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Review

End of life care in patients with malignant disease

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1. Introduction

Most cancer patients die in hospital [1]. The care of terminally ill patients often falls to junior doctors or nurses who will have had little specific training in the care of the dying. Relatively few dying patients will ever be seen by a member of a specialist palliative care team. If the management of the terminal phase is poor, it can be a source of great distress for patients (who may suffer unnecessary discomfort), for their families (who may have more difficulty in coming to terms with their bereavement) and for healthcare professionals (who may feel that they have failed in their duty of care).

Expertise in caring for dying patients has developed in hospices and specialist palliative care teams. Strong evidence for the effectiveness of this approach (in the form of randomised controlled trials) is generally not available. It is difficult to undertake research in palliative care. Studies are hindered by the poor performance status and the changing nature of symptoms in patients with advanced malignant disease, high attrition rates and difficulties inherent in obtaining consent for trials in terminally ill patients [2,3]. A recent systematic review concluded that specialist palliative care teams can improve the outcome of cancer patients [4]. Moreover, clinical experience suggests that the widespread adoption of a multidisciplinary palliative care approach would improve the care of patients dying outside specialist palliative care units. This paper provides a review of current 'best practice' in the management of the terminal phase.

2. General approach

2.1. Recognising when death is imminent

The terminal phase can be defined as the last few days prior to death in a cancer patient with progressive incurable disease for whom no further specific anticancer treatment is possible or appropriate. It is important to be able to recognise when a patient is entering this phase of their illness so that appropriate end-of-life care can be instituted. Typically, a patient who is dying is bed-bound and withdrawn, with increasing drowsiness, weakness and decreased mobility. A decrease in oral intake is matched by a decrease in urine output. The development of confusion, agitation and heightened anxiety is not uncommon [5]. It is not always easy to know when a patient has entered the terminal phase. Some patients with advanced disease may appear to be dying, but may in fact have an easily treatable, reversible cause for their deterioration (e.g. hypercalcaemia or uraemia). Conversely, it is sometimes clear to patients, their families and to other healthcare professionals that an individual is dying while medical staff are unable to recognise or to admit this fact and alter the goals of care appropriately.

2.2. Altering the goals of care

The recognition that an individual is dying should lead to a change of emphasis in their care. The futility of any further anticancer therapy should be acknowledged and the comfort of the patient should become paramount. Investigations and interventions should be kept to a minimum. High quality nursing care is essential. Routine observations (such as temperature, pulse and blood pressure) should be discontinued, but regular patient contact is still required in order to monitor any

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pain or discomfort and to keep relatives and carers informed of developments.

All treatments should be reviewed. Many medications can be discontinued (e.g. antibiotics, antihypertensives, antidepressants, laxatives, diuretics and prophylactic aspirin). In diabetic patients, the strict maintenance of normoglycaemia is no longer indicated. It is usually more appropriate to administer insulin 'as required' to treat symptomatic hyperglycaemia. Similarly, the beneficial effects of anticoagulants are likely to be overshadowed by the difficulties involved in monitoring therapeutic drug levels and the risks of bleeding. There is no consensus as to the best way to manage patients who have been taking regular corticosteroids prior to entering the terminal phase. Some clinicians advocate stopping these drugs along with other 'non-essential' medications, others are concerned that abrupt withdrawal of steroids may result in enhanced patient discomfort [6]. Many essential drugs can be administered parenterally to patients unable to take oral medications (see below).

The question of continuing parenteral administration of fluids to dying patients unable to drink is a controversial subject. Some argue that intravenous fluids should be continued in order to avoid dehydration, renal impairment and the subsequent accumulation of toxic metabolites leading to agitation [7]. Others believe that giving fluids to a dying patient is rarely necessary and that a degree of dehydration may well be beneficial in reducing oedema, pulmonary congestion, gut secretions and the need for toiletting [5,8]. Relatives may require reassurance that withholding intravenous fluids is unlikely to impact on survival. Some clinicians and/or relatives will still find the concept of withholding fluids unacceptable. In this case, up to 2 litres a day can be delivered subcutaneously (s.c) [9]. This route of administration has benefits over the intravenous (i.v.) route in that it avoids the need to re-site i.v. lines and monitor electrolytes.

