Chapter 15
Chronic Conditions and Cancer at the End of Life

David C. Currow and Jane L. Phillips

Abstract The majority of people diagnosed with cancer are older and therefore are likely to have co-morbidities at the time it is diagnosed and if the cancer progresses to advanced disease. Guidance in the process of managing long-term co-morbidities at the end of life requires clarity about the goals of care for the person's cancer, and for each of his/her co-morbidities. Why was a particular therapy started in the first place? What risk is the therapy mitigating, and does it need to be continued? Very few studies help to inform the process of ceasing medications. For example, with cachexia and its associated weight loss, frequently encountered in advanced cancer, the management of two of the most frequent conditions—hypertension and diabetes—will change. The need for anti-hypertensives will decrease or the person will risk postural symptoms and the need for lower doses of hypoglycaemic agents and liberalised diets will be hallmarks of managing diabetes in order to avoid hypoglycaemia. Mostly, this care is in the setting of multiple co-morbidities, making review a complex and continuing process. Changes in co-morbidities can also directly influence the anti-cancer therapies that are available to patients, because of characteristics of the drug itself or changes in metabolism or elimination. Adjusting chemotherapy in advanced disease also requires careful evaluation of the goals of palliative treatment—are there symptoms that can best be addressed by disease modifying treatments or are there other more direct, better tolerated symptom control therapies available? Not only will there be a need for active management of long-term co-morbidities, but people will need to adjust psychologically to these changes. Modifying the goals of treatment is often the most overt signal to people that their disease is progressing and therefore can be particularly confronting. Such changes will often precipitate, or are an opportunity for, much wider conversations about life, dying and death.

D.C. Currow (✉)
Discipline, Palliative and Supportive Services, Flinders University, Adelaide, Australia
e-mail: david.currow@cancerinstitute.org.au

J.L. Phillips
Faculty of Health, University of Technology Sydney, Ultimo, Australia

© Springer Science+Business Media Singapore 2016

B. Koczwara (ed.), *Cancer and Chronic Conditions*,
DOI 10.1007/978-981-10-1844-2_15

Keywords Co-morbid illness · Chronic illness · Diabetes · Heart failure · Chronic obstructive pulmonary disease · Renal failure · End-of-life care

Key Points

1. Clinicians need to actively manage the long term therapies for chronic co-morbid conditions as people experience the systemic changes of advanced cancer, reflected most overtly by cachexia.
2. As function declines and there are measureable systemic changes in muscle mass, fat mass and appetite, it is important to adjust prescribing for long term co-morbidities that may be affected by these changes. Such conditions include hypertension and diabetes as key examples.
3. Most people invest effort and energy in optimally managing their co-morbid illnesses to the best of their ability. Changing the goals of care for such people as systemic changes (weight loss, declining function) dictate the need to adjust these therapies is often a difficult psychological transition to make for patients (and their families).
4. Palliative anti-cancer treatments for symptom control, particularly late in life, need to be considered in the context of the other ways that symptoms can be managed. 'Palliative' chemotherapy must have a specific target symptom that otherwise cannot be well palliated.
5. Co-morbidities will have an increasing impact on whether or not to offer systemic therapies late in life. An adequate assessment of each co-morbidity and its impact on level of function and symptom control is needed in parallel with the assessment of the person's cancer.

15.1 Introduction

Adults with advanced cancer who have other active co-morbidities are at increased risk of adverse outcomes [1]. As cancer advances, its impact on people is dictated in three major ways:

1. The systemic effects of having uncontrolled cancer (most frequently manifest by increasing fatigue, weight loss (of both muscle and fat), loss of appetite and resulting changes in body habitus)
2. Local effects of the cancer (which are most often over-shadowed by the systemic effects of the disease)
3. Psychological transitions associated with these systemic changes. Managing these changes needs to be considered in the context of the person's disease progression, goals and palliative care needs (Fig. 15.1).

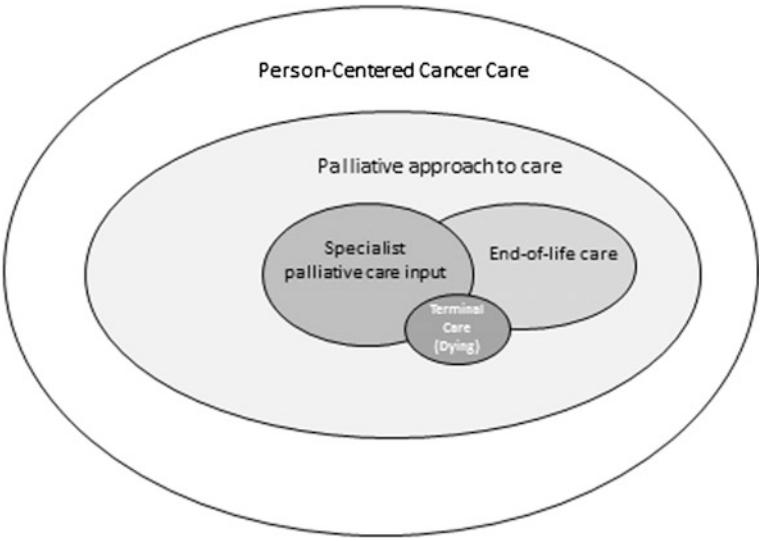

Fig. 15.1 Conceptualising the palliative management of advanced cancer and other co-morbidities

The systemic changes of advanced cancer demand the active management of co-morbid illnesses in order to optimise a person's function and avoid iatrogenic harm. With widespread and sometimes dramatic systemic changes, goals of care need to be reviewed frequently and adjustments made, not only to the goals as function declines, but also to therapies for long term co-morbidities. Such morbidities are frequently encountered in people with advanced cancer as older age is the most prominent risk factor for both cancers and co-morbidities.

