PALLIATIVE CARE AND COLORECTAL CANCER

Penelope Cotton, Peter Eastman, Brian H Le
1. Department of Palliative Care, Royal Melbourne Hospital, Parkville, Victoria, Australia.
Email: Brian.Le@mh.org.au

Abstract
Recent advances in anti-cancer treatment have seen improvements in survival for patients with metastatic colorectal cancer. Increasingly, patients with advanced disease are living longer, sometimes with significant morbidity related to the disease or its treatment. Integration of palliative care in the management of patients with advanced malignancy improves symptom control and quality of life for patients and their families. This article reviews the role of palliative care and provides an overview of current management for commonly experienced symptoms in patients with colorectal cancer.

Palliative care is defined by the World Health Organisation (WHO) as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.1 Palliative care encompasses symptom control and the provision of practical support across physical and psychosocial domains for patients and their carers, from first referral through terminal care and into bereavement.1

There is increasing recognition of the benefits of early integration of specialist palliative care can have for patients, particularly when provided concurrently with anti-cancer therapy.2 A landmark study published in 2010 demonstrated a range of benefits to patients with newly diagnosed stage IV non-small cell lung cancer.3 This study randomised patients at the time of diagnosis to early palliative care intervention with standard oncologic care or standard oncologic care alone. As expected, early palliative care involvement resulted in objective improvements in quality of life, symptom management and a reduction in ‘aggressive therapies’ at end of life. More surprisingly, patients in the early palliative care intervention arm had an increased median survival of 2.7 months compared to those who received standard oncologic care alone.3 The basis for this observed improvement in survival is the subject of ongoing discussion and research.4 With randomly allocated and evenly matched intervention groups for performance status, age, gender and disease stage, the survival benefit has been attributed to improvements in symptom control, quality of life and mood. This is supported by evidence of an association between increased symptoms, in particular dyspnoea and drowsiness, and shorter survival in cancer patients.5

The benefits of palliative care involvement on quality of life for cancer patients and their families have been demonstrated in two recent systematic reviews.6,2 Notwithstanding the methodological challenges related to research in this population, improvements were reported across a number of outcome measures including quality of life, patient satisfaction and end of life care.6,2 These results have been replicated across different palliative care settings, including hospital based consultation teams, community services and specialist inpatient units.6

Palliative care and colorectal cancer
Despite improvements in survival, colorectal cancer (CRC) is the second most common cause of cancer death in Australia.7 The prognosis for patients with advanced disease remains poor, with a five-year survival of 59% for stage III and 8% for stage IV disease.8 Both Australian and international data show patients with metastatic CRC experience significant symptoms throughout the course of their disease.9,10,11 Pain has been reported by up to 50% of patients,11 with other common symptoms including nausea, vomiting, bowel dysfunction and anorexia.9,11

Symptom management
Pain
Pain is a common complication of advanced cancer and is prevalent in all stages of disease.12 Uncontrolled pain is a source of significant distress, morbidity and disability for patients with cancer. Despite evidence-based pain management guidelines, there is significant variation in pain treatment, with inadequate pain control reported in over 80% of patients in some series.12,13,14 Effective management of cancer pain requires a holistic, multimodal and mechanism-based approach, regardless of disease stage.13,15 Multidisciplinary assessment is required to guide therapies such as radiotherapy and chemotherapy for the management of pain, and psychosocial supportive therapies are important to address concurrent sequelae of cancer pain.

There is strong evidence to support the effective and safe use of opioids in the management of cancer pain.16 More specific to CRC, they may be particularly efficacious in visceral type pain. Oral morphine, oxycodone and hydromorphone all have similar efficacy and toxicity in opioid-naïve patients.17 Recent guidelines from the European Association for Palliative Care suggest that any of these opioids can be used as first line for the management of cancer pain.18 Prescription of ‘around the clock’ coverage
with long-acting opioids, plus access to doses of immediate release ‘breakthrough’ analgesia, remains best practice for moderate to severe cancer pain. Doses should be carefully titrated according to individual pain requirements and response. Pre-emptive use of immediate release opioids should be considered for predictable episodes of breakthrough pain. In patients with co-morbid renal impairment, opioids should be used with caution and at reduced dose or frequency, with buprenorphine, fentanyl and methadone being safer alternatives, due to inactive metabolites and reduced adverse effects in significant renal impairment. However, transdermal patches (fentanyl and methadone) are best used in patients with stable opioid requirements, and methadone has wide variability in individual dosing and duration of action, with guidelines recommending its use only by experienced clinicians.

