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End of life issues

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ABSTRACT

Despite advances in cancer survival rates, end of life care remains a vital aspect of cancer management. The use of integrated care pathways can facilitate effective care of dying patients in a generalist setting. However, it remains important that staff are able to recognise the onset of the dying process, not only in order to make symptom control provision, but also that appropriate communication can occur with patients and those close to them. This allows the exercise of choice over place and style of care. The key symptoms at the end of life are restlessness, agitation, breathlessness, pain and noisy respiration from retained airway secretions. Ethical tensions arise from the assumptions that the use of opioids and sedatives hastens dying, but this is contradicted by available evidence.

1. Introduction

Although cancer five year survival rates are steadily increasing, the mortality associated with malignancy remains very large.[1] About 50% of people with colonic cancer will die inside a five year horizon, as will no less than 93% of those with lung cancer and 97% of patients with pancreatic cancer.[2] End of life issues are therefore integral to the management of oncological conditions.

However, this is an area where practice all too often falls short of what is needed. In the UK, 54% of all complaints reviewed by the Healthcare Commission relate to perceived deficiencies in care at the end of life and the Commission is preparing to conduct an in-depth review of palliative and end of life care in the National Health Service during 2008/2009.[3] UK Governmental action is already occurring in the shape of the End of Life Care Strategy, set up in 2006. Part of this Strategy is the use throughout the health service of the Liverpool Care of the Dying Pathway (LCP). The LCP systematises the approach to the management of the final stages of life that has been developed in specialist palliative care to enable generalist staff, particularly in hospitals, to apply its lessons for the benefit of the many people who die outside hospices.[4] Use of the LCP is considered to improve the process of care and by implication its quality, but the extent to which it is used remains variable, with barely 10% of deaths nationally being accompanied by use of the LCP.

A key reason for the non-use of the LCP is the failure of staff to recognise when a patient is dying and therefore eligible for the pathway.[5] This judgement is not always an easy one to make, but in cancer particularly there are significant signs that are usually present.

1.1. *How to diagnose dying*

It is important to make a diagnosis of dying, not only so that treatment may be tailored appropriately, but also so that patients may be made aware – if they so wish – of the stage of their illness and empowered to make choices about how the last phase of their life is managed. A few may want to die in hospital with all the medical technology available continuing until their last breath, but the vast majority express

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the desire to die at home. Although this proportion declines as the illness progresses and its realities reveal themselves to both patients and those close to them, it remains over half.[6] Despite this, most people in the western world die in hospital (56% in the UK). In part, this reflects the lack of effective end of life care in the community, although thanks to the cancer orientation of much specialist palliative care this is less true for people with malignant disease than that for others, but it may be relevant that the recent National Audit of care of the dying in British hospitals revealed that only 45% of 2672 patients across 118 hospitals were reckoned by staff to be aware that they were dying.[7] Most of the complaints about the care of the dying centre on failure in some aspect of communication, and to remedy this requires both the ability to communicate sensitively and also to have made a sufficiently accurate clinical assessment in order to know what it is that should be communicated.

Doctors consistently overestimate patients' survival and familiarity with the patients tends to make this worse.[8] Not surprisingly, poor functional status is a predictor of a less than 90 day survival, but so is a marked deterioration in an initially high performance score. Further predictive factors that have emerged from a systematic review of the literature are signs and symptoms of the cancer anorexia–cachexia syndrome and the presence of breathlessness or delirium.[9] The 'death rattle', caused by secretions retained in the airways because of inadequate ability to cough, lives up to its name by being predictive of death within 48 h, but occurs in only around 50% of cases.[10]

A person who shows at least two of the following four signs has a mean of two days to live: bedridden, semi-comatose, able to take only sips of fluid, no longer able to swallow tablets.[11] It has been noted that on average, patients dying of cancer develop respirations with jaw movements eight hours, peripheral cyanosis five hours and loss of the radial pulse three hours before death. However, most patients showed these signs less than two and a half hours before they died. Diminished consciousness was present 24 h prior to death in 84% and in 92% by 6 h before death.[12]

