alkylator the concept of pharmacokinetically guided dosing, and is another important piece of evidence supporting the validity and the potential value of the basic pharmacodynamic assumption of PGDE.

In conclusion, the prospective evaluation of Cl-941 and a few other drugs is giving support and momentum to the concepts of PGDE, defining areas where refinements are needed, generating new ideas, and expanding the role of clinical drug monitoring in the development and the use of anticancer agents. The goal of faster, safer and more rational clinical development of new drugs in oncology is more realistic today than six years ago, and should be pursued as one of the greatest opportunities of experimental drug therapy.

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Assessing the Quality of Life of Patients in Cancer Clinical Trials: Common Problems and Common Sense Solutions

"THE ABILITY to simplify means to eliminate the unnecessary so that the necessary can speak."

Hans Hoffman

"Simplification makes action possible in the face of overwhelming complexity; it also increases the odds of being wrong."

Michael Patton

IN RECENT years there has been growing interest on the part of individual investigators, funding agencies and regulatory bodies in broadening the scope of evaluation parameters employed in clinical research in oncology to include assessment of the impact of the disease and treatment on the functional, psychological and social health of the individual. Such quality of life investigations have played a prominent role in recent prospective, randomised trials of breast conserving therapy in operable breast cancer [1], intermittent vs. continuous chemotherapy in advanced breast cancer [2], and limb-sparing procedures in soft-tissue sarcoma [3]. Yet, clinical trial-based quality of life investigations remain the exception rather than the rule. In the past, the major obstacle to carrying out such studies was the lack of consensus on how quality of life should be defined, and the absence of valid and reliable quality of life instruments. While it would be overly optimistic to suggest that these conceptual and measurement issues have been entirely resolved, a great deal of progress has been made in developing psychometrically robust questionnaires for assessing the quality of life of chronic disease patients, in general, and cancer patients, in particular [4].

Much less attention has been paid to the myriad of practical and logistical problems surrounding the collection of quality of life data in cancer clinical trials. Yet, it is such implementation issues that may currently represent the most significant barrier to successful quality of life studies [5]. The extent to which practical problems encountered in quality of life investigations can result in unacceptable levels of missing data and patient loss to follow-up has been illustrated in several recent clinical trials in metastatic lung cancer [6, 7] and prostate cancer [8]. In all three of these studies, where quality of life was a central

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evaluation parameter, a significant percentage of patients (ranging as high as 75%) failed to complete the requisite quality of life questionnaires at the established follow-up intervals. The rate of decline in completion of questionnaires over time can be so severe as to preclude analysis of the serial data [6].

Inadequate patient accrual and follow-up in quality of life studies can introduce serious bias at each stage of the clinical trial process; bias that may compromise the representativeness of the study sample and, in extreme cases, may render the quality of life results uninterpretable. The first source of bias can be found at the institutional level. In many large scale, multicentre clinical trials, quality of life assessment is an optional component of the research design. Often, the centres that are willing to undertake such investigations have academic affiliations or can otherwise be regarded as centres of 'research excellence'. Such centres may have patient populations that are quite different from the more typical regional hospitals that also contribute patients to the medical trial. Thus, one runs the risk of accruing patients onto quality of life studies who are not representative of the sample of patients participating in the medical trial as a whole, let alone of the larger patient population of interest.

In principle, once a centre has agreed to collect quality of life data within a clinical trial, it is expected that such data will be obtained from all patients accrued onto that trial. In practice, however, this is rarely the case. When queried, physicians most often attribute patient exclusion to administrative mistakes, hectic outpatient clinics, and other such external factors. However, one cannot help suspecting that some patients are excluded from quality of life investigations for more substantive reasons (e.g., concern that the introduction of a formal quality of life assessment will affect adversely the doctor–patient relationship). If such systematic selection takes place, the representativeness of the quality of life study sample is further compromised.

The final and perhaps most serious form of bias occurs when patients are lost to follow-up during the course of a trial. Frequently, as patients become more ill and symptomatic, they will experience some difficulty in completing a questionnaire or may be unwilling to do so. Yet it is precisely at the point in time when patients are experiencing heightened treatment toxicities or disease progression that we may be most interested in assessing changes in quality of life. Particularly in those randomised trials where the treatments being compared differ significantly in toxicity, differential loss of patients to follow-up can introduce serious bias in the analysis of the quality of life data.