Neuropathic pain may occur in patients with CRC as a consequence of disease or its treatment. Recent evidence-based guidelines recommend two classes of medications for use as first-line adjuvants in the management of neuropathic pain: antidepressants (including tricyclics, venlafaxine and duloxetine); and anticonvulsants (including pregabalin and gabapentin). Opioids are effective in the management of neuropathic pain and are recommended in conjunction with adjuvant medications. Bisphosphonates are an effective adjunct in the management of malignant bone pain in addition to radiotherapy. Non-steroidal anti-inflammatory drugs may also be useful adjuvants, particularly in somatic-type pain, but can be associated with significant adverse effects.

Nausea

Nausea is a common symptom in patients with advanced CRC. The causes of nausea and vomiting are often multifactorial, including metabolic disturbance, partial or complete mechanical obstruction and iatrogenic causes. Aside from in post-chemotherapy or post-operative settings, there is limited high-level evidence to guide the management of nausea and vomiting in patients with advanced disease. Consideration should be given to the treatment (where appropriate) of reversible contributing factors such as hypercalcaemia, infection and known emetogenic medications.

Traditionally, decisions around antiemetic therapy have been mechanistically based, with management targeted at the proposed neurotransmitter pathways involved. However, the lack of strong evidence supporting this approach means that in practice, antiemetic choices are often derived from expert opinion or clinician familiarity. A recent systematic review concluded there was no evidence to favour either a mechanistic or empirical approach to the management of nausea in advanced cancer. Further studies, including a randomised phase III multicentre Australian study, are underway to better guide therapy for this common symptom.

A systematic review of antiemetics in advanced cancer found that metoclopramide had the greatest evidence to support its use. There was some evidence supporting serotonin (5HT3) antagonists, although they can be associated with worsening constipation. The butyrophenone anti-psychotic haloperidol is commonly prescribed for nausea in palliative care practice, however support for its efficacy as an anti-emetic is based on uncontrolled studies and expert opinion. Similarly, other antiemetics including corticosteroids, cyclizine and levomepromazine, which are often utilised as second-line agents, have only low-level evidence supporting their use.

Bowel obstruction

The development of malignant bowel obstruction is frequently associated with distressing symptoms, including pain and intractable nausea and vomiting. While malignant bowel obstruction may occur at any time in the disease process, risk increases in the advanced stages with reported rates of 4% to 24% for CRC. Surgical options to relieve malignant bowel obstruction in advanced cancer can be limited due to poor performance status or multilevel obstruction. Less invasive endoscopic stenting can be an option for selected patients with good results for symptomatic control described in the literature. Venting percutaneous endoscopic gastrostomy can be used to reduce vomiting in patients for whom other surgical procedures are not appropriate.

For many patients, invasive treatments are not appropriate and therefore medical management remains the mainstay of treatment. Medical management of malignant bowel obstruction by specialist palliative care utilises a combination of medications aimed at relieving symptoms and aiding resolution of the obstruction. These can include analgesics, corticosteroids, antisecretory agents (hyoscine, glycopyrrolate, ranitidine and octreotide) and antiemetics. A Cochrane review from 1999 concluded that the use of parenteral corticosteroids may facilitate the resolution of malignant bowel obstruction, although concerns have been raised about methodological flaws in studies addressing this question. Postulated mechanisms for this effect include direct anti-inflammatory activity and a reduction in malignant peri-tumoural oedema. A systematic review comparing ranitidine with proton pump inhibitors suggested that ranitidine is a more effective agent for reducing the volume of secretions and may therefore be valuable as an antisecretory agent in malignant bowel obstruction.