In order to adjust therapies for long term co-morbidities, it is necessary to understand in detail why a medication was commenced and the goals of that therapy.

15.1.1 A Framework for Managing Co-morbidities

One proposed framework is to consider the level of prevention being undertaken by prescribing a medication (primary, secondary, tertiary) and the likely timeframes for the onset of problems if the therapy were ceased (Fig. 15.2). Another way to consider this is to quantify the number needed to treat and the timeframes required to avoid an event in order to contextualise the real risk for the specific patient if the medication were to be ceased. This helps clinicians to have an approach to rational deprescribing when there is no evidence that addresses directly ceasing the medication in question.

Therapeutic benefit in context of prognosis	Prevention strategy		
	Tertiary (disease with symptoms)	Secondary (disease with no symptoms)	Primary (no disease)
Potential for short term complications requiring management until death. Independent of prognosis eg glucose lowering drugs	Inflammatory arthritis	Diabetes mellitus	Phenylketonuria
Long term benefits at population level. Ongoing therapy unnecessary in most with shortened life expectancy. Some short term benefits need consideration eg antihypertensive drugs	Pulmonary rehabilitation in chronic obstructive airways disease	Hypertension	Influenza vaccination
Long term benefits at population level. Little short or intermediate term risk of stopping eg cholesterol lowering drugs	Osteoporosis	Hyperlipidaemia	Some aspirin use in elderly people

Key

Treatment likely to be changed later and less in the course of life limiting illness

Treatment likely to be changed earlier and more in the course of life limiting illness

Fig. 15.2 Factors influencing the likelihood of continuing treatment for medical comorbidities in patients with life limiting illness, and examples of conditions in each category. Used with permission from Stevenson et al. [34]

15.1.2 Negotiating Goals of Care

Negotiating goals of care with people who have advanced cancer requires time and conversations that are both honest and respectful. This is often a time of confronting change for patients and especially for their families and friends. Resetting expectations and hence resetting goals is one of the most important conversations that a clinician can have as he/she sees the manifestation of systemic changes of advanced cancer. Although these are often very challenging conversations, especially when first introduced, they are also highly valued conversations by patients and their families. Not having these conversations risks patients making ill-informed decisions about their future, often leading to anger and disappointment regarding the decisions and actions they would prioritised if they had truly known their prognosis.

The process of negotiating goals of care often entails also considering people's fears and concerns: What is my prognosis? How will I die? Will I have uncontrolled

symptoms? Who is going to provide care for me? How can I ensure that my wishes are respected even if I am unable to speak for myself? Patients expect that clinicians will be able to brooch these topics (rather than expecting the patient to raise these issues) and answer these questions confidently and sensitively [2]. It is the opportunity to provide information on advanced care planning, and to facilitate these crucial, ongoing conversations.

Many people will also have long term symptoms that pre-date their diagnosis of cancer. These symptoms may require special consideration, especially if they have not previously responded to disease modifying or symptom-focused measures [3].

This chapter is divided into sections on

- Chronic non-communicable diseases
- Communicable diseases
- Multi-morbidities.

It is structured to outline the considerations for key decisions as people face the systemic changes of advanced cancer. The chapter covers major co-morbidities and illustrates how to approach the challenges of managing co-morbidities in advanced cancer. Such a chapter cannot cover all potential co-morbidities, but it can ensure that it illustrates a framework to apply to decision-making from first principles if a particular clinical scenario is not outlined.

15.2 Non-communicable Diseases

Chronic cardiovascular disease in cancer

Managing cancer patients with cardiovascular disease requires consideration of prognosis and the risk factors that are being managed to minimise the impact of cardiovascular disease.

15.2.1 Management with a Prognosis of Months to Weeks

Many people with cardiovascular disease may also be receiving palliative cancer treatment, some of which may cause cardiotoxicity. Cardiotoxicity in this group may manifest as myocardial ischemia, hypertension, arrhythmias, pericarditis or conduction defects that require attention [4]. These people require ongoing monitoring and optimisation of medications to prevent symptomatic decompensated heart failure requiring hospitalisation [5].

People with cardiovascular disease tend to be on a large number of medications. Beyond reviewing medications for dynamic conditions such as hypertension which are likely to change as a result of weight loss, many people will also be taking cholesterol lowering medications. If these are for primary or secondary prevention,

there is evidence that these can be safely ceased once a person is identified as having a limited prognosis [6].