2.3. Alternative routes of drug administration

Although many medicines can be stopped in the terminal phase, some drugs must be continued up to the moment of death. As it becomes increasingly difficult for patients to take essential medications by mouth, alternative routes of administration must be considered. The i.v. route is generally avoided in order to minimise patient discomfort. Some drugs can be given rectally (e.g. morphine, oxycodone, diazepam and non-steroidal anti-inflammatory drugs (NSAIDs)). The simplicity of this route makes it particularly suited for use in patients dying at home. Analgesia may also be administered transdermally, for example, by a fentanyl patch. Although this is a convenient route of administration, it provides limited flexibility in terms of dose titration. It has been suggested that transdermal fentanyl may not be so well absorbed in the terminal phase because of poor peripheral perfusion [10], but this does not seem to be a problem in practice [11]. The s.c. route is the most common route of drug administration to dying patients. Although criticised for contributing to the medicalisation of death [12], the ability to deliver drugs in this way has revolutionised the practice of palliative care. It must be noted, however, that, for the majority of drugs, this is an unlicensed route of administration. None the less, a large body of clinical experience supports the efficacy of this mode of drug delivery [13]. Drugs can be administered either by intermittent injection or by continuous infusion (over 12–24 h) via a syringe driver. Table 1 summarises the indications and typical dose ranges for drugs commonly used via the s.c. route in the terminal phase. Many of these drugs can be combined in the same infusion, the exception being cyclizine, which may precipitate if combined with diamorphine if the concentration of either drug exceeds 25 mg/ml, or if the pH of the resulting solution is >8 [14].

2.4. Communicating with patients, carers and other healthcare professionals

Good communication and interdisciplinary team working are an essential part of ensuring that the terminal phase is managed well. If a patient is still conscious as death approaches, it may be appropriate to involve him/her in decision making (e.g. about relaxing diabetic control or using sedation). More often than not, the patient will be unable to participate in discussions about their prognosis or management and regular liaison with the family/carers must be established or maintained. It is important to determine whether relatives wish to be present at the time of death and to record appropriate contact details for the next of kin. The primary care physician and other members of the community team may also wish to be informed of the patient's imminent death.

If the patient is not for resuscitation, this should be clearly documented in the notes. Whether or not it is necessary to discuss this with patients is an area of controversy [15]. Recent guidelines from the British Medical Association suggest that the decision should be discussed with all patients [16]. Other professional bodies have suggested that this is neither necessary nor appropriate in cases where resuscitation would be futile [17].

2.5. The management of common symptoms in the terminal phase

2.5.1. Prevalence of symptoms

The most common symptoms experienced by dying patients in a series of 200 consecutive hospice admissions

Table 1
Drugs commonly used during the terminal phase via subcutaneous (s.c.) infusion

	Indication	Usual dose range	Notes
Diamorphine	Pain relief	Titrate against pain relief and side-effects 10–40 mg/24 h	Parental opioid of choice in the UK. More soluble than morphine.
Midazolam	Anxiolytic Sedative Anticonvulsant	10–60 mg/24 h	Benzodiazepine. Widely used sedative for terminal agitation.
Levomepromazine	Antipsychotic Antiemetic Sedative	12.5–200 mg/24 h	Low doses are used for antiemesis, higher doses (25–200 mg) for patients requiring sedation.
Haloperidol	Antipsychotic Antiemetic	1.5–10 mg/24h	Used for treatment of delirium. Antiemetic commonly used to prevent opioid-induced nausea.
Cyclizine	Antiemetic	100–150 mg/24 h	May precipitate in a syringe driver (see text).
Hyoscine hydrobromide (hyoscine)	Noisy secretions	1200–2400 mcg/24 h	Relaxes bronchial and smooth muscle and reduces salivary secretions.
Glycopyrronium	Noisy secretions Colic	0.6–1.2 mg/24 h	More potent than hyoscine hydrobromide. No central side-effects.
Hyoscine butylbromide (buscopan)	Noisy secretions Colic	20–120 mg/24 h	Less hydrophilic than hyoscine and less likely to cause central nervous system (CNS) toxicity.