Octreotide, a somatostatin analogue, has been used in malignant bowel obstruction to reduce gastric secretions and minimise symptoms, although evidence supporting its use is mixed. A systematic review from 2007 reported that octreotide was more effective at relieving symptoms of inoperable bowel obstruction than the antisecretive hyoscine butylbromide, although patient numbers were relatively small in the included studies. However, recently concluded, yet to be published Australian multicentre randomised trial, did not demonstrate significant benefit for octreotide in either reducing malignant bowel obstruction associated vomiting or pain and nausea scores.

Constipation

Constipation has been defined as “the passage of small, hard faeces infrequently and with difficulty”. Chronic constipation is the commonest side-effect of opioids, and occurs in 40-70% of patients treated for cancer pain with oral morphine. Additionally, there are multiple other highly
prevalent causes of constipation in this patient population, including other medications, metabolic abnormalities (e.g. hypercalcaemia, uraemia), decreased mobility, neurological disorder/damage, autonomic neuropathy, altered dietary intake and depression.\textsuperscript{31,33}

Despite the prevalence of constipation in palliative care patients, it is underdiagnosed and undertreated.\textsuperscript{26} Reports suggest that up to 70% of patients with advanced cancer treated with laxatives continue to experience symptomatic constipation.\textsuperscript{25} Examination of the patient should include a focused rectal examination to assess faecal impaction and pelvic floor.\textsuperscript{24} Recent evidence suggests that plain abdominal x-rays, while frequently ordered in the investigation of constipation, correlate poorly with colonic transit time, faecal loading and symptoms of constipation, highlighting the importance of thorough clinical assessment.\textsuperscript{34,36}

While laxatives remain the mainstay of management, consideration must be given to modifying any contributing factors.\textsuperscript{31} There is no strong evidence to support the choice of a specific laxative, however guidelines suggest using a combination of stimulant and softening agents.\textsuperscript{31} Peripheral opioid receptor antagonists as separate therapy (e.g. methylnaltrexone) have been shown to be effective for refractory opioid induced constipation, although their use is not recommended in patients with bowel pathology.\textsuperscript{37} Combination opioid plus naloxone formulations have been reported to reduce opioid induced constipation without impacting on analgesia or precipitating withdrawal.\textsuperscript{38} These medications however, are contraindicated in liver dysfunction and inappropriate for patients with high opioid requirements and therefore their use in patients with advanced CRC may be limited.

**Psychosocial care and bereavement**

Patients with life limiting illness face many psychological challenges: grief about current or anticipated losses; fear and uncertainty about the future; regrets from their past; existential or spiritual issues and concerns about loved ones. Each person brings with them a unique burden of social and psychological vulnerabilities, balanced by their individual coping resources.\textsuperscript{39} Whether the patient with cancer has support or feels supported are major factors in how they manage socially, spiritually, physically and emotionally.\textsuperscript{40} Health professionals, particularly physicians, are perceived as important sources of support for patients and their families in time of serious illness.\textsuperscript{41}

Depression and other psychiatric disorders have a significant impact on the ability of patients to negotiate the challenges of life-limiting illness and are associated with significant suffering for patients and families.\textsuperscript{42} Depression leads to reduced quality of life, prolonged hospitalisation and causes significant distress for patients, caregivers and families.\textsuperscript{43} Identification of depression in palliative care patients is challenging, due to confounding effects of advancing disease.\textsuperscript{42} Approach to treatment should include good symptom management, fostering of social connections and relationships, pastoral and spiritual care.\textsuperscript{43} Choice of treatment modality must take patient function and prognosis into consideration. A recent Cochrane review demonstrated the effectiveness of psychotherapy in patients with incurable cancer, although onset of therapeutic effect can take up to six weeks and requires intensive patient participation.\textsuperscript{44}

