Education and debate

Chemotherapy for cancer patients who present late

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Doctors should not overlook the potential benefits of chemotherapy in patients with incurable cancer

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A patient presenting with an advanced curable cancer is usually regarded as a medical emergency and treated with chemotherapy and full medical support. However, a patient presenting with a chemosensitive but incurable cancer at an advanced stage may be offered only palliative care. We argue that giving reduced dose chemotherapy to very ill patients with incurable cancer can be beneficial. The benefits can include symptom control and buying a short window of time to allow the patient and family to come to terms with the diagnosis. The cancer patients we are discussing are those who are newly diagnosed with chemosensitive tumours and who have not had previous chemotherapy. They must be distinguished from previously treated cancer patients, who may be resistant to chemotherapy and in whom supportive palliative measures may be more appropriate.

Survival of patients with poor performance status

Trials in most malignancies show that poor performance status correlates closely with reduced survival^{1 2} and in some cases reduced response rate to chemotherapy.^{1 2} It is therefore easy to assume that patients presenting at an advanced stage with a poor performance status secondary to high tumour burden would gain little from chemotherapy. In the 1980s and early 1990s the trend was to increase the dose of chemotherapy in order to maximise response rates in cancers.¹ This led to increased toxicity in very ill patients and was especially unacceptable if the goal was palliation rather than cure. It is therefore not surprising that articles discouraged the use of chemotherapy in late presenting patients with poor performance status.¹

Eastern Cooperative Group/World Health Organization performance status scale

- 0 = Normal activity, no restrictions
- 1 = Restricted but ambulatory; able to carry out light work
- 2 = Ambulatory and self caring but unable to carry out light work; up more than 50% of waking hours
- 3 = Limited self care; confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled; totally confined to bed; may need admission to hospital

Reduced dose chemotherapy can benefit very ill patients with incurable cancer

In this article, unless otherwise specified, we use the term poor performance to mean Eastern Cooperative Group (ECOG) status 3 and 4 (box). Although ECOG status 4 may not always equate with the description moribund, we use the term to cover this category for simplicity.

Data on patients with extremely poor performance status or who are moribund are surprisingly scanty, and chemotherapy trials often exclude these patients.^{2 3} However, studies of small cell lung cancer that included patients with poor performance status, showed a survival advantage for those who received chemotherapy compared with those who did not.⁴

Quality of life

Evidence is increasing that patients with chemoresponsive tumours experience a better quality of life while receiving chemotherapy compared with those receiving only best supportive care.⁵ The concept of palliative chemotherapy given to alleviate tumour related symptoms, even if there is no survival advantage, is well established.^{5 6} In a trial among patients with non-small cell lung cancer, 54% of patients with ECOG status 3 had a symptomatic response.⁷ As patients respond to chemotherapy they regain their appetite and energy because the cancer anorexia-cachexia state begins to reverse. Interestingly, older studies suggest that chemotherapy can reduce pain from cancer even in the absence of objective tumour regression.⁸

No data exist on the benefits of chemotherapy for symptom control in moribund patients. Trials that include patients of ECOG grades 3 and 4 are unlikely to include many that have a life expectancy of days.

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Case history 1

A 66 year old woman presented with stage IV ovarian cancer. Debulking surgery left appreciable disease in the abdomen and a malignant pleural effusion. After surgery she deteriorated noticeably with oliguria, disseminated intravascular coagulation, respiratory distress, bleeding duodenal ulcer, sepsis, and *Clostridium difficile* diarrhoea. On day 11 after surgery, death seemed inevitable (albumin 9 g/l). As her only hope of improvement was reversing the primary underlying malignant pathological process, she was offered a trial of carboplatin chemotherapy. A moderate dose, 500 mg, was given and 48 hours later she began to improve. She survived nine months after further standard outpatient chemotherapy, and she and her husband were thankful for the extra time and symptomatic relief chemotherapy had given her.

Clinicians who use chemotherapy judiciously in moribund patients recognise that some gain a useful response. We have seen several moribund patients who have benefited from chemotherapy in situations where other clinicians may not have considered treatment. In some, the quality time gained has enabled the patient and family to come to terms with the diagnosis and prepare for death.

It is probably the ability of chemotherapy to reverse the negative metabolic effect of the cancer that relieves symptoms. For example, in two cases we have even seen reversal of disseminated intravascular coagulation (case history 1) and appreciable survival benefit. The second case history describes a patient in whom reduced dose chemotherapy transiently shrank the tumour, allowing the patient a few extra days of quality life so that family memories are of "her being well and happy," according to a letter written by her relatives. Doctors and nurses may not think chemotherapy was beneficial in this case, but clearly the patient and relatives did.

These three patients show how chemotherapy can sometimes reverse the catastrophic physiological state of terminal cancer, even in seemingly hopeless cases. Without clear prospective studies it is impossible to say how often this occurs, but the phenomenon is well recognised among oncologists. Chemotherapy has too often gained a bad name either because of confusion of chemotherapy toxicity with the systemic effects of the

malignancy or because of the inappropriate prolongation of treatment when the tumour becomes resistant.¹

Toxicity

Doctors are often worried that patients who do not respond to chemotherapy will suffer unnecessary toxicity. Undoubtedly, full dose chemotherapy is more toxic in patients with poor performance status.⁹⁻¹⁰ Radford et al showed that among patients with small cell lung cancer, those with poor performance status had more septic episodes than those with good performance after full dose chemotherapy; septic episodes were also related to the intensity of chemotherapy regimen.⁹