15.2.2 Managing Hypertension at the End of Life

Most people will benefit from having their anti-hypertensives reduced or ceased once cachexia is evident. The therapeutic goal should be to avoid any postural symptoms and any ensuing falls. Routine monitoring for this group includes a full assessment, addressing reversible factors and palliating refractory symptoms, irrespective of the underlying cause of the disease (cancer or heart failure).

15.2.3 Symptoms in People with Chronic Cardiac Disease—Pain

Pain in people with heart failure may be related to underlying cancer or heart failure, including refractory (stable) angina especially if there is worsening anaemia, gross edema, immobility or diabetic neuropathy. Key considerations for this group is to avoid if possible medications with anti-cholinergic activity (pro-arrhythmogenic) and, if possible, avoid non-steroidal anti-inflammatory drugs which can increase salt and water retention [7, 8].

15.2.4 Symptoms in people with chronic cardiac disease—breathlessness

Breathlessness: The pharmacological management of breathlessness includes regular, low dose extended release morphine. Benzodiazepines are not recommended, but could be considered if panic is triggering the breathlessness and psychological interventions have not been effective. Supplemental oxygen is unlikely to be of benefit for routine palliation of breathlessness in the absence of hypoxaemia [7, 8]. Non-pharmacological management includes exercise, breathing training, walking aids, psychological interventions, and hand-held (battery operated) fans [7, 8].

15.2.5 Symptoms in People with Cardiac Disease—Edema

Edema is often a major symptom, worsened by hypoalbuminemia late in the course of cancer. Pharmacological management includes diuresis as appropriate, including

parenteral diuretics. Non-pharmacological management includes appropriate fluid restriction which may have to be modified across the last months of life, weight monitoring and good skin care [7, 8].

15.2.6 Symptoms in People with Chronic Cardiac Disease—Fatigue

Cancer and heart failure are both multi-system systemic disorders causing skeletal muscle loss, which contributes to both breathlessness and fatigue. The patient's heart failure will be exacerbated by anaemia [5]. which is not uncommon in this group and may worsen fatigue. Non-pharmacological management, if someone still has a reasonable level of function, includes gentle graded exercise. It is also important to consider if people have episodic hypoxia due to sleep disordered breathing such as obstructive sleep apnoea, or central hypoventilation syndromes, or poorly controlled symptoms contributing to the person's fatigue. Other causes of fatigue such as poor nutritional intake, side effects of medications (beta blockers), hypokalaemia, hypothyroidism or depression need to be considered and treated accordingly [7, 8].

15.2.7 Advance Care Planning

Timely advance care planning is essential because patients in this group are at risk of a sudden cardiac death and/or cognitive impairment and need to be provided with an opportunity to plan accordingly [9–11]. Consideration of deprescribing of the cardiovascular medication needs to be sensitively discussed with the patient and undertaken in partnership with their treating heart failure team. Similarly if a plan for deactivation of implantable cardioverter-defibrillator in patients with New York Heart Association functional class IV symptoms had not been previously formulated, this also needs to be devised in partnership with the patient and their team [12].

15.2.8 Management with a Prognosis of Days to Hours

Once the diagnosis is made that prognosis is limited, these patients do not require any further investigations, but rather the focus ought to be on optimising palliative symptom management through careful history and clinical assessment, and effective patient and family communication about the goals of care.

Pharmacological management includes treatments for pain and breathlessness. If the person is on opioids for pain or for breathlessness and is unable to swallow, *c*onvert usual opioids to an equivalent subcutaneous dose (eviQ [3] on-line opiate

calculator; www.eviq.org.au) [13]. If the person is opioid naïve, small doses of parenteral (subcutaneous or intravenous if there is central access) morphine 1–2.5 mg can be given regularly for pain or for breathlessness.

If the person has heart failure and is unable to swallow, he/she may benefit from subcutaneous frusemide 20–40 mg daily or twice daily; topical nitrates may still be required in the terminal stages of a life-limiting illness for relief of chest pain and oxygen should be given for anyone who is hypoxemic.

Non-pharmacological treatments include elevating the head of the bed if there is any suspicion of heart failure, regular mouth and pressure area care, and reassurance to families and friends about the absolute commitment to providing comfort. If the person has an implantable defibrillator, ensure that it is turned off [12].

15.2.9 How Does Chronic Cardiac Disease Impact on Therapies Directed Against the Cancer?

People who have heart or vascular conditions at the time they are diagnosed with cancer are especially vulnerable to the cardiovascular effects of some cancer treatment (radiotherapy chemotherapy and hormone cancer treatments). Cardiac toxicity is the most common cancer therapy complication, which has increased since the advent of molecularly targeted therapies. The new cancer therapies have contributed to a rise in unexpected cardiac toxicities, especially when added to more conventional chemotherapies [14]. Heart failure is the unfortunate manifestation for many of these toxicities, especially related to anthracyclines [14].

15.2.10 Recalibrating Self-management

The symptom burden associated with cancer and the persons' heart failure necessitates that any self-management plans be reviewed frequently to ensure that they are reflecting the person's changing well-being and that they continue to be helpful.

