general population. It is reasonable, therefore, that these children should be tested in some way, but clearly the standard clinical tests are contraindicated. We suggest that all infants with a family history of osteogenesis imperfecta or with suggestive clinical signs, such as unusually blue sclerae or large fontanelles, should be tested by other methods. The recent improvements in ultrasound screening mean that this is probably the method of choice at present.¹⁰

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Current Issues in Cancer

Quality of life: philosophical question or clinical reality?

Maurice L Slevin

This is the thirteenth in a series of articles examining recent developments in cancer

Quality of life is the new catch phrase in cancer medicine. Like happiness it is one of those terms that we all understand but for which adequate definitions do not exist. The focus on quality of life for cancer patients has come with the realisation that while dramatic improvements have taken place in the treatment of the less common cancers, and while adjuvant chemotherapy has improved the cure rate for several common cancers when diagnosed and treated in the early stages, most advanced common cancers remain incurable. In these circumstances treatment is given with the intention of providing maximum prolongation of good quality life. This, however, is not always a simple task as the treatment required for the cancer is often associated with side effects which can impair quality of life.

Cancer and its treatment often create havoc and chaos in the lives of patients and their families while other diseases such as ischaemic heart disease, which are a greater cause of death in the population, do not invoke the same degree of panic. Patients with metastatic cancer often have only minor symptoms and have to cope with the realisation that something has been growing inside them without their knowledge and while they were feeling well. This lack of symptoms may paradoxically make the illness seem more frightening and less controllable. In addition, the cause of the illness cannot usually be explained, the description of the disease is likely to be complex and confusing, and it is apparent that even the experts do not have all the answers. Furthermore, people are often told "there is nothing we can do for you," and this error is often compounded by an inaccurate prediction such as "you have six months or a year to live." It is therefore not surprising that patients with cancer often feel more miserable and despondent than patients with other potentially fatal illnesses and that quality of life is a much bigger issue in cancer than it is in other equally life threatening diseases.

It is now generally agreed that quality of life should be measured as an integral component of most cancer trials, particularly where treatments are given with palliative intent.¹ However, this is easier said than done. Time is short in busy cancer clinics, and with increasing emphasis on trials including large numbers of patients carried out mainly in district general hospitals the logistics are formidable.

In practice quality of life data can usually be

collected in only a subset of patients within a trial and particularly in those centres where specialist nurses are available. Provided randomisation takes place within each centre this should not introduce significant bias.

Which instruments should we use?

A vast array of quality of life questionnaires is currently on offer. Maguire and Selby carried out an excellent review of available measures on behalf of the Medical Research Council Cancer Therapy Committee.² They assessed several instruments looking at clinical utility, ease of administration, and scoring and also reliability and validity. They concluded that the best current method for assessing the key dimensions of quality of life was the Rotterdam symptom checklist.³ The hospital anxiety depression scale⁴ was also particularly useful for assessing anxiety and depression.

The Rotterdam symptom checklist comprises 30 items, each rated on a 4 point scale measuring physical and psychological dimensions of quality of life. It is easy to score and can be divided into different subsets. There are two main subscales, one for physical complaints and one for psychological issues. It has been suggested that this scale does not adequately cover sexual or social dimensions of quality of life and additional physical items have been proposed for use with specific groups of cancer patients.

The hospital anxiety and depression scale was specifically designed to measure anxiety and depression in patients who were physically ill and therefore excluded somatic symptoms of depression, such as weight loss and constipation, which might also be related to the illness. It is a self rating scale and has two subscales for anxiety and depression. Its validity has been confirmed in several studies. It has the advantage of being short and easy to understand and having a simple scoring system. A score of 7 or less implies normality, 8 or 10 is borderline, and 11 or more suggests significant anxiety or depression.

These two scales thus represent the most practical and reliable measures for assessing the quality of life at this time. The European Organisation for Research and Treatment in Cancer questionnaire,⁵ which is currently in the final stages of development and validation, offers the possibility of a scale which is easy to score and is designed to measure key dimensions

Imperial Cancer Research Fund, Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE
Maurice L Slevin, consultant physician

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Dr G M Mead.