1.2. *Appropriate treatment at the end of life*

Appropriate treatment at the end of life involves more than giving the right drugs in the right amounts, although this is fundamental. By this stage of the illness, the person with cancer should already be known to a specialist palliative care team, where such a service is available but, if not, now is the time for referral to be made. It should also be known whether the patient has a valid advance directive or a health care proxy as guides to their wishes concerning end of life care. Cultures differ as to whether the information that death is now not too far away properly belongs to the patient in the first instance (if they want it) or to their family, but it has been suggested that veiling bad news from patients is associated with more agitation and hence more need for sedation at the end of life.[13] However, the principal reason for sharing this information is that doing so enables the ill person and their family to make adult choices about how they would like the end of life to be managed. If this is to be at home, the facilities must exist to provide and administer any required medication in a timely manner,[14] which implies the existence of a community team that has the requisite knowledge to anticipate symptom control needs and provide for them, and is available 24 h a day. There must also be access to professional nurses and to nursing equipment at home. Even then, much of the care will come from family and friends, whose support is vital. Without the commitment of at least two informal care givers and the cooperation of the family doctor, a home death becomes much less likely in developed countries.[15]

The accessibility of a specialist palliative care in-patient unit is valuable for the resolution of particularly difficult symptoms, or for end of life care when insufficient support is available at home or family members can no longer cope. In the latter case, it is important for future adjustment during bereavement that families receive reassurance about the quality of their caring efforts prior to the admission, and the appropriateness of seeking in-patient care now. Even when death does take place in a hospice or other in-patient unit, usually over 80% of the patient's last year of life will have been spent at home and afterwards families feel that they have indeed cared for the person themselves.[6]

Once the end of life has been recognised, not only further anti-cancer treatments but also a number of other therapies become irrelevant and should therefore be stopped. Examples are drugs whose long-term prophylactic effect has now been overtaken, such as statins, and drugs for which the requirement is likely to have lessened because of changes in activity or physiology, for example antihypertensives, oral hypoglycaemics, diuretics and cardiac failure medications. The medications that are now necessary are those that deal with the key symptoms encountered in dying people.

1.3. *Key symptoms in dying*

1.3.1. *Pain*

Contrary to popular fears *pain* if managed well before end of life is not a particular problem at the end of life, tending to diminish in the last days to weeks.[16–18] Nevertheless, it is common for both patients and those close to them to fear that death will be accompanied by a crescendo of pain and adequate analgesia must be ensured to the very close of life. As swallowing becomes difficult for most people in the last 48 h or so before death, this will entail a change from oral to parenteral medication, usually in the form of an opioid. Whether given as morphine, which remains the most commonly used (and cheapest) opioid drug, or as one of the more recently available alternatives such as oxycodone, the subcutaneous route of administration is entirely adequate and is less reliant on the attendance of medical staff than the intravenous. If analgesia is already being provided as a transdermal formulation of fentanyl or buprenorphine, these can be continued in the final stages of life, but they do not lend themselves to responding flexibly to any changes in analgesic requirements and so it is necessary to provide access to an injectable opioid as well. If renal function deteriorates, active opioid metabolites, which are principally eliminated by this route, will tend to accumulate to cause additional drowsiness and myoclonus, particularly in the presence of phenothiazines. Because of their lack of active metabolites, the opioids of choice in this situation are the methylpiperadine deriva-

tives, fentanyl, alfentanil and sufentanil, although it should be noted that some accumulation of the parent drug can still occur in renal failure.[19] Table 1 gives the approximate conversion ratios of some commonly used opioids.

1.3.2. *Breathlessness*

It has been noted that *breathlessness* is associated with the onset of dying, whether or not there is known lung involvement by cancer. This is not necessarily a signal to initiate oxygen therapy: in a cancer palliative population, oxygen was no better than compressed air in relieving dyspnoea and those by whom it was preferred were not necessarily hypoxic.[20] A systematic review has concluded that there is a small but worthwhile beneficial effect of oral and injected opioids on the symptom of breathlessness[21] and, despite the widespread caution exercised in the use of opioids in patients with respiratory impairment for fear of respiratory depression, these drugs, orally or subcutaneously, are the cornerstone of palliation of breathlessness in patients with advanced cancer. Although there are opioid receptors in the airways, nebulised opioids have thus far failed to demonstrate beneficial effects over and above that of saline. Given the close association between breathlessness and anxiety, it is unsurprising that anxiolytics have also found a role in the management of dyspnoea. Benzodiazepines may also contribute by means of their muscle relaxant properties. At the end of life, low doses of midazolam (2.5 mg stat or 10 mg/24 h subcutaneously) can complement the effects of opioids on breathlessness.

1.3.3. *Secretions*

Around half of dying people will develop the so-called '*death rattle*', caused by the inability to cough up airway secretions, which consequently collect to create a characteristic sound as breath bubbles through them. At this advanced stage of their illness, few patients seem disturbed by the sound, but it can be upsetting for families and friends gathered around the bed unless its origin is clearly and reassuringly explained. Addition of an anticholinergic agent to the infusion will at least reduce death rattle in 50–80% of cases but the remainder are resistant, probably because the rattle is the result of infection.[12] No convincing evidence has been presented as to the superiority of one anticholinergic drug over another in this context. However, glycopyrronium bromide (0.6–1.2 mg/24 h s.c) is less likely to cross the blood-brain barrier and cause either sedation or paradoxical excitatory effects than hyoscine hydrobromide (1.2–2.4 mg/24 h).