were noisy respirations, urinary dysfunction (incontinence or retention), pain, restlessness and agitation, dyspnoea, nausea and vomiting, sweating, jerking/twitching and confusion [18]. Fatigue, generalised weakness, drowsiness and anxiety have also been documented as common in retrospective chart reviews [19].

3. Symptom management

3.1. Pain

Pain is the most common and most feared symptom of advanced malignant disease. In the UK, the analgesic used most commonly in the terminal phase when a patient is no longer able to take oral medications is diamorphine (diacetylmorphine) given s.c. via a portable syringe driver. This synthetic analogue of morphine is more suitable for s.c. infusion because of its greater solubility. The s.c. dose of diamorphine for the treatment of chronic pain is one-third of the oral morphine dose. In addition to providing pain relief by a continuous infusion, 'as required' (p.r.n.) injections can also be given for breakthrough pain. The usual dose for 'breakthrough analgesia' is one-sixth of the total 24-hourly dose. The requirement for frequent 'breakthrough' doses, suggests that an increase in the 24-h infusion dose is required. The usual practice is to increase the total daily dose of the infusion by one-third, or to add the extra 'as required' dose requirements in the previous 24 h into the baseline dose for the next 24 h.

As death approaches, co-analgesics (e.g. non-opioid analgesics, anticonvulsants, antidepressants or NSAIDs) are usually discontinued. If considered essential, it is possible to continue some co-analgesics parenterally (e.g. rectal or s.c. NSAIDs or s.c. corticosteroids). To compensate for discontinuing these drugs, it may be necessary to increase the diamorphine dose, although some series have shown a stabilisation or decrease in opioid requirements just prior to death [18,19]. In rare cases, sedation is used as the only means of providing relief from pain in a patient with severe and intolerable distress that can not be controlled by other means [20].

3.2. Terminal restlessness

The term 'terminal restlessness' encompasses the agitation, anxiety, fear, mental distress, general discontent and unease of patients that may be seen as death approaches. As well as mental anguish, there are likely to be physical manifestations in the form of restlessness, inability to get comfortable, tossing, turning and fidgeting. This is a complex syndrome with multiple possible causes (Table 2). When an easily correctable cause for the restlessness is identified, specific treatment can be instigated (e.g. catheterisation for urinary retention and increased analgesia for uncontrolled pain). For the majority of patients, however, no specific cause for the restlessness is ever identified. Under these circumstances, sedation is often used for symptomatic relief.

The benzodiazepine midazolam, an anxiolytic sedative with amnesic and anticonvulsant properties, is the agent most frequently used in this context. There are

Table 2
Causes of terminal restlessness

Cause of terminal restlessness	Examples
Disease process	Brain metastases or primary tumour Infection and/or pyrexia Paraneoplastic syndromes
Physical discomfort/ uncontrolled symptoms	Uncontrolled pain Full bladder Constipation Dyspnoea Nausea Pruritis
Psychological distress	Anxiety, fear, anguish Non-organic psychiatric disturbance
Drug side-effects	Opioids NSAIDs Hyoscine hydrobromide
Drug withdrawal	Alcohol Benzodiazepines Corticosteroids
Metabolic disturbances	Hypercalcaemia Renal failure Hepatic failure Adrenal failure

NSAIDs, non-steroidal anti-inflammatory drugs.

several descriptive studies documenting the use of this drug in the palliative care setting both at home and within inpatient units [21,22]. Midazolam can be given by intermittent s.c. injection or by continuous infusion. The dose can be titrated according to clinical need. A typical starting dose for terminal agitation is 30 mg/24 h, but doses of up to 240 mg/24 h have been reported [23]. This drug may be of particular use in patients with brain metastases or a history of seizures or myoclonus as it is also an effective anticonvulsant.

