate dosing interval and must not be confused with breakthrough pain syndrome. Different from breakthrough pain, the onset of end-of-dose pain is more gradual, and it is usually resolved by increasing doses of opioids and adjuvants or by shortening the dosing intervals.

Drugs with long-acting presentations, such as morphine and oxycodone, can be optimized by decreasing the dosing intervals from 12 hours to 8 hours. The prescription of transdermal fentanyl, which theoretically should be replaced every 72 hours, could result in inadequate pain relief in some patients. A pain-free period that lasts 48 hours, followed by pain recurrence, is a relatively common complaint in clinical practice. In these circumstances, changing the patch every 48 hours could be appropriate.

Cancer pain is a complex syndrome, encompassing several clinical presentations with different temporal patterns that can even occur in the same patient during the disease course. Figure 1 illustrates the most common presentations of breakthrough pain.

General Treatment Principles and Nonpharmacologic Measures

The patient must have an orientation in the areas of relaxation techniques, psychologic support, behavioral

changes, and increasing activity without overexertion. A psychiatric consultation might be needed in cases of severe disability or for orientation about orthotic devices. Spinal orthosis can relieve breakthrough pain during spinal flexion and rotation in patients with vertebral metastatic disease. Incident pain related to long bone or vertebral fractures may require orthopedic treatment. Fractures of the femoral head or neck are usually treated with cemented hemiarthroplasty, and intramedullary devices are best suited for diaphyseal fractures. However, studies focusing on quality of life and morbidity for those procedures are lacking, and choosing the best candidate for an orthopedic surgery remains a challenge.

The use of around-the-clock opioids and adjuvants according to WHO guidelines for cancer pain is recommended for baseline pain control. Opioid rescue doses should be prescribed for breakthrough pain. One study found that up to 40% of patients with breakthrough pain taking long-acting opioids were not prescribed an opioid rescue dose for pain exacerbations.[10]

Breakthrough pain can also be related to acute conditions such as skin infections, mucositis, perforated viscus, and vascular emergencies that demand prompt correction of the subjacent cause.

Radiotherapy and Radioisotopes

Radiotherapy and radioisotopes must be considered for incident pain related to bone metastases. Palliative external beam radiotherapy in the form of hemibody or focal bone irradiation has been successfully used for metastatic bone pain.

Doses of radiotherapy lower than required for tumor eradication and limited to the painful lesion are effective for pain control, with complete pain response being achieved in about 30% of patients.[16] Typical palliative radiotherapy regimens range from 400 to 800 cGy in one fraction to 3000 cGy in 10 fractions. In the scenario of sudden back pain related to spinal cord compression, early radiotherapy could be the difference between preserving a patient's mobility or paraplegia.

Radioisotopes are radioactive agents administered intravenously to deliver radiation to multiple metastatic sites in a focal manner. Strontium-89 and samarium-153 have been the 2 radioisotopes most examined for bone pain. The main advantages of using radioisotopes include the ease of administration, the ability to treat multiple sites of metastatic disease, and the potential to combine them with other treatments, such as chemotherapy or external beam radiation. Hemibody irradiation used to be indicated for multiple bone metastases but is associated with visceral toxicity and has been replaced by radioisotopes. Radioisotopes are not devoid of side effects, however, and myelotoxicity is a potential complication with these drugs. Complete pain response after administration of radioisotopes has been reported to be 20% to 30%,[17] with many patients reporting good pain control for as long as 6 months. In a pilot study, a samarium infusion reduced opioid consumption and incidental pain due to multiple bone metastases from prostate cancer.[18]

As mentioned, radiotherapy and radioisotopes are not free of adverse effects. Nausea, vomiting, hematologic depression, and visceral toxicity can occur as a result of these therapies. An integrated approach involving the radiation oncologist and the palliative care team should minimize the complications and increase the efficacy of the treatment.

Pharmacologic Measures

Adjuvants

Nonsteroidal Antiinflammatory Drugs and Corticosteroids

Nonsteroidal antiinflammatory drugs (NSAIDs) may be effective in breakthrough pain episodes related to nociceptive mechanisms such as bone metastases. Visceral pain and mixed pain syndromes could also respond to NSAIDs.[19] Although not addressed specifically for breakthrough pain, NSAIDs have been found useful for baseline pain control when prescribed according the WHO guidelines.[20]

A breakthrough pain guideline suggested that NSAIDs can be used as a rescue medication in patients who are not taking this drug for basal analgesia, especially in the form of fast release, sublingual, or parenteral formulations.[21] Long-term efficacy and safety of NSAIDs is unknown, however, and they should only be prescribed for a short period of time.