15.3 Diabetes

Diabetes remains highly prevalent across the community and given that prevalence of diabetes and cancer both increase with age, this is a frequently encountered co-morbidity in the population of people with cancer. With increasing rates of obesity around the world, there is an increasing rate of metabolic syndrome, with increased insulin resistance creating a large group of people with type II diabetes. Sensitively managing diabetes in the setting of advanced cancer requires careful attention to detail and sometimes difficult discussions with patients and their families.

15.3.1 Management with a Prognosis of Months to Weeks

The principles of managing diabetes with a prognosis of months are similar for type I and type II diabetes. Fundamentally, there is a need to adjust goals of care. Avoiding long term micro- and macro-vascular complications ceases to be the primary goal of care as their genesis takes prolonged periods of hyperglycaemia.

The clinical aims when managing diabetes once it is recognised that the person has advanced cancer is to:

- make every effort to minimise the risk of hypoglycemia as untreated hypoglycemia can cause death in minutes,
- reduce the risks of symptomatic hyperglycemia.

The threshold for symptoms from hyperglycemia will vary from person to person but is likely to be above twice the upper limit of blood sugar levels required for glycaemic control.

For people with type II diabetes:

- monitoring can often be relaxed to daily or less frequent if they are stable; and
- dietary restrictions can often be relaxed simultaneously, allowing a wider choice of foods.

The latter is important given that people who are experiencing cancer anorexia cachexia syndrome (CACS) often have reduced appetite and marked changes in food preferences. Allowing a broader range of foods may better support oral intake at a time when this can be difficult. For people with cachexia, the associated weight loss often means that the medications for glycaemic control will have to be reduced markedly in any case.

For people with type I diabetes, a similar approach to management is needed with:

- revised glycaemic controls;
- a relaxing of dietary restrictions (especially in the presence of anorexia); and
- adjustment of insulin doses especially in the presence of marked weight loss.

15.3.2 Management with a Prognosis of Days to Hours

In type II diabetes, oral hypoglycaemic agents are often stopped safely in the last days of life. Ensuring that a small dose of insulin is available for any resultant symptomatic hyperglycaemia is often all that is required. Diet can be liberalised to include anything that a person desires.

In type I diabetes, it is necessary to continue a small (and diminishing) dose of insulin to avoid ketoacidosis. Once more, monitoring can be reduced and diet expanded in order to match the person's rapidly changing metabolic environment.

15.3.3 How Does Diabetes Impact on Therapies Directed Against the Cancer?

There are a number of impacts that diabetes can have on therapies late in life. Most frequently, the challenge is the use of medications that induce diabetes or worsen glycaemic controls. Widespread use of glucocorticoids is the pre-eminent cause of this. (Of note, although often used to stimulate appetite, glucocorticoids also accelerate muscle loss through catabolic pathways at a time when cachexia is already causing profound loss of muscle.) New classes of agents such as ghrelin agonists also cause hyperglycaemia in a small number of people taking them.

15.3.4 Recalibrating Self-management

Most people with diabetes are highly motivated to optimise their care of the condition. For most diabetics, glycaemic control has required major lifestyle changes which need to be maintained daily over many years with incredible attention to detail.

It is likely that many people will have difficulty adjusting to liberalised diet and changed medications as the goals of glycaemic control are shifted from avoiding long term complications of hyperglycaemia to the short term complications of hypoglycaemia as appetite worsens and oral intake and exercise become less predictable. There may well be a time of people feeling very psychologically unsettled with changed goals of care. The ability to adjust to new goals of care and to need to consult health professionals about management that patients have managed for years or decades can be very confronting for patients.

15.4 Renal Impairment/Renal Failure

Mild to moderate renal impairment is frequently encountered in people with advanced cancer. One in 15 people have marked renal impairment reflected in raised serum creatinine when first diagnosed with cancer, but using a more conservative threshold for renal insufficiency, one in two people will have abnormal renal function when diagnosed with cancer using Cockcroft and Gault criteria for calculating creatinine clearance, mostly in the presence of a ‘normal’ serum creatinine [15]. In the setting of advanced cancer, people with end-stage renal disease include people with:

- Progressive renal failure unrelated to the cancer
- An acute insult (often from the treatment of cancer or cancers such as multiple myeloma) superimposed on, or causing, chronic kidney disease

- Local factors such as post-renal obstruction by a cancer
- A malignancy itself that may be a consequence of previous renal transplantation.

In considering the management of renal failure in the setting of advanced cancer, the underlying insults leading to kidney disease are important only where they are currently remediable because they are worsening renal function.

15.4.1 Management with a Prognosis of Months to Weeks

For most people with renal insufficiency, a prognosis limited to months or weeks may not change the symptoms experienced nor the measures introduced for symptom control. If renal function is stable because of chronic disease that is not progressing, symptom control can continue with careful ongoing review of renal function.

For people on dialysis, symptom control related to advancing cancer can provide some challenges but, by using medications that are short acting, symptoms can be well controlled.

Symptoms from severe renal insufficiency that may co-exist with advancing cancer include (in order of prevalence) fatigue, pruritus, constipation, anorexia, pain, sleep disturbance, anxiety, nausea, restless legs syndrome and depression. On dialysis, the top four symptoms are pain, fatigue, pruritus and constipation [16]. Although many of these symptoms are frequently encountered in other settings, restless legs syndrome is most frequently seen in the setting of renal insufficiency.