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including symptoms of disease, side effects of treatments, physical functioning, psychological distress, social interaction, sexuality, body image, and satisfaction of medical care. This scale will also have modules to make it specifically applicable to individual cancers.

The questions of validity and reliability should be left to the appropriate experts. What is clear is that any form that takes more than a few minutes to fill out will in practice not be completed on a regular basis, and any questionnaire which is difficult to score will not prove feasible. The questionnaires must also be completed by the patients as doctors and nurses are notoriously unreliable at estimating patients' quality of life: assessments on the same patients vary greatly among different doctors and nurses.⁶

The incorporation of quality of life measures in clinical studies is fortunately receiving a higher priority and often provides information which would be unobtainable by other means. The overall balance of benefit versus toxicity, especially where the treatment is given with palliative intent can be obtained only by careful documentation of quality of life. Despite the limitations of the current instruments their use has already provided fascinating and often non-intuitive information in clinical trials.

Surgical patients

An evaluation of quality of life and functional results after surgery for gastric cancer showed clear evidence of the superiority of total gastrectomy or distal gastrectomy over proximal gastric resection.⁷ This goes against the conventional wisdom that total gastrectomy is associated with greater morbidity than partial gastrectomy, which has meant that total gastrectomy was often not used despite its advantages in achieving adequate safety margins. As a result of this trial the authors concluded that proximal gastric resection gave inferior quality of life to total gastrectomy and the last technique should therefore be preferred.

Several studies have compared quality of life after mastectomy with that after breast conserving treatment for carcinoma of the breast. A review of these studies found no solid proof of more favourable psychological adjustment after breast conserving treatment, indicating that these women need as much counselling support as patients who have mastectomy.⁸ However, several studies reported better body image and sexual functioning after breast conserving treatment.⁹⁻¹² The assumed disadvantage of breast conserving treatment, that women would experience a greater fear of recurrence, was not evident in these studies. In fact, this fear seemed more intense after mastectomy. These studies have been extremely helpful in enabling doctors to guide patients as to the likely psychological effects of either procedure and to focus support where it is most needed.

Chemotherapy: striking a balance

Quality of life evaluations have similarly helped our understanding of the effect of chemotherapy on patients' lives. A particularly difficult subject is the use of adjuvant chemotherapy in premenopausal patients with breast cancer. The problem with adjuvant therapy is that all patients are exposed to significant side effects for benefit in only a proportion of the patients.

A recent study looked at a large randomised trial comparing a single cycle of preoperative adjuvant chemotherapy with six cycles of conventionally timed chemotherapy.¹³ The quality of life would be expected to be significantly worse with the longer, more intensive chemotherapy but at five year follow up the

patients who had received the longer therapy had better five year survival than those who received a single preoperative cycle. The quality of life was evaluated by using Q-twist, which looks at the quality adjusted time without symptoms. Despite the greater initial toxicity with the more intensive and longer chemotherapy these patients had a longer freedom from disease and less time with the problems of recurrent disease and its treatment. There was thus an improvement in both quantity and quality of life for patients who received the more intensive therapy. With longer follow up this difference would be likely to increase.

One of the earliest studies looking at the effect of treatment on quality of life in advanced breast cancer was carried out by Priestman and Baum in the mid-1970s.¹⁴ This study used linear analogue self assessment scales to compare subjective responses in a trial of patients with advanced breast cancer randomised to endocrine or cytotoxic treatment. The higher response rate in patients receiving cytotoxic chemotherapy correlated with a better overall quality of life than that found in patients receiving endocrine therapy despite the higher incidence of side effects with cytotoxic chemotherapy.

Another trial in advanced breast cancer was conducted by the Australian/New Zealand breast cancer trial group, which randomised patients to receive either continuous or intermittent combination chemotherapy.¹⁵ In the patients receiving intermittent therapy treatment was stopped after three cycles if the disease did not progress. If the disease later progressed the treatment was given for a further three cycles.