Given the extent of problems reported in the literature in incorporating quality of life evaluations into cancer clinical trials, and the far-reaching implications that such problems can have for the integrity of these investigations, it is essential that guidelines be established for the planning and conduct of such studies in the future. To some extent, we can derive such guidelines by carefully scrutinising past efforts that have failed. Fortunately, however, we do not have to limit ourselves to the negative case. Several clinical investigations reported in recent issues of *The European Journal of Cancer* provide ample evidence that, with sensible planning and careful monitoring of data collection procedures, quality of life studies can be carried out with a high degree of success.

Van Holten-Verzantvoort and her colleagues reported on a prospective, randomised trial to assess the efficacy of supportive pamidronate treatment in reducing morbidity due to bone metastasis in patients with advanced breast cancer [9]. Quality of life was assessed every 3 months with a short (i.e., 17 item) questionnaire. Of the 167 patients accrued onto the medical trial, 144 (86%) participated in the quality of life investigation. Over the course of the study (median follow-up of approximately 18 months), 96% of the required questionnaires were returned to the trial office, of which 80% were evaluable.

Hürny and his colleagues report in the *European Journal of Cancer* on the interim results of two on-going randomised clinical trials of adjuvant treatment in operable breast cancer being carried out by the International Breast Cancer Study Group [10]. In both studies patients are asked, at intervals of 3 months, to complete a questionnaire assessing selective quality of life domains (e.g., coping, physical well-being, appetite), as well as a measure of psychological distress. The large majority (87%) of patients accrued onto the trial, to date, have completed the pretreatment questionnaire, and 72% have completed all questionnaires required through the first 9 months of the study.

The high compliance rates reported in these studies are all the more striking given the fact that they are multicentre in nature and, in the latter case, international in scope. All three studies are characterised by the use of short, simple quality of life measures, a relatively non-demanding data collection schedule, and the availability of specific individuals to coordinate and monitor the quality of life component of the research at both the central and institutional levels.

Drawing from the experiences, both positive and negative, of these and other researchers active in the field [5, 11–16], a number of common sense recommendations can be forwarded for maximising the participation of clinical investigators and patients alike in clinical trial-based quality of life investigations.

Formal review of the quality of life component of a clinical trial should be required as an integral part of the protocol review process. Introduction of quality of life studies as an 'afterthought' once a medical trial has been activated is only inviting disaster. Depending on the composition of the protocol review committee, it may or may not be desirable to seek advice from external reviewers specialised in this area of research.

Particularly for research groups with little or no prior experience with quality of life studies, sufficient time should be scheduled for establishing the scientific credibility and clinical relevance of quality of life investigations. Use of concrete examples from the research literature is perhaps the most effective way of winning over minds, if not hearts.

Substantial efforts should be devoted to assuring that the clinical investigators understand why quality of life parameters are to be included in a given clinical trial. How will the quality of life data contribute to answering the central research questions? How will the quality of life data be integrated with the more conventional clinical parameters? If convincing answers cannot be provided to these questions, perhaps it is time to rethink the study.

Quality of life investigations should preferably be a mandatory component of the clinical trial. If this is not possible, then it should be made clear to those centres agreeing to collect quality of life data that this should be done for all of their patients accrued onto the medical trial.

As suggested by the two quotations at the beginning of this paper, simplicity of methods and procedures may be the key to successful quality of life investigations. Simplicity should be reflected in the total number of quality of life assessments required over the course of a trial, as well as the time and effort required of patients per assessment. If you have the sinking feeling that the study design includes too few data collection points, then you are probably on the right track. At the same

time, by limiting the number of quality of life measurements, it is all the more essential that points of measurement be selected that will yield maximal information on the effect of the treatment and the natural history of the disease on patients' quality of life.

The collection of quality of life data should be planned around scheduled visits to the outpatient clinic. It is the rare hospital administrator, or patient for that matter, who will accept additional clinic appointments solely for the purpose of administering questionnaires. Use of alternatives to in-clinic data collection procedures should be considered, particularly during the follow-up period of a study. Mail or telephone-administered questionnaires can facilitate efficient data collection that is not dependent on clinic routine.

While it is advisable to consult an expert in measurement when selecting quality of life instruments, it is important that he or she has at least one foot in clinical reality. What looks good in a textbook may not work so well out on the ward (e.g., lengthy questionnaires to increase reliability, balanced positive/negative item wording to avoid acquiescent response sets, etc.).

There are a number of challenging statistical issues surrounding the analysis of quality of life data. These include the handling of longitudinal data (with missing data), and dealing with multiple endpoints. Technical support should be sought from a statistician trained specifically in social science statistical methods and capable of translating relatively sophisticated statistical matters into terms that are understandable to the average clinical researcher.