Pharmacological management of restless legs syndrome in end-stage renal disease relies on non-ergot dopamine agonists with the more recent approval of gabapentin. Most studies have been underpowered and it is difficult to identify characteristics of either the likelihood of responding to medications or only experiencing toxicities [17]. Non-pharmacological treatments include intra-dialysis exercise including the use of exercise bikes which have collateral benefits of improving aerobic fitness and also patterns of sleep.

15.4.2 Management with a Prognosis of Days to Hours

Part of the challenge of providing excellent care for someone on dialysis and simultaneously facing advanced cancer is the discussion about when dialysis should cease. This conversation requires great skills and empathy. Most patients will have thought about the issue and will expect that their physicians will raise this topic respectfully and confidently. The decision to withdraw dialysis ultimately rests with

the patient in consultation with the people that he/she trust to help make decisions like this.

Few data are available about the focus required to provide good symptom control in end-stage renal disease and advanced cancer. Symptom control especially for pain, breathlessness and restless legs will be the focus of the process.

15.4.3 How Does Renal Impairment Impact on Therapies Directed Against the Cancer?

Before initiating systemic palliative anti-cancer therapies, it is important to assess renal function (which diminishes with age), co-morbidities that may affect renal function (such as heart failure), medications that may worsen renal function, medications that may be affected by worsening renal function and hydration status [18]. Approximately one half of all cycles of chemotherapy will require some dose adjustment due to renal insufficiency [15].

Most directly, renal impairment affects the choice and dosing of many systemic therapies for cancer treatment, many of which may be considered even in the setting of advanced cancer.

> Systemic anti-cancer therapies that require dose adjustment in the setting of renal insufficiency include: cyclophosphamide, ifosfamide, docetaxol, vinorelbine, carboplatin, cisplatin, zoledronate, etoposide, topotecan, capecitabine, pemetrexed and methotrexate.
>
> Systemic therapies that may worsen renal insufficiency include: gemcitabine, carboplatin, cisplatin, oxaliplatin, epirubicin, doxorubicin, paclitaxel, irinotecan. trastuzumab, zoledronate and methotrexate [15, 18].

In people on dialysis, the safe and effective administration of chemotherapy becomes a key consideration. This is a highly specialised area with few data to inform practice.

> Chemotherapy frequently used for treatment in people on haemodialysis where dose adjustment is still needed include cisplatin, oxaliplatin and carboplatin, cyclophosphamide, capecitabine, methotrexate, irinotecan, etoposide, docetaxel, and vinorelbine [19].

For people with cancer and renal insufficiency, careful consideration of the most appropriate analgesic is also required as morphine and its derivatives (codeine) are not recommended for people with severe (stage 5) kidney disease (calculated creatinine clearance of less than 10 mL/min) due to accumulation of active metabolites and opioid toxicity. Buprenorphine, fentanyl, hydromorphone or oxycodone are preferred opioids in severe kidney disease [20].

15.5 Liver Impairment/Liver Failure

Hepatic impairment may be due to:

- Infiltration of the liver with cancer
- Obstruction to the biliary tree by cancer including local lymph nodes
- Long term disease

Globally, the most common non-malignant causes of hepatic impairment include viral hepatidities (although the burden of disease will change with increasing immunisation rates against hepatitis B and highly effective treatments now available for hepatitis C) and alcohol. The ability to metabolise some drugs and the liver's synthesising function for key proteins can have a major influence on the therapeutic choices in late stage disease.

Symptoms manifest as a result of worsening hepatic impairment include fatigue, pain, itch, ascites and progressive cognitive impairment. Cognitive impairment can be frustrating for the patient and his/her family.

15.5.1 Management with a Prognosis of Months to Weeks

Fatigue is commonly experienced by people with advanced cancer, and is more pronounced in the presence of co-existing liver disease. While the mechanisms driving fatigue in both cancer and liver failure continue to be poorly understood, anaemia, medications (i.e. anti-histamines, anti-emetics, anti-depressants and analgesics) and anorexia all contribute to this debilitating symptom. As sarcopenia is more pronounced in this population, with 15–50 % of patients with cancer and 30–45 % with liver failure having CT defined sarcopenia, it is likely to play a role [21]. Managing fatigue in this population is predominately focussed on non-pharmacological interventions, such as:

- Promoting physical activity;
- Spacing activities;
- Reserving energy for important and enjoyable activities;
- Accessing assistance with instrumental activities of daily living; and
- Nutritional support.

Managing pain in the presences of liver failure requires careful consideration of the analgesic type and dose. Paracetamol use in the context of chronic alcohol use can lead to unexpected toxicity, while more cautious titration of codeine and morphine is needed to avoid precipitating encephalopathy or coma. Non-steroidal anti-inflammatory medications should also be avoided in this population.

Persistent itch is another distressing symptom that is challenging to manage. Whilst there is no universally effective medication a number of drugs are often trialled [22]. Non-pharmacological interventions such as avoiding soap, shampoo and hot water on the skin, and using bath oil, a soap substitute and soothing lotions and avoiding vaso-dilating food and drinks (e.g. coffee, alcohol and spices) provide some comfort.

