Quality of life after cytotoxic chemotherapy: discussion paper[1]

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Introduction

Cytotoxic chemotherapy is the art of differential poisoning, the aim being to destroy the tumour before the drugs kill the patient. Unfortunately, it is still distressingly easy to get the balance wrong. Although some 40 different cytotoxic drugs are currently commercially available in the UK, all suffer from the same fundamental defect: an inability to distinguish between normal and malignant cells. Thus all dividing cells within the body are at risk and some degree of toxicity is inevitable. Almost all these drugs will cause some degree of bone marrow suppression and give rise to subjective symptoms of anorexia, nausea and vomiting. In addition, individual agents have specific toxicities which may well cause the patient distress, for example, alopecia (with doxorubicin, cyclophosphamide and others), and painful peripheral neuropathy (with the vinca alkaloids and cis-platinum).

Despite these disadvantages, there have been some notable successes following the use of cytotoxic drugs in malignant disease. Over the last twenty years, survival in acute lymphatic leukaemia in children has risen from virtually zero to well over 50% (Mauer & Simone 1976) and in the later stages of Hodgkin's disease, which was also previously incurable, ten-year survival figures are of the order of 75% (DeVita 1981). These cancers, however, account for less than 5% of all malignant disease and the great majority of our patients suffer from carcinomas and sarcomas, the solid tumours. In these conditions, once patients have developed local recurrence or metastatic disease after initial radiotherapy or surgery, only about 1% may be cured by intensive cytotoxic therapy (testicular teratomas being the major example). In patients with carcinoma of the ovary, carcinoma of the breast and small-cell cancer of the lung, survival times can be increased, but cure is virtually unknown. For a number of other carcinomas, including those of the gastrointestinal tract and head and neck, there is a relatively small (20 to 30%) chance of transient tumour shrinkage with drug treatment, but no evidence of improved survival. For most remaining cancers, including carcinomas of the bladder, uterus and kidney, cytotoxic drugs have virtually nothing to offer. Overall it has been estimated that, taking all advanced or inoperable cancers, only some 4% are potentially curable by cytotoxic drugs and less than 20% may expect prolongation of survival as a result of these agents (DeVita 1982)

Given the severe toxicities of many of the agents used, it is, therefore, important to assess the relative risks and benefits before embarking on treatment, particularly for those patients in whom cure or improved survival is unlikely. In order to do this as accurately as possible, some form of measurement of subjective parameters is necessary, as well as objective measurement of tumour shrinkage. This was recognized as long ago as 1948 when Karnofsky developed his ten-point rating scale (Karnofsky & Burchenal 1948) (Table 1). This has been criticized on the one hand for being too superficial in that it assesses only physical aspects of the patient's condition and is assessed by an observer (usually the physician) rather than the patient himself. On the other hand, the scale has been criticized as too complex and attempts have been made to simplify the number of categories from ten to five or four. By the mid 1970s, however, when the limitations of cytotoxic therapy, particularly in the solid tumours, were becoming recognized, the need for a more sensitive

Table 1. The Karnofsky scale (Karnofsky & Burchenal 1948)

Normal	10
Minor signs or symptoms	9
Normal activity with effort	8
Unable to continue normal activity but cares for self	7
Requires occasional assistance with personal needs	6
Disabled	5
Requires considerable assistance and medical care	4
Severely disabled and in hospital	3
Very sick: active support treatment necessary	2
Moribund	1

measure of subjective toxicity was apparent and since that time a number of systems have been devised and tested. What follows is a personal account of experience with two such methods.

LASA
Linear analogue self-assessment (LASA) is a standard form of psychological testing. The technique is as follows: in order to answer a given question, for example 'How tired do you feel today?', a 10 cm line is drawn and the ends of the line labelled with the extremes of the parameter being measured, thus 'Not at all' and 'Very tired indeed'. The patient is then asked to mark on the line where they fall between those two extremes. The distance along the line from one end to the patient's mark can then be measured and a score out of ten obtained. In 1975, in collaboration with Professor Baum, a twenty-five point linear analogue questionnaire was devised. This included ten aspects related to symptoms of disease and side effects of treatment (e.g. pain, nausea), five relating to psychological problems (e.g. anxiety, depression), five relating to physical aspects and five covering personal relationships. After an initial pilot study to test the reliability of the technique (Priestman & Baum 1976), the questionnaire was used to measure subjective effects of treatment in a prospectively randomized study comparing endocrine and cytotoxic therapy in women with advanced breast cancer.

The objective results of treatment have been reported previously (Priestman *et al.* 1978) as have the details of subjective evaluation (Baum *et al.* 1980). In summary, the patients receiving cytotoxic therapy experienced a far greater incidence of treatment-related side effects than those on hormonal treatment, but overall scored significantly better for general well-being. It was felt that this apparent paradox was explained by the difference in objective response between the two groups: 49% compared to 21% ($P < 0.02$), and that the toxicity of treatment experienced by the cytotoxic-treated patients was more than offset by the symptomatic relief they experienced as a result of objective tumour shrinkage. This view was reinforced by an analysis of the cytotoxic-treated patients, comparing responders with non-responders, where it was clear that if response was not apparent within 6–8 weeks of commencing therapy then side effects rapidly became intolerable. We concluded, therefore, that provided objective tumour regression was seen, even quite severe side effects such as persistent nausea and vomiting and alopecia were well-tolerated, but that if no response was apparent treatment toxicity soon became unbearable.