The use of cyclooxygenase 2 inhibitors with reduced gastrointestinal toxicity has not been studied in cancer patients, and cyclooxygenase 2 inhibitors

should not be prescribed routinely for cancer pain.[22] These drugs, however, should be considered in patients at high risk of gastrointestinal bleeding, possibly in combination with proton pump inhibitors.

Corticosteroids have been used for bone pain mainly because of their antiinflammatory properties. Prednisone, in low doses, improved pain control in up to 40% of patients with prostate cancer and metastatic disease.[23] Corticosteroids have been reported to be useful for pain associated with perineural edema, spinal cord compression, and bowel obstruction.[24-26] The risk of peptic ulcer disease is increased when corticosteroids are combined with NSAIDs. Discontinuation of 1 of those drugs or prescribing a gastroprotective drug is strongly advised.

Bisphosphonates

Bisphosphonates are synthetic analogs of pyrophosphate characterized by a phosphorus-carbon-phosphorus backbone that renders them resistant to hydrolysis. Bisphosphonates inhibit osteoclast activity by cellular mechanisms that affect osteoclast attachment, differentiation, and survival. In a preliminary report, Mercadante et al[27] described a dramatic improvement in incidental pain after courses of intravenous doses of 90 mg of pamidronate.

Zoledronate acid is a third-generation bisphosphonate that is 2 to 3 times more potent than pamidronate and is effective for both osteoblastic and osteolytic metastases. Zoledronate improves pain control and reduces skeletal events in different tumor types.[28,29]

Ibandronate is a new bisphosphonate with unique properties. Phase III studies have shown that intravenously and orally administered ibandronate is efficacious for the prevention of skeletal events and for the reduction of metastatic bone pain for up to 2 years.[30]

Antisecretive Drugs and Colicky Breakthrough Pain

Hyoscine butylbromide (scopolamine) and octreotide have been used for relieving abdominal spasms and bowel obstruction. Scopolamine decreases peristalsis in smooth muscle by blocking muscarinic receptors and interfering with the ganglionic neural transmission in the bowel wall. A continuous infusion of scopolamine at a dose of 60 mg daily could control pain in nonoperable bowel obstruction.[31]

Octreotide, a somatostatin analogue, decreases gastrointestinal motility and reduces gastric, pancreatic, and intestinal secretions. Octreotide seems to have a shorter onset of activity compared with scopolamine; however, no significant differences were found for colicky pain.[32]

Drugs for Lancinating, Shocking, or Burning Breakthrough Pain

Paroxysms of lancinating, shocking, or burning pain are common presentations of breakthrough pain, usually related to some degree of nerve injury. In fact, neuropathic pain may be a risk factor for the occurrence of breakthrough pain.[33] Different classes of drugs, such as antidepressants, anticonvulsants, and antiarrhythmics, have been used for refractory neuropathic cancer pain. Because no studies have addressed the effectiveness of each of these drugs on the treatment of breakthrough pain, they are still prescribed by many physicians based on their personal experience, syndrome characteristics, and presumed drug mechanisms of action.

It is generally accepted that antidepressants could be useful adjuvants in neuropathic cancer pain. Tricyclic drugs, such as amitriptyline, imipramine, nortriptyline, and desipramine, are the most commonly used compounds. The elderly population is especially prone to side effects such as sedation, delirium, and orthostatic hypotension. Tricyclic antidepressants should be avoided in patients with significant heart disease, including heart failure, significant hypertension, conduction abnormalities, and arrhythmias. For those who have contraindications to tricyclic compounds or who cannot tolerate the side effects, another antidepressant should be considered. The selective serotonin reuptake inhibitors duloxetine and venlafaxine are some of the potential alternatives. Evidence for prescribing those drugs is scarce, however, and comes mostly from studies of nonmalignant neuropathic pain.[34,35]

Although anticonvulsants such as carbamazepine and phenytoin have been used to treat neuropathic pain, gabapentin has replaced those drugs as the anticonvulsant of choice for cancer pain. Gabapentin is thought to work by blocking calcium channels, thus increasing synthesis and the release of γ-aminobutyric acid. Gabapentin has no major drug interactions and does not induce hepatic enzyme activity. In 2 prospective studies, a daily dose of 300 to 1800 mg of gabapentin reduced pain

scores and improved tolerance to daily living activities in patients with neuropathic pain related to cancer.[36,37] Gabapentin has also improved incidental pain and decreased morphine consumption in an acute pain setting.[38] To our best knowledge, the roles of the newer anticonvulsants such as pregabalin, topiramate, and vigabatrin in the management of cancer pain are unknown.