Table 1 – Conversion ratios from oral opioids to subcutaneous morphine or alfentanil

Oral opioid	To obtain dose of s.c. morphine divide oral dose by:	To obtain dose of s.c. alfentanil divide oral dose by:
Morphine	2	30
Tramadol	8	120
Oxycodone	1	15
Hydromorphone	Multiply by 4	4

Note: Opioid conversion ratios are always approximate. They suggest a starting point but the dose may subsequently have to be either increased or decreased depending on response.

1.3.4. *Restlessness*

A generalised *restlessness*, which may be due to pain but also to anxiety, has to be distinguished from focal myoclonic jerks and is frequently seen in patients in the last days of life. Rather than persist with opioid medication for restlessness it is more appropriate to use a benzodiazepine, either instead or in addition, for its anxiolytic and muscle relaxant properties. Restlessness may be associated with an acute confusional state that occurs in 15–20% of palliative care patients,[22] though figures of up to 85% have been reported, especially towards the end of life.[23] In a few, restlessness and delirium build to a level of *agitation* that is not contained by benzodiazepines or antipsychotics and here phenobarbital and propofol (intravenous route only and in an egg-based medium, so unsuitable for many patients) have been used in rare situations.[24,25] Unless the clinician has an index of suspicion and assesses for opioid toxicity (myoclonus, agitation, sedation, hallucinations and paradoxical increase in pain, often generalised) some patients will be mislabelled as having terminal agitation instead of opioid-induced agitation. This is a fundamental part of patient assessment. Some patients who have been considered to have extreme agitation, requiring extreme measures such as propofol, are highly likely to have been experiencing opioid toxicity. Diagnosis is critical as we know from patients who recover that this is extremely frightening and distressing despite sedation.

1.4. *Ethical issues*

End of life care appears to have gained the reputation of being fraught with ethical difficulties. In part, this is due to the legalisation of euthanasia for the terminally ill in the Netherlands and Belgium and persistent attempts to introduce similar legislation in other countries, particularly in the English speaking world. It also seems to be due to continuing concerns, both lay and professional, regarding the potential effect of morphine and sedatives in curtailing life. Bluntly, is good symptom control possible without shortening life? The frequent discussion of the moral concept known as the Principle of Double Effect bolsters the impression that doctors engaged in end of life care are regularly bringing about their patients' death in the name of symptom management.[26]

Briefly put, the Principle of Double Effect states that an action, which causes a serious adverse effect that has been foreseen, even death, is morally allowable if the intention behind the action was to do good and the adverse effect was not the means of achieving the good outcome.[27] Use of Double Effect has been criticised because of the inherent difficulty in knowing truly the intention of another, or even oneself, and also on the grounds that an action that is foreseen might as well be intended.[28] Defenders of Double Effect point out that the concept of intent is well understood in law and is a routine part of the assessment of guilt in criminal cases; there will be evidence from the behaviour of the doctor as to his intention: for instance, was the final dose of morphine the result of a gradual process of titration against pain response or was it

a sudden increment quite disproportionate to what had been given before? They also point out that the fact that the *possibility* of a result has been foreseen does not imply that the result is a *certainty*. In the event, it might not have happened.

However, studies have repeatedly found a lack of association between absolute opioid dose or incremental opioid dose and length of survival in palliative care cancer populations.[29] In the largest and most sophisticated examination of the issue so far, 725 hospice in-patients with end-stage cancer, lung or heart disease were followed until death.[30] In this group, length of stay was *positively* correlated with the maximum daily opioid dose received, even when that dose exceeded 1.8 g/day – around 15 times the UK and Japanese average for such patients.[31,32] Neither absolute nor percentage change in dose was linked with survival. In fact, multivariate analysis found no factor combination capable of explaining more than 8% of the variation in survival time, suggesting that the overwhelming contribution to the timing of death was the individual's disease severity.

The use of sedative drugs at the end of life also gives rise to concern, not helped by the use of the unfortunate phrase 'terminal sedation', which might be taken to suggest that the sedation itself precipitates the terminal event. As with opioids, it is of course possible to kill people with sedatives but the issue is whether this needs to happen as the unavoidable price of adequate symptom control in the last days of life. There is also a legitimate concern that sedation might be used as a cover for euthanasia; it has been noted that in recent years, a small decrease in the number of cases of (regulated) euthanasia in the Netherlands has been matched by an increase in the use of (unregulated) continuous deep sedation.[33] It is also not reassuring to find that the reported use of sedation in end of life care varies from 1%[34] to 88%.[35] The fundamental question arises; who made the diagnosis of 'end of life' in these cases?