Effectiveness of antidepressants in the treatment of depression in palliative care is widely agreed throughout the literature, however there are few controlled or comparative studies.\textsuperscript{42} Choice of pharmacotherapy must take into account patient factors such as prognosis, renal function, previous antidepressant history and comorbidities.\textsuperscript{42} Clinical guidelines based on current evidence recommend the use of selective serotonin reuptake inhibitors or mirtazapine as first line pharmacotherapy for depression in palliative care patients.\textsuperscript{42} In selected patients where prognosis is very limited (less than four weeks), a trial of psychostimulant medication may be appropriate.\textsuperscript{45}

Grief and bereavement is a normal response to the death of a loved one. Each loss is a unique experience with the requirement for bereavement support depending on resilience and the diverse needs of each person affected.\textsuperscript{46} Complicated grief is defined as a grief response that is severe and/or prolonged and is associated with a range of negative social, psychological and physical outcomes for bereaved carers, including increased morbidity and mortality.\textsuperscript{47} While evidence suggests that provision of bereavement counselling to resilient individuals is not beneficial and may actually be harmful, the literature consistently demonstrates benefit to those experiencing or at risk of complicated grief.\textsuperscript{46} Clinical practice guidelines suggest that all cancer services should screen carers for the risk of complicated grief, which includes factors such as limited social support networks, symptoms experienced and timing and location of death.\textsuperscript{48,49}

**Conclusion**

Early integration of palliative care is increasingly recognised as an effective component of multidisciplinary cancer care. Despite this, there is little specific reference to palliative care in many of the international colorectal practice guidelines. The European Society for Medical Oncology clinical practice guidelines for patients with metastatic CRC, for example, while emphasising that optimal treatment should be discussed in a multi-disciplinary setting and that care should be seen as a continuum determined by appropriate goals of care, does not mention palliative care.\textsuperscript{50} In Australia, the 2005 National Health and Medical Research Council colorectal cancer clinical practice guidelines makes only brief reference to the benefit of palliative care in the management of advanced disease.\textsuperscript{51} Given the symptom burden associated with advanced colorectal disease, the ongoing expansion of clinical trials designed to optimise approaches to symptom management and the increasing evidence base supporting an integrative approach between oncology and palliative care, this situation will hopefully change in coming years and palliative care will become a more prominent feature of future clinical guidelines for colorectal and other cancers.
Table 1: Recommendations

<table>
<thead>
<tr>
<th>Guideline – Palliative Care should be integrated early following diagnosis of advanced disease, even in the absence of physical symptoms.</th>
<th>Level of Evidence</th>
<th>Practice recommendation</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative care interventions should be introduced early as a component of care as they can improve the quality of life of patients with cancer.</td>
<td>II</td>
<td>Recommend</td>
<td>2, 4, 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline – Patients with colorectal cancer should be assessed regularly and routinely for pain and other symptoms.</th>
<th>Level of Evidence</th>
<th>Practice recommendation</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms in advanced colorectal cancer are common and can usually be effectively managed.</td>
<td>I</td>
<td>Strongly recommend</td>
<td>9, 10, 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline – Psychosocial interventions including bereavement support are important.</th>
<th>Level of Evidence</th>
<th>Practice recommendation</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial care can improve the quality of life for patients, and bereavement support for those with complicated grief improves outcomes.</td>
<td>III</td>
<td>Recommend</td>
<td>39, 41, 44, 49</td>
</tr>
</tbody>
</table>

References

29. Curvo D, Quinn S, Hardy JR, McCaffrey N, Eckermann S, Abernathy A. A multi-site, fixed dose, parallel arm, double-blind, randomised, placebo-controlled trial of intravenous octreotide or placebo with regular parenteral ranitidine and dexamethasone in the control of vomiting associated with malignant bowel obstruction. Paper presented at 7th World Research.
Congress of the European Association for Palliative Care; 2013 May 30 – June 2; Prague, Czech Republic.


35. Davis MP. Cancer constellation: are opioids really the culprit?. Support Care Cancer. 2008;16(5):427-429.