Lidocaine is a local anesthetic and also an antiarrhythmic drug. By suppressing neuronal ectopic discharges, lidocaine has been used for deafferentation and central pain. It produces analgesia by the blockade of peripheral and central sodium gate channels, including in the spinal dorsal horn. In a recent meta-analysis, lidocaine and mexiletine, an oral lidocaine analogue, were superior to placebo in relieving neuropathic pain.[39] Despite frustrating results in cancer pain,[40] many physicians have prescribed subcutaneous or intravenous lidocaine infusion. Oral mexiletine has been prescribed to guarantee a long-term analgesic effect in patients who respond to lidocaine infusion. Unfortunately, the benefits of lidocaine infusion are transitory, mexiletine side effects (nausea, vomiting, tremor) are common, and mexiletine efficacy for breakthrough pain has not been studied.

Postherpetic neuralgia and postsurgical pain related to mastectomy or thoracotomy frequently are associated with lancinating or sharp breakthrough pain. The lidocaine patch can decrease pain scores in these patients, but a full response may require up to 4 weeks in some patients.

There are many reports of ketamine efficacy for refractory cancer pain. Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. Antagonism of the NMDA receptor could reverse opioid tolerance and relieve some types of neuropathic pain. Clinical studies demonstrated that a low hourly dose of 0.1 to 0.4 mg/kg intravenous or subcutaneous ketamine may improve analgesia.[41-43] Intranasal ketamine has been applied for breakthrough pain with promising results.[44] Unfortunately, because of the lack of clinically relevant randomized controlled trials and concerns about psychomimetic side effects, the drug should be reserved for refractory cancer pain, especially when opioid tolerance or neuropathic pain is present.

Opioids

Opioid analgesics remain the mainstay of management for breakthrough pain. Although the weak opioid tramadol has been shown effective for nonmalignant breakthrough pain,[45] its use in cancer pain is limited because of its slow onset, long duration of activity, and ceiling effect. Typical breakthrough pain episodes are abrupt, with a duration of 30 minutes, and the intensity of pain is reported to be severe to maximal in 92% of patients.[33] Therefore, the ideal opioid and route of administration must offer fast onset, high potency, and short duration of action. Although frequently reported as a potential route of administration, we consider rectal administration uncomfortable for most patients and therefore inadequate for long-term management of breakthrough pain. In this section we discuss the most common routes of opioid administration for breakthrough pain.

Oral

Immediate-release formulations of morphine, oxycodone, and hydromorphone are reasonable options for predictable pain episodes. It has been suggested that a preemptive approach, which consists of optimization of the basal opioid therapy instead of treating the pain after onset, should be attempted in incidental pain related to bone metastases.[46] However, for many patients the oral route is not ideal.

During spontaneous pain events, the oral administration of morphine commonly results in inadequate blood levels until 30 minutes after treatment.[47] Although a preliminary study has suggested that a rapid onset of analgesia could be achieved with oral methadone,[48] more studies are necessary before recommending this drug as a safe opioid for breakthrough pain, especially because of its unpredictable pharmacokinetic profile.

Intravenous and Subcutaneous

Opioid administration by parenteral routes yields a shorter time to peak analgesic effect compared with oral administration.[49] The subcutaneous route has been widely used to treat cancer pain. It is safe, simple, and a reliable route of opioid administration. To increase patient comfort and avoid multiple injections, a plastic cannula can be easily inserted in the subcutaneous tissue, which is especially useful for opioid administration at home.

A comparison between subcutaneous and intravenous morphine administration demonstrated that

pain relief was achieved faster with intravenous administration.[50] Intravenous morphine has been shown to fit the temporal pattern of breakthrough pain, and at a dose equivalent to 20% of the total daily oral dosage, is reported safe and effective in breakthrough pain.[51] Intravenous morphine has been reported to be safe and efficient for episodic pain in cancer patients receiving transdermal buprenorphine for baseline pain control.[52]

Oral Cavity

The oral cavity can be used for rapid opioid delivery and absorption. Lipophilic agents can be absorbed and pass through the oral mucosa, avoiding the first-pass metabolism in the liver and achieving plasma concentrations within minutes. Kunz et al[53] described the successful use of sublingual sufentanil for breakthrough pain control.[53]

Oral transmucosal fentanyl citrate (OTFC) is a fentanyl-containing matrix that dissolves in the mouth and is the first opioid analgesic delivery system specifically used for breakthrough pain. Oral transmucosal fentanyl citrate has been shown effective for breakthrough cancer pain[54-56]; however, because of a poor relationship between oral doses of opioid and the OTFC dose for breakthrough pain, a dose titration is required.[57] A common recommendation is to start OTFC in small doses of 200 to 400 μg and titrate upward according to the individual's need. Oral transmucosal fentanyl citrate doses for breakthrough pain are usually not related to the baseline analgesic regimen,[58] and the most appropriate opioid dose must be identified according to an individual titration.