Ascites may be due to either cancer, liver failure or a combination of both [23]. If the underlying cause of the ascites cannot be managed, then symptom management becomes the goal of treatment. Abdominal paracentesis is indicated if it is causing pain, breathlessness or nausea and vomiting, and only if the coagulation profile permits. Diuretics need to be ceased for 24 h immediately prior to and after paracentesis.

Assess and manage any post-paracentesis adverse effects such as hypovolaemia, hypotension, renal dysfunction, perforated viscus, peritonitis or fistula formation. Patients with ascites due to liver failure, who have had abdominal paracentesis where more than five litres has been drained may benefit from concentrated albumin replacement therapy. If not already in place, sodium restriction and oral diuretics need to be initiated [23]. The use of ACE-inhibitors and angiotensin receptor blockers in patients with chronic liver failure and ascites maybe harmful, so their use in this population needs careful consideration [23].

Liver failure is associated with changes in central neural transmission that result in:

- Alterations in behaviour
- Cognitive dysfunction
- Mood disorders
- Sleep disturbances (inversion of the day/night cycle).

which impact on patients' quality of life [24]. People with advanced chronic liver disease frequently develop hepatic encephalopathy that causes a wide spectrum of neuropsychiatric symptoms from subclinical neurological or psychiatric abnormalities through to coma [25].

Cognitive changes due to liver failure will be exacerbated in the presence of delirium and/or cerebral secondaries. These distressing and debilitating symptoms severely affect the lives of patients and their families. In addition to initiating early advance care planning conversations in this population, patients and families need to be made aware of the reasons for any cognitive impairment and supported to cope with these changes.

15.5.2 Management with a Prognosis of Days to Hours

Managing gross ascites is a potentially common problem for this population. If abdominal paracentesis is contra-indicated, the discomfort and breathlessness

associated with gross ascites is best addressed through the use of opioids. If SC opioid administration is required, care needs to be taken to ensure that the SC cannula is not located in an oedematous area. Anti-emetics often need to be maintained to manage a hypomotile gut or a squashed stomach and to minimise nausea and vomiting.

15.5.3 How Does Hepatic Impairment Impact on Therapies Directed Against the Cancer?

Markers of hepatic impairment sufficient to suggest dosing changes in chemotherapy include raised bilirubin or the presence of ascites due to liver dysfunction [18]. The impact of hepatic impairment on drug metabolism is far more difficult to predict from hepatic function tests than renal impairment using creatinine clearance [26, 27]. Further, severe renal impairment is likely to alter medications with hepatic metabolism through a number of mechanisms acting on the liver.

Chemotherapy likely to require dose adjustments in the setting of hepatic impairment include: docetaxel, paclitaxel, doxorubicin, epirubicin, gemcitabine (in the presence of hyperbilirubinaemia), irinotecan (hyperbilirubinaemia), erlotinib, sorafenib, and vinorelbine [26]. Imatinib may cause hepatic dysfunction and should be ceased without rechallenge if this occurs [26].

15.6 Advanced Respiratory Disease

Obstructive lung disease is highly prevalent in resource rich, and even more so in, resource poor countries. Smoking remains the world's primary cause of obstructive lung disease. As this is also the most frequent lifestyle choice related to lung cancer, many people with lung cancer have co-existing symptomatic chronic obstructive pulmonary disease. It means that for many people diagnosed with lung cancer, breathlessness on exertion or while carrying out the activities of daily living will already be part of everyday life.

Less frequently, chronic lung disease is caused by restrictive diseases, most frequently related to idiopathic pulmonary fibrosis, connective tissue diseases or occupational exposures. For those, particularly with occupationally related lung disease, smoking rates are relatively higher than the population in general, often leading to severe breathlessness.

15.6.1 Management with a Prognosis of Months to Weeks

The management of respiratory diseases themselves is unlikely to change greatly even when advanced cancer creates a limited prognosis. As such, the major implication for people with co-existing cancer and chronic respiratory diseases relates to symptom management.

As cancer worsens, breathlessness also tends to worsen. As such, focus on the symptom of chronic breathlessness once the underlying causes have been optimally treated is the focus of care. As noted in the section on heart failure, non-pharmacological and pharmacological approaches are need for most people. Many clinicians are concerned about introducing regular, low dose oral extended release morphine, but there is good evidence that this safely relieves breathlessness even in people with co-existing chronic obstructive pulmonary disease (COPD) [28, 29].

Pain is frequently encountered in late stage respiratory disease, and its genesis is usually multifactorial. Adequate treatment of pain is necessary to optimise quality of life in the setting of advanced cancer. Musculoskeletal pain is a major source of discomfort, especially with weight loss which includes loss of muscle. Both regular paracetamol and non-steroidal anti-inflammatory medications have a key role to play in optimising analgesia for people with cancer and respiratory disease.

Fatigue is frequent, especially as people expend greater proportions of diminishing energy on the activities of daily living. Pacing such activities is a management plan, but is very difficult to put into practice for many people. Other manifestations of fatigue include leg tiredness that for many people is more likely to limit exertion than breathlessness [30].