Reducing the dose and hence intensity of chemotherapy should reduce the incidence of septic complications in sick patients.⁹ The dose in the first cycle should be reduced to about 50-75% of full dose. In subsequent courses the dose needs to be escalated as soon as possible because dose reduction in the whole course of chemotherapy is associated with poorer outcomes and inferior quality of life.¹¹ Now that newer less toxic chemotherapy drugs, powerful antiemetics, and haemopoietic growth factors are available, the opportunities to palliate with chemotherapy without risk of toxicity may be far greater. Age should not be a contraindication to treatment as response rates are similar in elderly people, although haematological toxicity may be higher.¹¹⁻¹²

Support after chemotherapy

Ray-Coquard and colleagues showed that, for a variety of tumour types, patients with poor performance status were most at risk of an early death after chemotherapy.¹³ Although half the deaths were due to progressive disease, nearly half were due to sepsis after full dose chemotherapy. Successive Medical Research Council leukaemia trials have shown that fastidious supportive care of patients after chemotherapy, including the use of prophylactic antibiotics, enhances survival.¹⁴ If late presenting, moribund patients are to be offered the best chance of benefiting from chemotherapy, they also need to be given full medical supportive care until it is clear whether they are responding. Two cycles of chemotherapy seem sufficient in most tumour types as an initial trial.¹

Unfortunately, we have no way of predicting which moribund patients with potentially chemosensitive tumours will respond to treatment. Patients and family need to be fully informed that chemotherapy may not work, that the main aim is to attempt symptom palliation, and that some patients may not gain improved survival. Palliative and active management need to coexist.

Patients' perspective

Many dying patients want to retain control as long as possible.¹⁵ Buying quality time to allow patients to put their affairs in order and to come to terms with death is one of the most effective ways we can help them retain control. Chemotherapy may allow the patient time to pass through the stages of the initial strong emotions of facing the threat to the calmer acceptance stage.¹⁶ Additionally, studies suggest that sudden death

Case history 2

An 82 year old woman was diagnosed with acute myeloid leukaemia with pre-existing myelodysplasia and complex cytogenetics. Her prognosis was very poor. During the 12 days after diagnosis she deteriorated rapidly with increasing white count ($65 \times 10^9/l$) and cachexia. Death was expected within 1-3 days. Relatives were due to arrive from abroad, and she chose to try a single reduced dose of daunorubicin 40 mg and cytarabine 200 mg intravenously. She vomited twice but within 24 hours felt much better, got out of bed, and started to eat (white count $35 \times 10^9/l$). She enjoyed three days with the family and then deteriorated rapidly and died. The family were grateful for the quality time with her that the chemotherapy had given.

Summary points

Patients of all ages who present late with chemoresponsive tumours may benefit from chemotherapy

A few patients will gain improved survival while others may get symptom relief or time to prepare for death

Many patients in this situation would choose to try chemotherapy

Patients need to be carefully supported medically, especially if frail at the time of treatment

General physicians and surgeons should refer these patients for an oncology opinion

is associated with a more severe early grief reaction among relatives than is expected death.¹⁷

Slevin and colleagues showed that cancer patients wanted to try chemotherapy at predicted success rates far below the level which doctors, nurses, and the general public thought reasonable.¹⁸ In their study, patients would consider a trial of chemotherapy for relief of cancer related symptoms even if there was only a 1% chance of success, despite mild toxicity. Similarly, they would accept major toxicity for a 10% chance of symptom relief. Silvestri et al showed that 68% of patients with non-small cell lung cancer would accept chemotherapy if it significantly reduced the symptoms of the cancer with no survival benefit, even if there was a 20% chance of experiencing side effects from the chemotherapy.¹⁹

Conclusions

We argue from extrapolation of current data and from anecdotal experience, that reduced dose chemotherapy can be beneficial even in late presenting moribund patients. Full supportive medical care must be given to optimise the chances of a response. Prospective trials are needed to determine the response rates and benefits.

Although healthcare professionals may be reluctant to give chemotherapy to very ill patients, patients are often keen to try it even if the benefits may be small. Most late presenting, moribund cancer patients will present to surgeons and physicians in district general hospitals. It is therefore important that generalists consider referring such patients to an oncologist.

Contributors and sources: SJB and SMBR work as haematologists and also care for patients admitted with solid tumours. SJB was lead clinician for cancer services for Bexley for six years. CDS is a chest physician with an interest in palliative care. PGH is a consultant medical oncologist at Guy's and St Thomas's Hospital NHS Trust since 1982. He has been principal investigator in many national and international trials, with particular interest in the areas of gynaecological cancers, lung cancers, elderly people, and quality of life. Information was obtained from literature searches in the Cochrane Library, Medline, and Embase databases.

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Professor Roger Williams: An Apology

In the 23 November 2002 issue of the *BMJ* we published an article entitled "Institutional Corruption in Medicine" by Peter Wilmshurst (*BMJ* 2002;325:1232-1235). The article concerned the falsified research of Dr Anjan Kumar Banerjee, whose registration was suspended by the Professional Conduct Committee of the General Medical Council in November 2000. It has been drawn to our attention by Professor Roger Williams, professor of hepatology at the Royal Free and University College Medical School, London, that readers may have understood the article to mean that Professor Williams (who was then director of the Liver Unit at King's College Medical School, London) had turned a blind eye to Banerjee's fraudulent research or had been party to a cover-up. We are happy to confirm that it was never our intention to make any such suggestion, which would plainly have been untrue, and to express our sincere apologies to Professor Williams for any distress and embarrassment that he has been caused.