Levomepromazine, a phenothiazine closely related to chlorpromazine, was originally developed as an antipsychotic and is still used in this context. It is highly sedative and can be a useful alternative to midazolam for the control of terminal restlessness, especially in patients who are confused, anxious or agitated [24,25]. The only other major side-effect is postural hypotension which is unlikely to be a problem in bed-bound patients. The drug is usually administered via a continuous s.c. infusion. It is important to be aware that the dose necessary to control confusion or agitated delirium is likely to be much higher than that commonly used for the control of nausea and vomiting (see below). A typical starting dose for terminal sedation is in the range of 50–75 mg/24 h but this can be increased to 300 mg/24 h [26]. As with all phenothiazines, there is a theoretical risk of lowering the seizure threshold in patients with brain metastases or a history of seizures. Non-organic psychological disturbance is common in patients during the terminal phase [27]. For this reason, it may be more appropriate to use levomepromazine (which is also antipsychotic) as a sedative rather than midazolam. No comparative studies have been undertaken comparing the efficacy of these two drugs.

Haloperidol, a butyrophenone, is less sedating than levomepromazine with fewer antimuscarinic side-effects, but a tendency towards greater extrapyramidal side-effects [28]. It is used 'firstline' as a sedative in some units. Haloperidol has been shown to be superior to either lorazepam or chlorpromazine in the management of confusion/delirium in patients with AIDS [29].

Rarely, a patient who is not adequately sedated on maximum doses of midazolam, levomepromazine or haloperidol may benefit from the addition of phenobarbitone given as intermittent s.c. injections or by a continuous infusion.

The issue of sedation in terminal care remains controversial. The frequency of use varies greatly in published series between different units and in different countries (20–68%) [20].

3.3. Dyspnoea

Dyspnoea is recognised as being a difficult symptom to treat at all stages of the cancer trajectory, but becomes an increasing problem with advanced disease. The prevalence of dyspnoea has been shown to increase from 17 to 28% during the 4 weeks before death [19]. Dyspnoea was noted as a problem in approximately half the patients admitted to a hospice, but to be present in almost 80% of patients who died within 1 day of admission [30].

There is some evidence that opioids are effective in the palliation of dyspnoea [31]. At earlier stages of the illness, an attempt is usually made to treat dyspnoea without causing sedation. With advancing disease, the goals of care change and the most appropriate treatment is often to reduce the patients' awareness of their dyspnoea. At this stage, the sedative effects of opioids or benzodiazepines are usually desirable.

3.4. Noisy secretions

As death approaches, it is not uncommon for patients to lose the ability to clear secretions from their upper airways. This can lead to noisy and laboured respirations that are often referred to as the 'death rattle'. The reported prevalence varies from 25 to 92% [32]. It is generally assumed that this symptom is not distressing for patients themselves, as they are usually unconscious by the time it becomes apparent. It is often most distressing, however, for attending relatives, carers and other patients on the ward. The first step in managing this symptom is good communication. Carers should be reassured that the noises emanating from the patient do not indicate that they are in pain, nor that they are