Unfortunately, many people with advancing cancer and respiratory disease find themselves in a cycle of breathlessness leading to anxiety, reducing the person's exercise which, in turn, leads to more deconditioning and worsening breathlessness. This cycle is understandable and, with advancing disease is often very difficult to break.

15.6.2 Management with a Prognosis of Days to Hours

In the terminal stages of advanced cancer, breathlessness and fatigue are two symptoms that tend to worsen (in contrast to almost all other symptoms). Contributing factors include loss of muscle mass and, in some people, disease progression of intra-thoracic malignancy. Few interventions are likely to reduce fatigue predictably and, in people with worsening breathlessness, increasing reliance on pharmacological interventions will be required if the symptom is troublesome to the patient. As noted in the cardiology section, if anxiety is a major component of breathlessness then there may be a place for an anxiolytic such as a benzodiazepine.

15.6.3 How Does Respiratory Impairment Impact on Therapies Directed Against the Cancer?

Rarely does respiratory impairment limit the treatment of cancer. Breathlessness may, however, be sufficiently troublesome that people may choose not to attempt or continue disease modifying therapies.

15.7 Neurological Conditions

Chronic neurological conditions rarely have a direct implication for treatment of advanced cancer. Major issues can arise with progressive neurological diseases where cognition, mobility or swallowing are affected. Of particular concern is:

The ability to make informed decisions about treatment (and assimilate the implications of not pursuing a particular path (in order to ensure that the consent is truly informed).

The ability to take medications orally is important for:

- Acute symptom control related to cancer treatments
- Anti-cancer treatments
- Symptom control for co-existing diseases.

Mostly, there are parenteral variants that are able to ensure excellent anti-cancer therapies and good symptom control.

15.8 Mental Health Concerns

15.8.1 Management with a Prognosis of Months to Weeks

The prevalence of depression for people with advanced cancer is no different for that of the general public. However, it is often under-diagnosed and under-treated in people with advanced cancer. Patients with mild to moderate depression need to be provided with access to counselling and support, while those with a major depression will need treatment with anti-depressants. Any pharmacological treatment needs to be considered alongside potential drug-drug interactions, altered pharmacokinetics due to hepatic or renal impairment and the impact of cachexia, and monitored accordingly [31]. Variations in withdrawal syndromes and the washout period before a new anti-depressant can be initiated are based on specific anti-depressant drug type (i.e. SSRIs, tricyclics and MAOIs).

Any deprescribing of long term antipsychotics needs to be discussed with the patient and their usual psychiatric team and appropriate monitoring and psychological support provided.

15.9 Communicable Diseases

15.9.1 HIV/AIDS

Certain cancers are more common in people living with HIV, and the risk of developing cancer is amplified when their infection is poorly controlled (low CD4 count). Cancers such as Kaposi sarcoma, Non-Hodgkin lymphoma and cervical cancer are all AIDS defining cancers [32].

15.9.2 Management with a Prognosis of Months to Weeks

Managing the needs of this population is complex and requires an integrated multi-disciplinary team approach. Anti-retroviral treatment needs to be maintained in this population as it helps prevent the development of opportunistic infections and allow for the use of standard cancer treatments. However, ongoing antiretroviral treatment is associated with potential adverse effects than need to be prevented or managed [31].

Despite, the social progress made since HIV was initially identified, a person living with HIV may experience social stigma and isolation, marginalisation and be estranged from their family of origin. Advance care planning in addition to providing people living with HIV and cancer with an opportunity for reconciliation with others, provides an opportunity for conversations about appointing a power of attorney and/or enduring guardian who can make financial and clinical decisions, when the person is no longer able to.

15.9.3 Management of HIV with a Prognosis of Days to Hours

In additional to usual palliative care, the most important intervention is to maintain anti-retrovirals for as long as possible or until the person is unable to swallow, to prevent the latent development of opportunistic infections.

15.9.4 How Does HIV Impairment Impact on Therapies Directed Against the Cancer?

Antiretroviral use is associated with numerous drug interactions which are too numerous and complex to list. However, an evidence based point of care resources is available to assist clinicians identify these interactions [33].

15.10 Multi-morbidity

Most patients with advanced cancer have more than one co-morbidity. Currently, there are few data about how to manage several co-morbidities in a coordinated and logical way. Most clinical decisions are made using guidance for a particular co-morbidity and few take into account the impact of other co-morbidities. Even fewer data are available about the role of how to safely prioritise the management of several co-morbidities in the clinical setting of advanced cancer. For example, in the setting of marked cachexia with co-existing heart and renal failure, the balance of clinically conflicting goals of achieving adequate renal perfusion and adequate blood pressure, while minimising left sided heart failure becomes more challenging as cancer advances.

15.11 Future Direction for Research and Practice

The rational management of multi-morbidities in general is in its infancy. How to provide scientific rigour around how to do this in the setting of advanced cancer is at an even more fundamental level. Fully understanding the underlying patho-physiology of cachexia and identifying ways to reverse it or slow its progression requires much more work.

Deprescribing studies in large populations are necessary to ensure that the timing of dose decrements or cessation are based on the best available evidence. These studies can be undertaken but there is too little commitment from funding bodies to provide resources for these fundamentally important works.

