



The top ten things that must be known about end of life therapy in patients with advanced cancer

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Summary End of life is an issue that affects every human being sooner or later. Several aspects at the end of life should not be neglected to achieve good symptom control. Basic knowledge and skills on symptom control and palliative care are important to support patients in this threatening phase of their life. Palliative care should not be provided only at the end of life. The concept of early integration of palliative care is increasingly coming into focus. Nevertheless, at the end of life there are some important facts and issues that should be taken into account. This short article provides a list of ten important facts at the end of life that are important for the authors. Prognostication, early integration, benzodiazepines, death rattle, palliative sedation, standard therapy for refractory dyspnea, opioids in renal failure, psilocybin, denial and reduction of drugs at the end of life will be discussed in detail.

Keywords Early integration · Relevant symptoms at the end of life · Psychedelic prodrug · Medication at the end of life

Introduction

Increased life expectancy and better health care allow people to live longer and to manage many chronic conditions better [1].

The impact of serious, life-threatening, and life-limiting diseases on society and health systems is increasing [2]. It is estimated that by 2060, 47% of all people will die with serious health-related suffering [3].

Nevertheless, even in modern society, people still will have to face end of life decisions. Hence, the importance of treatment at the end of life is still an issue that should be discussed routinely. Skills on how to provide good care at the end of life should not only be taught at medical schools, but also be implemented in the routine work of every medical doctor, not only specialists for palliative care. Palliative care and end of life care should not only be provided by clinicians specialized in palliative care, but also by clinicians without palliative care specialization (primary palliative care).

The following list (Table 1) is neither a review of the current literature nor an official recommendation or guideline, but an enumeration of issues that seem important to the authors when they were asked to give recommendations on what must be known about end of life therapy by physicians providing primary or specialized palliative care. We do not claim the list to be complete.

1. Prognostic assessment is always difficult, also at the end of life

Terminally ill patients, their relatives and also health-care providers want sufficient information to allow them to adequately ‘prepare’ for the end of their lives, including the wish to know about when approximately

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Table 1 The top ten things that must be known about end of life therapy

1. Prognostic assessment is always difficult, also at the end of life
2. Early integration of palliative care is important
3. Are benzodiazepines better than neuroleptic drugs for terminal delirium?
4. What should we know about death rattle
5. Do not perform palliative sedation with opioids
6. Opioids are golden standard for refractory dyspnea in advanced cancer patients
7. Morphine or hydromorphone in renal failure?
8. Psilocybin can reduce fear of dying
9. It is hard to face the facts—denial means survival
10. Less is more: reduce drugs!

they will die, and how they could expect their physical condition to deteriorate [4]. In general, clinicians are not very good at predicting survival in patients with advanced cancer [5]. Hence, the Prognosis in Palliative care Scale (PiPS) was developed as a result of a large prospective multicenter study involving over 1000 patients with advanced cancer [6]. In this study, in patients with advanced cancer no longer being treated, a combination of clinical and laboratory variables could reliably predict 2-week and 2-month survival [6]. A study was established to determine whether patient-rated data would provide better prognostic estimates than clinician observer ratings [7]. In this study, all models performed as well as, or better than, clinicians' estimates of survival. Recently, an updated overview of prognostic models in advanced cancer highlighted the role of prognostic calculators and concluded that prognostic models and prognostic websites are currently available to augment prognostication in the advanced cancer setting [8]. In that regard, www.predictsurvival.com provides the output for seven prognostic indices simultaneously based on 11 variables. Still, prognostication, especially in the last days of life, remains difficult and the exact forecast of the time of death is not feasible. Prognostication is very important not only for patients and their relatives, but also for many important healthcare decisions at the end of life.

2. Early integration of palliative care is important

Palliative care is 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 [9]. International guidelines recommend that patients with advanced cancer should receive dedicated palliative care services, early in the disease course, concurrent with active treatment [10]. Providers may refer family and friends to caregivers of patients with early or advanced cancer to palliative care services. Early delivery of patient-directed care by specialist palliative care teams alongside tumor-directed treatment promotes patient-centered care [11].