A new formulation, the fentanyl buccal tablet, has shown promising results in controlling breakthrough pain in cancer in a randomized, double-blind study.[59] Compared with OTFC, the fentanyl buccal tablet provides more rapid and efficient delivery of fentanyl.[60] Although apparently efficient and safe, this new formulation still requires more studies with more patients enrolled before being incorporated into clinical practice.

Interventional Pain Management

Spinal Analgesia

Patients with breakthrough pain can experience refractory pain and severe side effects from opioid therapy, especially when the need for rescue doses increases. Intraspinal analgesics have been used with success in these patients.[61] Several drugs and systems have been used to provide adequate pain relief. A combination of local anesthetic, opioid, and clonidine has been shown to be particularly useful.[62-64]

In a small study, an intrathecal bolus of levobupivacaine 0 (25%, 1.5 mg) was well tolerated and effective for breakthrough pain episodes related to cancer in patients managed with intrathecal catheters.[65]

The decision between an epidural or intrathecal route of drug administration is usually based on the patient's life expectancy, epidural metastasis, impending cord compression, and risk of complications. Intrathecal administration has been shown to be more effective than the epidural route and less susceptible to fibrosis around the catheter tip.[66]

Intrathecal infusions are especially useful in patients with somatic cancer pain. The intrathecal catheter insertion must be guided by fluoroscopy to position the catheter tip close to the pain dermatome. The ability to program the spinal pump to deliver a bolus dose is limited to some modern devices. Therefore, during the titration period, it is highly recommended that an immediate-release opioid be prescribed by an alternative route—oral, intravenous, or subcutaneous—for breakthrough pain.

Vertebroplasty

Vertebral collapse caused by metastatic disease is frequently the source of incidental pain in cancer patients. Pain is the initial complaint in 95% of patients with osteolytic destruction of the vertebral bodies secondary to metastatic disease or multiple myeloma.[67]

Vertebroplasty is a technique in which strong glue is injected through a needle into a collapsed or weakened vertebra to keep the vertebra from collapsing further and causing symptoms of cord compression. Percutaneous vertebroplasty has been used to control movement-related breakthrough pain due to vertebral fracture, thus improving quality of life in cancer patients.[68] In addition, vertebroplasty can be combined with chemotherapy, radiotherapy, neurodecompression, and instrumentation.[69] The main risk of vertebroplasty is related to cement extravasations, which could lead to radiculopathy, embolism, and death. Most cement extravasations are asymptomatic, however, and the risk of significant complications is low when vertebroplasty is performed by a physician.