choking. When secretions first begin to accumulate, it is usual to administer an antimuscarinic agent in order to 'dry' the secretions. The choice of drug used is largely empirical and varies between centres [33]. Hyoscine hydrobromide (hyoscine) relaxes bronchial smooth muscle to reduce airway resistance and reduces salivary secretions. Unfortunately, it also crosses the blood–brain barrier and can cause unwanted side-effects in patients who are conscious (e.g. confusion, hallucinations and behavioural abnormalities). An alternative is hyoscine butylbromide (buscopan). This drug is less lipophilic than hyoscine hydrobromide and less likely to cause central nervous system toxicity [34]. Glycopyrronium is the drug used 'first line' in some centres. It is more potent than hyoscine hydrobromide and does not cause sedation or agitation. Each of these drugs can be given by intermittent or continuous s.c. injection. One audit has shown very little difference between hyoscine hydrobromide, hyoscine butylbromide or glycopyrrolate with respect to control of secretions at the time of death [33]. In patients who have already developed noisy secretions, antimuscarinic medication may not improve the situation. Under these circumstances, the noisy breathing may be alleviated by repositioning the patient. Occasionally, it may be necessary to clear secretions using suction.

3.5. Nausea/vomiting

Nausea and vomiting can be problematic in patients dying with bowel obstruction or metabolic disturbance (e.g. hypercalcaemia and uraemia). The antiemetics used most commonly in the terminal phase are shown in Table 1. In order to ensure that adequate doses of these drugs are absorbed, they should be administered parenterally (usually by s.c. injection). Levomepromazine and haloperidol are sedative at higher doses. In the terminal phase this may be beneficial. Haloperidol is often given concurrently with diamorphine to prevent opioid-induced nausea.

3.6. Convulsions

Convulsions are rarely a problem in the terminal phase. Many anticonvulsants are only available in oral or i.v. formulations. Phenytoin and sodium valproate have relatively long half-lives such that drug levels may remain therapeutic for some time after the cessation of oral drugs [5]. Thereafter, seizures can be controlled by diazepam given rectally or midazolam or phenobarbitone delivered parenterally.

3.7. Terminal crises

Rarely, a terminally ill patient will suffer a sudden catastrophic event directly or indirectly attributable to their disease, e.g. haemorrhage or sudden asphyxia. The priority is for carers to react in a controlled and reassuring way so as to minimise patient distress. If the event is likely to be terminal and no active interventions are planned, it is usually appropriate to render the patient unaware of the situation as soon as possible. A survey of palliative care units in the UK revealed that the most common combination of drugs used in this circumstance was diamorphine plus midazolam. An opioid dose of 30–50% of the usual daily dose is likely to relieve distress yet not shorten life should the event resolve spontaneously [35]. It is important that the risk of a terminal crisis should be anticipated and that appropriate drugs are prescribed in advance of such an event occurring.

4. Mechanisms for improving the management of dying patients

4.1. Education

As a general rule, 'active management' of the terminal phase represents no more than good quality holistic medical care appropriate to the stage of an individual's disease. This approach will not in itself result in premature death and patients with a self-limiting or potentially reversible cause for their recent deterioration will not be denied the opportunity to recover. Many clinicians and relatives require reassurance in this respect, as there is sometimes a fear that making a 'diagnosis of dying' can become a self-fulfilling prophesy.

4.2. Care pathways

Care pathways are mechanisms for integrating clinical guidelines into routine practice [36]. A pathway for care of the dying has been developed by Ellershaw and coworkers [37]. Standardised assessments are undertaken on patients who enter the pathway and the reasons why the pathway was not followed are documented. The pathway was originally developed for use in a hospital support team to improve care of patients dying in a general hospital. It has since been used in hospices and nursing homes. Introduction of the pathway into an institution provides a clear management plan for doctors and nurses caring for patients in their terminal phase. It also generates data about how closely the pathway is followed and allows for regular audits to be undertaken to ensure that standards are being maintained.

5. Conclusions

The majority of common adult cancers, especially those presenting with metastatic or advanced disease,

remain incurable. Terminal care is an important aspect of the total care of cancer patients and should not be ignored or avoided. Palliative care services are expanding, but are still not available in all institutions. The keys to improving patient care in this area will be better education of medical and nursing staff and the introduction of care pathways.

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