There is strong evidence that early integration of palliative care in the treatment of patients helps to develop a good relationship with the patient and to provide palliative care during the last days of life [11, 12]. The early involvement of palliative medicine specialists and/or hospice services for dying patients can facilitate optimal symptom management and transitions of care at the end of life.

3. Are benzodiazepines better than neuroleptic drugs for terminal delirium?

The prevalence of delirium in palliative care patients is high [13]. A recent study has suggested there is no role for antipsychotic medication in the management of delirium in palliative care patients, which is different from previous expert opinion [13]. Other recent findings suggest there may be a role for the use of antipsychotics in combination with benzodiazepines in the management of agitated delirium [14, 15].

Regarding terminal delirium, the goal of care should be to maximize comfort, recognizing that patients are unlikely to recover from their delirium. A recent randomized trial suggested that lorazepam in combination with haloperidol as rescue medication was more effective than haloperidol alone for the management of persistent restlessness/agitation in patients with terminal delirium [16]. In patients with refractory agitation, benzodiazepines may be administered as scheduled doses or continuous infusion for palliative sedation [13].

4. What should we know about death rattle?

Death rattle (respiratory tract secretion) is a rather common symptom in dying patients. Physicians often reassure relatives that we believe that patients do not suffer from death rattle. However, it is difficult to ascertain whether patients suffer from this symptom or not. Different medication regimens have been studied, that is, scopolamine, glycopyrronium, hyoscine butylbromide, atropine, and/or octreotide. A current literature review from 2014 does not support the standard use of antimuscarinic drugs in the treatment of death rattle [17]. Nevertheless, data from a recent study suggest the prophylactic use of hyoscine butyl-

bromide as an efficient method to prevent death rattle, whereas the late administration produces a limited response, confirming data from traditional studies performed with anticholinergics [18].

5. Do not perform palliative sedation with opioids!

Palliative sedation is performed in terminally ill patients to manage one or more refractory symptoms (e.g. refractory pain, vomiting, dyspnea, agitated delirium, unstoppable bleeding) [19–21]. Although physical and psychological symptoms cannot be eliminated, they can be relieved enough to adequately temper the suffering of the patient and family [20]. Palliative sedation remains a measure of last resort used at the end of life to relieve severe and refractory symptoms. It is performed by the administration of sedative medications in supervised settings and is aimed at inducing a state of decreased awareness or absent awareness (unconsciousness). The intent of palliative sedation is to relieve the burden of otherwise intolerable suffering for terminally ill patients [19]. Neither the administration of palliative sedation nor the degree of sedation hastens death in otherwise terminally ill patients [22]. Midazolam is a short half-life benzodiazepine with a rapid onset of action and is often prescribed for palliative sedation [20]. Alternatives include levomepromazine, chlorpromazine, phenobarbital and propofol [20]. It is inappropriate to use opioids for sedation [23, 24]. Palliative sedation with opioids is contraindicated, but nevertheless, must be continued as pain therapy or therapy against refractory dyspnea during palliative sedation. Palliative sedation should always be performed with sedative drugs and in addition, adequate symptom control is mandatory.

6. Opioids are gold standard for refractory dyspnea in advanced cancer patients!

Dyspnea is a common, very distressing symptom in advanced cancer patients that challenges them, their relatives, and healthcare professionals [25, 26]. Opioids are the most effective and widely studied agents available for palliation of dyspnea in palliative care patients, especially in patients with advanced and incurable cancer [27]. In addition, other adjuvant therapies such as oxygen, noninvasive positive pressure ventilation, and hand-held fans may also be used. Benzodiazepines may also be helpful in select patients, but neither benzodiazepines nor oxygen showed significant benefit in clinical trials [28]. In addition, there is insufficient literature available to draw a conclusion about the effectiveness of steroids for treating persistent dyspnea in advanced cancer patients.

