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Cost Effectiveness in the Treatment of Advanced Solid Tumours

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When the treatment of advanced cancer is palliative in intent, evaluation of quality of life is of paramount importance in judging the effectiveness of treatment. The balance between adverse effects (costs) and benefits has been particularly difficult to determine with cytotoxic drugs. An approach to this problem using medical audit is described. It has been found to be a reliable method which has demonstrated a highly significant correlation between achievement of objective regression and acquisition of benefit. The method is now undergoing corroboration by a prospective study.
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INTRODUCTION

IN THE treatment of advanced solid tumours, it is rarely, if ever, realistic for its intention to be curative. The aim of palliation is to control the disease in order to make life as active and symptomless as possible with the least adverse effects from treatment. It is, therefore, understood that the patient's life expectancy will almost certainly be severely shortened by the illness and so evaluation of the effectiveness of treatment must pay special attention to the quality of remaining life.

Methods for the palliative treatment of cancer include direct antitumour treatments such as surgery, radiotherapy, endocrine treatment and cytotoxic chemotherapy in addition to purely symptomatic treatment such as with analgesics and antiemetics. A further useful approach in the palliation of metastatic bone disease is the use of bisphosphonates to inhibit the osteoclastic destruction of bone stimulated by paracrine factors from tumour cells.

The most contentious treatment in palliative care is the use of cytotoxic chemotherapy because of the potentially severe side-effects which may impair quality of life. While high toxicity can readily be accepted when cure is achievable, such as in acute lymphoblastic leukaemia or testicular teratoma, these effects can outweigh any therapeutic value when response frequencies are low and of short duration. For the present, most cancers for which chemotherapy is used can only be considered palliative in intent. These include carcinomas of the breast (except adjuvant use), lung, alimentary tract, ovary, uterine cervix, endometrium, head and neck, kidney and bladder, soft tissue sarcomas, brain tumours, melanoma and low-grade lymphomas.

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INTENTION OF TREATMENT

The intention of palliative chemotherapy will normally be to effect symptomatic relief through the achievement of tumour regression. Prolongation of life is not normally a primary objective, although this may be achieved in certain circumstances, for example, through the regression of lymphangitis carcinoma or liver metastases. A further intention of treatment may, on occasion, be to prevent or delay certain expected complications, an example being the reversal of early signs of brachial plexopathy in advanced breast cancer.

Sometimes there is a strong temptation to give cytotoxic treatment even when there is no realistic chance of a response to treatment. This may be initiated by the oncologist in an attempt to engender hope or to avoid giving bad news. Pressure to give

treatment may sometimes come from the patient or relatives, perhaps from perceived unreal expectations suggested by medical practitioners or the media.

Before chemotherapy is given, a clear statement in the patient's case records of the precise intention of treatment should be given so that all medical and nursing personnel involved are clear on this point. The note should also indicate precisely what information has been given to the patient and the family.

EVALUATING EFFECTIVENESS

The evaluation of palliative chemotherapy needs to weigh the benefits (symptom relief, objective response, improved activity, extended survival) against the costs (physical toxicity, psychological morbidity, social disruption, financial). It must also include a number of outcome judgements such as the acceptability of the treatment plan for the cancer and whether or not it was reasonable for a particular patient, the contribution of investigations and the adequacy of support services. This should facilitate a global assessment of the utility of treatment and lead to analyses of its predictability. Should benefit have been acquired, then its duration should be able to be calculated. This information can then be used for estimating patient benefit month costs which could then be used in the wider context of resource utilisation in health care systems.

Deciding what is an appropriate treatment plan for a specific cancer and for a particular patient is difficult and demands that the benefits expected should exceed unwanted effects by a worthwhile margin. A treatment plan which is in general acceptable for a given cancer, may not be so for an individual patient in whom other co-existing factors may influence appropriateness. These include activity status, which may be related to age, the co-existence of other diseases, the metastatic pattern, the function of the bone marrow, liver and kidneys, exposure to previous treatment and the expressed wishes of the patient.

Ideally, the decision on what is appropriate treatment and investigation for a cancer should be apparent from the medical literature, particularly clinical trials. However, for clinical trials to produce interpretable information, the patients are usually highly selected. The information gained should give a precise indication of the treatment's efficacy, but not necessarily how this should be incorporated effectively for use in general routine management. Decisions for individual patients, therefore, need additional information in which the medical literature is supplemented by collective clinical experience. An attempt to achieve this for cytotoxic chemotherapy has been published [1].

MEDICAL AUDIT

A danger of this approach is that setting standards which are not based on sound scientific information could be inappropriate. It is, therefore, essential that predetermined criteria of appropriateness are correlated with outcome. This can be achieved by the use of medical audit which is defined as the systematic critical analysis of medical activity, including procedures used for diagnosis and treatment, the use of resources and the resulting outcome for patients. If audit shows that the predetermined standards are not achieving the desired outcomes, changes need to be implemented, new standards set and audited again in a continual cycle aimed at improving medical care.

The audit process has been applied to the evaluation of palliative chemotherapy [2]. It entails the detailed scrutiny of case records and is dependent upon them being clearly written and interpretable. This is greatly facilitated if medical records are structured. Assessing the usefulness of treatment is done by awarding positive points for beneficial outcomes such as symptom relief and deducting points for adverse effects such as gastrointestinal toxicity. For symptom relief, positive points are awarded for chemotherapy provided the effect has not been confounded by the concomitant use of other symptomatic treatments or radiotherapy. For treatment to be deemed worthwhile, a positive score is needed. If there is no relief of symptoms and no objective response, treatment is not worthwhile. If symptoms are relieved and/or there is a response, treatment is only considered worthwhile if there is either no or only mild toxicity. If toxicity is severe, treatment is only considered to be worthwhile if the duration of benefit after stopping treatment is greater than the duration of treatment. For a toxic treatment, the duration of benefit starts from the end of treatment, but for a non-toxic treatment, duration is taken as the time elapsed from the start of treatment. Time is also deducted from the duration of benefit for time spent in hospital for treatment-related problems.

This method has been applied to the assessment of palliative chemotherapy in a series of patients with advanced breast cancer. The response frequency [3] to first-line chemotherapy was 38%, but only 16% on second-line treatment with no responses being seen on subsequent regimens. Using the above rules, treatment was deemed to be worthwhile for 34% of first-line regimens, 11% for second-line regimens with no benefit being seen with subsequent treatments. The duration of benefit, when it occurred, was approximately 6 months for either first- or second-line treatment. There was a strong correlation between objective response and worthwhileness. This is a reassuring finding as the relevance of objective response criteria to palliative treatment has sometimes been questioned.

The audit approach to the evaluation of palliative chemotherapy using the above method has been found to be reliable. However, it is based on a retrospective review of case records and the judgements have been made by medical and nursing personnel. In order to be sure that this method is relevant to patient care, it needs corroboration by a prospective study in which the views of the patients themselves are collected prospectively. Several reliable instruments now exist to measure quality of life and can be used in correlative exercises to establish the validity of the medical audit of chemotherapy as a meaningful method of establishing its effectiveness for patients.

Cost–benefit analyses in the treatment of advanced solid tumours are complex. They involve measurement of phenomena which are inherently unmeasurable and comparing those which are inherently incomparable. Nevertheless, they are of such importance to patients that they must be pursued and several recent developments in methods for quality of life evaluation give encouragement for this approach to be pursued.

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