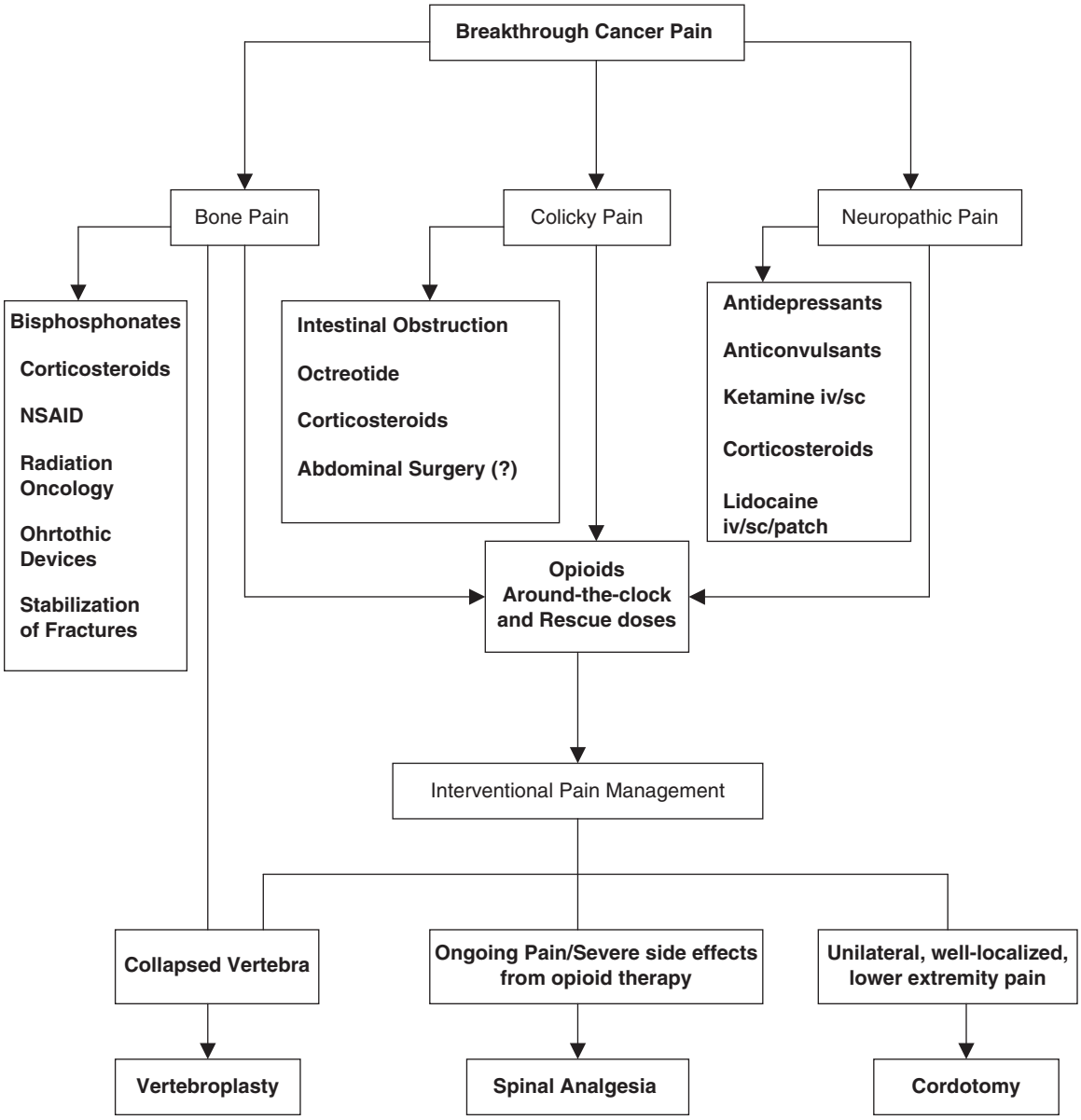

Figure 2. Multimodal approach for breakthrough cancer pain management. (NSAIDS = nonsteroidal antiinflammatory drug; iv = intravenous; sc = subcutaneous.)

Cordotomy

Neuroablative techniques aimed at interrupting pain transmission have been described for refractory cancer pain. One of those techniques, cordotomy, has been shown useful for incidental pain[70,71] and should be considered when all medical and minimally invasive techniques have failed, especially in the terminally ill patient. It usually produces pain relief in unilateral, well-localized, lower extremity pain syndromes; however, the risk of serious complications after cordotomy, such as dysesthesia, fatigue, respiratory failure, and clinical deterioration, is reported to be high.[26,71,72]

Conclusion

Some controversy exists about the semantic definition of breakthrough pain in various countries, but it is well accepted that breakthrough pain is a prevalent syndrome affecting as many as 89% of cancer pain patients. Incidental pain from bone metastases is the most common type of breakthrough pain. Neuronal

or visceral injuries usually are the cause of spontaneous breakthrough pain. Surgical stabilization of fractures and the use of orthotic devices restore mobility and might prevent pain in some patients. Radiotherapy and radioisotopes should be considered for metastatic bone pain.

Although opioids are considered the first-line agents, adjuvants are important and should be prescribed according to specific clinical syndromes. Patients who complain of severe opioid side effects and ongoing pain should be evaluated for a trial of intraspinal administration of opioids and adjuvants, provided that the catheter tip is positioned close to the pain dermatome.

Preliminary evidence suggests that patients with breakthrough pain related to vertebral collapse could benefit from vertebroplasty. Cordotomy should be considered in terminally ill patients with well-localized, unilateral, and incidental pain.

In our view, if a systematic and multimodal approach (Figure 2) that consists of a combination of medications and interventions were to be adopted in every patient with breakthrough pain, it would probably improve the therapeutic success in this challenging syndrome.

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