This observation has considerable relevance to patients undergoing adjuvant cytotoxic therapy. In this situation all clinical disease has been removed by primary surgery or irradiation and treatment is given because of the possible presence of micrometastases which might be destroyed by drug therapy. The patient has no definite measure of the success of treatment and, therefore, side effects are likely to become a major preoccupation. Two studies which have set out to measure the subjective impact of adjuvant chemotherapy would seem to confirm this view. Palmer and his colleagues (1980) at the Royal Marsden Hospital used a detailed questionnaire to assess subjective toxicity and found that 79% of patients receiving combination cytotoxic therapy found treatment interfered with their

lifestyle and of these 29% found treatment unbearable. In Manchester, Maguire *et al.* (1980) used present-state interviews to assess psychiatric morbidity and found an overall incidence of 81% for problems such as anxiety, depression and sexual problems in women receiving chemotherapy compared to 50% in those who underwent mastectomy alone.

EORTC questionnaire
In 1979 the European Organization for Research and Treatment of Cancer (EORTC) formed a Study Group to look at the evaluation of quality of life in cancer patients. Following initial discussions within the Group, Dutch psychologists, led by Dr Fritz van Dam at the Antoni von Leuvenhoekhuis, prepared a preliminary questionnaire for evaluation in clinical trials. This comprised some thirty-five questions: twelve related purely to physical performance and were simply answered yes or no; ten related to mood but were phrased positively (e.g. 'Yesterday I had the feeling things were going my way') and the patient had to answer from one of seven options ranging from 'Very much so' to 'Not at all'; eleven questions again related to mood but were negatively phrased (e.g. 'Yesterday I felt depressed') and the patient chose from six options; finally there were two global questions relating to overall well-being with six and seven options for reply respectively.

We have recently used this questionnaire as part of an evaluation of high-dose medroxyprogesterone acetate (MPA) therapy in women with advanced breast cancer (Johnson *et al.* 1983). One reason for being particularly anxious to monitor subjective response in this series was that previous reports had suggested that the increase in appetite, pain relief and improved performance status, resulting in an improved quality of life, were sometimes seen in the absence of objective tumour shrinkage.

Scores for subjective assessment were available for 5 patients who had an objective response and 12 with progressive disease. The final method of analysis for the subjective assessment questionnaires has yet to to be determined, but in our series sequential total scores for each patient were compared with the baseline, pre-treatment score, in order to ascertain whether, during MPA therapy, individual scores rose (indicating improved well-being) or fell (indicating a deterioration in quality of life). The mean change in scores with time for responders and treatment failures is shown in Figure 1. Overall the responders' scores rose above pre-treatment levels whilst on MPA, whilst those for non-responders fell. A repeated measures analysis of variance for the 5 responders and 10 non-responders who had completed data over the first eight weeks of treatment showed that the mean difference in score between the two groups was statistically significant ($P = 0.04$). There was a tendency for the scores to decline with time in both groups and an overall negative linear relationship between score and time was just significant in the responders ($P < 0.05$) but not in the non-responders ($0.10 < P > 0.05$). However, the heterogeneity of regression was also highly significant in both groups ($P < 0.01$, $P < 0.001$). There were marked fluctuations in scores for individuals, and Figure 2 charts an example of this. Here the patient's score reflected the progress not of her own disease, which steadily improved to complete remission, but the fluctuations of her husband's terminal illness.

Work has continued to define the optimum method for analysis of the subjective data, but these results suggest that the EORTC method may be an accurate measure of day-to-day quality of life in the individual, but that this does not necessarily correlate with the effects of treatment. Certainly there was no evidence from our survey to support the view that MPA has a euphoriant effect in those who fail to achieve an objective remission. Equally, however, there was no evidence that high MPA levels decreased the quality of life.

Conclusions
The two methods described, and in particular the linear analogue technique, give us accurate and sensitive tools for measuring subjective toxicity. They also provide a basis for relating this toxicity to the more global concept of quality of life, though it must be conceded that this is an area where further refinement is needed.
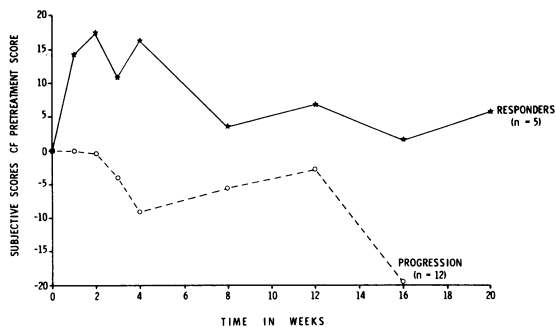
Figure 1. Change in subjective scores during high-dose MPA therapy for responders and patients with progressive disease
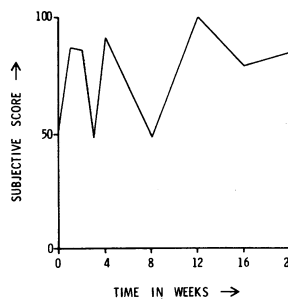

Figure 2. Changes in subjective score during high-dose MPA therapy for Mrs MB

I do feel, however, that we have now reached a stage where these systems should be incorporated in all new cytotoxic drug evaluations and comparative trials of different agents in order to document accurately the subjective impact of therapy, and thus define more critically the real place for cancer chemotherapy which at present is almost certainly used far too often in completely inappropriate situations where the only results are enormous expense to the Health Service and extreme distress to the patient.

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