Chemotherapy and quality of life

- More effective therapy is usually associated with better quality of life
- More intensive treatment is therefore not always associated with lower quality of life
- Side effects may be less important than control of disease
- Patients may report improved quality of life despite showing no objective response. This could be related to
 - minimal tumour shrinkage giving relief of symptoms
 - increased medical attention
 - provision of hope

The other arm of the study received continuous chemotherapy. The results of this study were counter-intuitive. Overall quality of life, response to treatment, and time to ultimate treatment failure all favoured continuous therapy. One possible explanation is that patients who were receiving intermittent chemotherapy had increased anxiety when they were not having treatment. However, the changes in quality of life were also found to be significant independent predictors of survival. This suggested that the quality of life reflected the state of the metastatic disease and that the increased side effects of chemotherapy were outweighed by the benefit the patients received from having better disease control.

In the early 1980s Gough *et al* looked at quality of life in a group of patients with advanced colorectal cancer who were treated with chemotherapy of relatively low toxicity.¹⁶ Although only a few patients achieved an objective response, most felt that they had benefited from chemotherapy. Several possible reasons for this benefit can be suggested, including placebo effect, provision of hope, or increased medical attention associated with being in a study.

A Scandinavian study looking at two regimens of chemotherapy in advanced symptomatic colorectal cancer provides further insight into the relation between disease control and quality of life.¹⁷ Only a few patients with advanced colorectal cancer respond and chemotherapy is given with palliative intent. The negative effect of chemotherapy on the majority of patients who did not respond might be expected to lead to an overall reduction in quality of life. In this study 22 patients were randomised to single agent 5-fluorouracil and 22 to 5-fluorouracil combined with methotrexate and leucovorin rescue. The response rate was greater with the more intensive chemotherapy. With the 5-fluorouracil alone one patient had a partial response and two had stable disease, whereas with the more intensive chemotherapy five had partial remissions and seven had prolonged stationary disease. The more intensive therapy was, however, also associated with more side effects. Despite the increased side effects 55% of patients given combined chemotherapy rated themselves as having improved quality of life compared with only 9% of the single agent group. The side effects of treatment influenced quality of life ratings negatively in only one patient. This suggests that the intensive chemotherapy was superior as palliative treatment in this study.

Advanced non-small cell lung cancer is particularly difficult to treat, being only moderately radiosensitive, and intensive chemotherapy including cisplatin gives a response in only 20-40% of patients with very minor effects on survival. A Norwegian study compared the quality of life in patients with non-small cell lung cancer randomised to receive either radiotherapy or chemotherapy.¹⁸ Quality of life decreased in the chemotherapy treated patients two weeks after starting treatment. However, after this there was a general improvement in the quality of life for both the chemotherapy and the radiotherapy groups despite the fact that the chemotherapy was repeated every third week for four cycles and that treatment related side effects did not decrease during the second, third, and fourth cycles of chemotherapy. This study again suggests that side effects were not the major determinants of quality of life. The overall improvement in quality of life in both groups, despite a response in only a minority, suggests that the benefits may be related to the optimism and support provided by close medical supervision.

Alternative medicine

Many patients with advanced cancers that are incurable with conventional treatment seek alternative methods of treatment. Practitioners of alternative medicine claim that the non-toxic natural therapies may result in cures and prolongation of life and undoubtedly give a better quality of life. A study from the United States compared a group of patients with advanced cancer treated by a conventional oncologist in a standard medical setting with a carefully matched group who were receiving conventional treatment as well as alternative therapy at a well known clinic.¹⁹ The alternative regimen included injections of BCG and a vaccine said to enhance the patients' natural immunity as well as a strict vegetarian diet and coffee enemas. The study was not randomised as patients who received the alternative therapy were self selecting. This is clearly a limitation of this study. The study found no difference in survival between the two groups but the quality of life scores were consistently better among patients treated with conventional therapy, despite the fact that a greater proportion of these patients had received chemotherapy with the attendant side effects. The patients who had selected themselves to receive alternative therapy may have had unknown

factors which contributed to their poorer quality of life, but the study suggests that the assumption that alternative therapies necessarily enhance the quality of life is not valid.

It is clear from these studies that many factors contribute towards quality of life in patients with cancer including quality of symptom control. Symptom control may be related to the effectiveness of therapy, social functioning, the degree of emotional support, and the extent to which the patient feels hopeful and optimistic. Maximum symptom control is the first priority in trying to improve quality of life. It is a nonsense to focus on emotional support when someone has uncontrollable pain or vomiting. One of the main arguments in favour of patients with advanced incurable cancer seeing cancer specialists is the availability of expertise in symptom control which may be lacking in non-specialist centres. It is also clear from the above quality of life studies that the control of the disease may be an important aspect of symptom control even when the effect of treatment on survival is minimal.