Distressing restlessness or agitation occurs not infrequently in people who are dying or beginning to die. Communication is minimal or impossible at this stage and the only practicable way of providing relief is the use of a degree of sedation. This does not mean that the patient is necessarily rendered unconscious provided that the sedative is used in a manner analogous to opioid analgesia, i.e. a minimum dose is given at first and then gradually increased until the target symptom is just controlled. Provided the patient is comfortable, their level of consciousness is immaterial. One reason behind the widely discrepant frequencies of sedation in the literature could be that some authors confine the use of the term to the induction of coma for severe and intractable symptoms, which is an uncommon situation, whereas others count any use of a potentially sedative drug and hence derive much higher figures.[36]

A systematic review of sedation in end of life care found that the weighted mean duration for which sedation was employed, calculated from a total of ten studies that had examined this issue, was 2.8 days.[37] This figure could imply either that sedative use generally results in death within 72 hours or that sedation is a response to symptoms which are arising from the dying process.

To help decide between these possibilities, the same review analysed five studies that recorded the survival of patients, either from admission to death for in-patient units or from commencement of service involvement to death for domiciliary-based teams. In each case, survival of patients receiving sedation was either not significantly different from that of patients who did not have sedatives or, in one case, showed a clear difference in favour of the sedation group. The explanation for this finding may be the role of delirium in precipitating breakdown of care at home and consequent admission to a specialist palliative care unit. Patients who had this particular symptom problem would have been admitted at an earlier stage of their illness than those who did not experience delirium either at all or until they were actually dying.

Nevertheless, concern about the potential misuse of sedation at the end of life has stimulated the formulation of guidance on when and how such treatment should be used. An international group of palliative care clinicians has conducted a literature review and attempted to develop internationally accepted definitions and recommendations based on the published literature.[38] This group has coined the term 'palliative sedation therapy', and emphasises that this is a treatment for symptoms that cannot be controlled in any other way than the use of sedatives. This is a conclusion that should be reached only after adequate experience and expertise has been brought to bear: there is evidence that doctors who are tired or are inexperienced in palliation are more likely to use sedation, perhaps inappropriately.[39] There is an issue here with any doctor who is 'burnt out' including palliative care doctors who can convince themselves that it is the appropriate move for management. This is why even very experienced doctors should always seek another opinion with difficult symptom control issues.

If palliative sedation is being considered, there should also be consultation with those close to the patient as well as the patient himself if this is practicable, which it generally will not be. Sedation should be achieved with sedatives, as noted earlier, and not with opioids, which are inefficient for this purpose.

In the relatively rare instances where deep continuous sedation is used disease should be irreversible and advanced, with death expected within hours to days. In this context, the use of artificial hydration is usually not clinically required, and at this stage of illness might increase the risk of noise from respiratory secretions as well as of both pulmonary and peripheral oedema, although the evidence on these points is mixed.[40] However, the provision of artificial hydration is a clinical judgement that might become relevant at any stage of a terminal illness and is not simply a question that arises in the context of sedation.[41,42]

It is worth returning to the much-quoted Principle of Double Effect and asking whether it is actually needed in the practice of effective end of life care. The answer from the evidence to date is 'no', although this is not to argue against its validity as an ethical concept. There will be times when treatment given for relief of symptoms hastens or precipitates a terminally ill patient's death and the Principle may be called into play just as it is from time to time in other arenas of clinical practice, perhaps particularly acute surgery. However, if a doctor finds it necessary to call upon the Principle frequently in order to excuse his practice of palliation there is something

wrong. Properly conducted palliative care is not euthanasia by another name. It does not kill patients.

2. Conclusion

Good care at the end of life requires attention not only to good symptom control but also to the quality of communication and the patient's wishes about how and where they wish to be looked after. To do all this well is important, not only for the comfort of the person who is dying, but also as a public health measure for their family and friends, whose memory of the death and what led up to it is likely to colour their future attitudes to health care and serious illness in themselves and others. The impression remains, amongst both the public and some professionals, that effective symptom control frequently causes shortening of life. The evidence contradicts this impression, and it is important for the specialty of palliative medicine, as well as for the clarity of public debate, that the clear distinction that exists between palliative care and euthanasia is not blurred.

Conflict of interest statement

None declared.

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