References

1. Bayliss EA, Reifler LM, Zeng C et al (2014) Competing risks of cancer mortality and cardiovascular events in individuals with multimorbidity. J Comorbidity 4(1):29–36
2. Clayton JM, Hancock KM, Butow PN et al (2007) Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. Med J Aust 186(12):S77–S108
3. Currow DC, Clark K, Kamal A et al (2015) The population burden of chronic symptoms that substantially predate the diagnosis of a life-limiting illness. J Palliat Med 18(6):480–485
4. Rushton M, Clark R, Brideson G, Damarell R (2015) The effectiveness of non-pharmacological interventions for the management of cancer treatment-induced cardiotoxicity: a systematic review protocol. JBI Database Syst Rev Implementation Rep 13(5):53–73
5. Hunt SA, Abraham WT, Chin MH et al (2005) ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure). American College of Cardiology. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf

6. Kutner JS, Blatchford PJ, Taylor DH Jr et al (2015) Safety and benefit of discontinuation statin medications in the setting of advanced life-limiting illness. JAMA Int Med 175(5):691–700
7. Gadoud A, Jenkins SM, Hogg KJ (2013) Palliative care for people with heart failure: summary of current evidence and future direction. Palliat Med 27(9):822–828
8. Phillips JL, Johnson M, Currow DC (2015) Heart failure and palliative care: are we there yet? Cardiol Today 5(1):13–16
9. Goodlin SJ (2009) Palliative care in congestive heart failure. J Am Coll Cardiol 54(5):386–396
10. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC (2007) Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 9(5):440–449
11. Australian Health Ministers' Advisory Council (2011) A national framework for advance care directives. Available online at: www.ahmac.gov.au. AHMAC (Sep 2011)
12. NSW Agency of Clinical Innovation (2014) NSW guidelines for deactivation of implantable cardioverter defibrillators at the end of life. NSW Health, Sydney
13. Cancer Institute NSW (2010) eviQ: Cancer treatments online. https://www.eviq.org.au/. Accessed on 25 May 2010
14. Jarkowski A, Glode AE, Spangenthal EJ, Wong MK (2011) Heart failure caused by molecularly targeted therapies for cancer. Pharmacotherapy 31(1):62–75
15. Launay-Vacher V, Oudard S, Janus N et al (2007) Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer 110(6):1376–1384
16. Murtagh FE, Addington-Hall J, Higginson IJ (2007) The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis 14(1):82–99
17. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C et al (2014) Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. Kidney Int 85(6):1275–1282
18. Lichtman SM, Wildiers H, Launay-Vacher V et al (2007) International society of geriatric oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 43(1):14–34
19. Janus N, Thariat J, Boulanger H et al (2010) Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol 21(7):1395–1403
20. Australian Adult Cancer Pain Management Guideline Working Party (2014). Cancer pain management in adults. Cancer Council Australia, Sydney (2015)
21. Peterson SJ, Braunschweig CA (2016) Prevalence of sarcopenia and associated outcomes in the clinical setting. Nutr Clin Pract 31(1):40–48
22. Beuers U, Boberg KM, Chapman O et al (2009) EASL clinical practice guidelines: management of cholestatic liver diseases. J Hepatol 51(2):237–267
23. Runyon BA (ed) (2012) Management of adult patients with ascites due to cirrhosis: update 2012. American Association for the Study of Liver Disease. _documents/141020_Guideline_Ascites_4UFb_2015.pdf
24. D'Mello C, Swain MG (2014) Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders. Brain Behav Immun 35:9–20
25. https://www.aasld.org/sites/default/files/guideline_documents/hepaticencephenhanced.pdf
26. Field KM, Michael M (2008) Part II: Liver function in oncology: towards safer chemotherapy use. Lancet Oncol 9:1181–1190
27. Verbeek RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 64(12):1147–1161
28. Ekstrom M, Nilsson F, Abernethy AP, Currow DC (2015) Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. Ann Am Thoracic Soc 12(7):1079–1092
29. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC (2014) Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 348:g445
30. Wilcock A, Maddocks M, Lewis M, England R et al (2008) Symptoms limiting activity in cancer patients with breathlessness on exertion: ask about muscle fatigue. Thorax 63(1):91–92

31. Therapeutic Guidelines (2010) Palliative care (version 3 ed). Therapeutic Guidelines Limited, Melbourne
32. American Cancer Society (2014) HIV infection, AIDS, and cancer. http://www.cancer.org/acs/groups/cid/documents/webcontent/002295-pdf.pdf
33. HIV Drug Interactions http://www.hiv-druginteractions.org
34. Stevenson J, Miller C, Abernethy AP, Currow DC (2004) Managing comorbidities in patients at the end of life. Br Med J 329(7471):909–912

Further Reading

35. Olver I (ed) (2010) The MASCC textbook of cancer supportive care and survivorship. Springer, Berlin
36. Clark K, Currow DC (2007) Emergencies in palliative medicine (Ch 9). In: Walsh D et al (eds) Textbook of palliative medicine. Elsevier, Oxford University Press
37. Cherny NI, Fallon MT, Kaasa S, Portenoy R, Currow DC (eds) (2015) Oxford textbook of palliative medicine 5th ed. Oxford University Press, UK