Cost versus benefit in cancer treatment

The provision of hope is one aspect that is rarely addressed by doctors, being more in the realm of philosophers than of the medical profession. However, a study asking patients with cancer, about to undergo chemotherapy, to balance the price they were prepared to pay in terms of side effects for a particular degree of benefit showed that most patients would accept toxic chemotherapy for minimal benefit in terms of survival or prolongation of life.²⁰ This result was not changed when the patients were given the questionnaire after receiving chemotherapy. This shows the extent to which many people require hope at almost any price. This is not an excuse for giving inappropriate toxic and expensive therapy to patients with little or no chance of benefit. However, it does emphasise that a part of the benefit patients obtain from palliative chemotherapy is the hope that treatment brings. It explains why patients enter trials of experimental therapy despite being told that the chances of benefit are small.

Similar results were found in a study looking at what improvement in survival would justify six months of adjuvant chemotherapy for breast cancer. Women who had received adjuvant chemotherapy were asked what improvement in survival would make such treatment worthwhile. Almost half of the women judged that a 1% improvement in five year survival would justify treatment. A 10% improvement in five year survival would be acceptable to 80% of the women who were treated. These women had all received cytotoxic adjuvant chemotherapy for their breast cancer and were therefore in a good position to evaluate the toxicity of treatment.

Emotional support

Emotional support is something which doctors may feel is more appropriately delegated to nurses, psychologists, or social workers. However, a study asking cancer patients from whom they most wanted and most got emotional support showed that their first choice was their doctor and that the more senior doctors were seen as being capable of giving more emotional support.²¹ Undoubtedly patients have much less time with the senior doctors than with more junior doctors and nurses and these data are therefore somewhat paradoxical. It must be concluded that patients get emotional support from receiving what they believe to be accurate and authoritative information. This is probably the single most important means of overcoming panic and restoring a sense of control

Good palliative treatment and counselling help improve quality of life

over a patient's life. However, information is not always positive and the quality of delivery of information may be important.²² It is almost always negative to tell people that they have a fixed life expectancy. The averages apply to populations and not to individuals and to give people a fixed life expectancy removes hope and provokes depression and despondency. It is more appropriate and helpful to indicate that while life might be very short if things go badly, the length of life could still be long and cannot be estimated if things go well.²³

Counselling patients with cancer

There is considerable evidence that counselling patients with cancer is helpful in relieving anxiety and depression and in improving fighting spirit and quality of life. Counselling need not be prolonged and indefinite as a recent study of adjuvant psychological therapy, using an average of six hours of counselling, has shown.²⁴ There is even a suggestion (as yet unconfirmed) from a randomised trial that group therapy for patients with cancer may improve survival.²⁵

Many patients with cancer undoubtedly experience severe psychological distress. Despite this the proportion of patients with cancer who accept counselling, even when it is available, remains low. Counselling is a routine part of the management of patients with HIV related diseases and it seems a pity that it is not incorporated as part of the standard package of treatment offered to patients with advanced cancer, especially those being treated with palliative intent.

Conclusions

Today we are in a better position to treat patients with palliative chemotherapy with minimisation of side effects than ever before. The use of effective modern single agents for palliative chemotherapy, which cause less side effects, together with symptom control with drugs such as ondansetron or granisetron, which reduce nausea and vomiting, allows doctors to offer

patients a chance of benefit with minimal cost and maintain a hopeful outlook. Quality of life studies comparing modern single agent therapy with combination chemotherapy in advanced cancers are now needed.

Research into quality of life cannot compete for the spotlight with treatment designed to improve survival, and indeed it would be inappropriate for it to do so. However, the current reality is that most advanced cancers are treated with palliative intent and quality of life issues are of primary concern. The quality of symptom control, the use of the least toxic effective chemotherapy, possibly going back to single agents in many cases, may significantly reduce the physical effects of cancer and its treatment. In addition doctors can contribute substantially to emotional support by understanding the patient's need for information thereby giving them back a sense of control while not removing all hope.

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