7. Morphine or hydromorphone in renal failure?

Morphine is the reference opioid against which the effectiveness and side effects of other opioids are evaluated. Its metabolites morphine-3-glucuronide and morphine-6-glucuronide (M6G) accumulate in the presence of renal impairment, enhancing the spectrum of side effects. In patients with renal failure, up to 15 times higher M6G concentrations were measured compared to patients without renal impairment [29]. The resulting high plasma levels and CNS (central nervous system) concentrations of the active metabolite M6G can lead to prolonged respiratory depression, chronic nausea and even coma following administration of usual morphine doses.

Hydromorphone, a semisynthetic derivative of morphine, is primarily metabolized to hydromorphone-3-glucuronide (H3G). Similar to M3G (morphine-3-glucuronide), H3G lacks an analgesic effect but may cause dose-dependent myoclonus, agitation, and seizures in rats [30]. Evidence in humans is conflicting. In clinical practice, hydromorphone often is used preferentially over morphine in patients with renal impairment [31].

A retrospective analysis found that in patients treated with hydromorphone, not only pain intensity was significantly reduced, but also side effects such as nausea and vomiting as well as myoclonus and sedation were less present [32].

A meta-analysis of eight studies suggested that hydromorphone provides slightly better clinical analgesia than morphine [33]. Additional potential clinical pharmacological advantages with regard to side-effects, such as safety in renal failure or during acute analgesia titration, were based on limited evidence in this meta-analysis [33].

Currently, data are still conflicting [31]. While some consensus guidelines recommend a risk-stratified approach to opioid use in renal impairment based on the presence of potentially active opioid metabolites [34, 35], often in practice, hydromorphone is utilized preferentially, viewed as a safer alternative to morphine with decreased risk of adverse effects [31].

Based on limited evidence, pharmacokinetic data, and current expert guidelines, hospice and palliative care clinicians should consider cautious use of morphine and hydromorphone in mild-to-moderate renal impairment. When using higher opioid dosing for longer duration of time, close monitoring for neurotoxic effects is necessary [31].

8. Psilocybin can reduce fear of dying

Psilocybin is a naturally occurring psychedelic pro-drug compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms. As a prodrug, psilocybin is quickly converted by the body to psilocin, which has mind-altering effects similar, in some aspects, to those of Lysergic

acid diethylamide (LSD), mescaline, and DMT (N,N-Dimethyltryptamine). In general, the effects include euphoria, visual and mental hallucinations, changes in perception, a distorted sense of time, and spiritual experiences, and can also include possible adverse reactions such as nausea and panic attacks [36].

Psilocybin is an addictive substance according to Appendix V (V.1. Substances and preparations listed in Appendix I of the United Nations Convention on Psychotropic Substances (Section 2 [2] of the Narcotics Act)), and these drugs may not be prescribed according to Austrian law.

Two clinical studies concluded that psilocybin can reduce fear of dying.

Clinically significant anxiety and depression are common in patients with cancer and are associated with poor psychiatric and medical outcomes. Historical and recent research suggested a role for psilocybin to treat cancer-related anxiety and depression. In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress [37].

Another study investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety [38]. Further studies are needed to investigate the impact of psilocybin in end of life care.

9. It is hard to face the facts—denial means survival

Patients with newly diagnosed, incurable cancer use a variety of coping strategies. So do their relatives [39]. One of these coping strategies is denial. Is it always necessary for medical doctors and palliative care teams to reverse denial?

A study found that strategies used by relatives could be categorized into four different areas: thinking that the death is far off in the future; hoping for an improvement; living in the present; and utilizing the family and personal network [40]. The loved ones used these strategies in order to learn to live with the fact that their spouse had been diagnosed with an incurable illness.

Maybe it helps if health care professionals would not always categorize coping strategies that help not only patients, but also their relatives as negative denial process, but maybe think of it as a coping strategy that helps those affected, patients and their loved ones, to survive.

10. Less is more: reduce drugs!

And last but not least: Reducing drugs in the dying patient to the drugs that support comfort care will definitely lead to better outcomes in symptom control.

Conflict of interest G. Kreye, B. Heidecker, and E.K. Masel declare that they have no competing interests.

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