If this has not previously been done, the study measures should be pretested on the specific patient population of interest. This is particularly important in international trials, where cultural factors may weigh heavily in the choice of appropriate quality of life instruments. Patients should be asked to provide feedback regarding the form and content of the questionnaire. How long does it take for patients to complete the questionnaire? Is assistance required? Are there questions that are difficult to understand or are distressing? Are there important issues that are not covered by the questionnaire? Similarly, the study procedures should be pilot tested and tailored where necessary to the local situation.

Think ahead when determining acceptable levels of patient burden. As patients become more ill and symptomatic, they may be incapable of completing a questionnaire or may be unwilling to do so. It may be possible to lengthen the period that patients remain on-study by assuring that assistance is available for completing the questionnaires, or by administering them in the form of a brief interview.

If the patient population of interest suffers from serious cognitive impairment, or if it is expected that such impairment will develop over time (e.g. patients with brain tumours or brain metastases), consider employing proxy raters of the patients' quality of life (e.g. health care providers, family members) throughout the entire course of the trial. Such proxy ratings should be interpreted with the necessary caution. At best, they can only be viewed as an approximation of the patients' illness and treatment experience.

Consideration should be given to establishing separate decision rules for the clinical and quality of life components of the trial with regard to when a patient goes 'off-study'. Disease progression itself should not necessarily signal the end of the quality of life data collection. To the contrary, continued follow-up may yield a more balanced picture of the relative costs and benefits of treatment that differ in terms of both clinical efficacy and toxicity.

A key individual should be identified in each local setting who will take responsibility for monitoring the quality of life component of the clinical trial. This can be a physician, a nurse, or a data manager. It may be preferable to select someone who is not also responsible for coordinating the medical aspects of the study.

The trial investigators should be provided with regular updates regarding their compliance with the quality of life study requirements. In this way, local problems can be identified and hopefully resolved in a timely manner. Periodic reporting of interim results of the quality of life investigation can also serve as an important source of reinforcement for continued participation in the study.

In relation to the other costs involved in carrying out clinical trials, the budget required for quality of life investigations is usually quite modest. Nevertheless, it is important to keep in mind that you get what you pay for. The level of financial support provided to establish the research infrastructure for a quality of life study should be commensurate with the demands placed on the participating institutions and their professional staff.

Following most or even all of these recommendations cannot, of course, guarantee the success of a quality of life study. Much still depends on the willingness of individual clinical investigators to involve themselves in an area of research with which they may have little experience or formal training. Conversely, social scientists need to familiarise themselves with the substantive research questions of importance to clinicians and to develop a greater sensitivity to the very real practical constraints operating within clinical trial settings.

Such collaborative efforts hold tremendous promise for deepening our understanding of the relationship between disease as a biologic process and illness as a personal and social phenomenon. The yield from quality of life studies can contribute significantly to our common goal of developing evaluative models that reflect an optimal balance between quantitative and qualitative definitions of therapeutic success.

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Papers

The Activity of Single-agent Carboplatin in Advanced Seminoma

A. Horwich, D.P. Dearnaley, R. A'Hern, M. Mason, G. Thomas, G. Jay and J. Nicholls

Between 1982 and 1990, 70 patients with advanced metastatic seminoma were treated with 4–6 courses of single-agent carboplatin (SAC) administered at 400 mg/m^2 every 3–4 weeks. Treatment was of low toxicity and no patients suffered neurotoxicity, ototoxicity or significant renal damage. There was only one episode of neutropenic sepsis and no thrombocytopenic bleeding. The median follow-up of surviving patients was 3 years. 16 patients have relapsed and 4 of these 16 have died, thus the actuarial 3-year relapse-free survival was 77% (95% CI 65–86%), cause-specific survival was 94% (95% CI 82–99%) and overall survival was 91% (95% CI 80–96%). The risk of relapse was reduced by post-chemotherapy irradiation (PCRT) to involved nodes, occurring in 1/20 patients treated with PCRT compared with 11/31 who could have been treated but were not ($P = 0.04$). Of the 16 patients who relapsed, 12(75%) have been salvaged with combination chemotherapy and remain free from further relapse with a median follow-up of 18 months. Though this level of survival is equivalent to that obtained with initial cisplatin-based combination chemotherapy, the recurrence rate indicates that SAC remains an investigative treatment, except for unfit patients.
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INTRODUCTION

METASTATIC SEMINOMA is exquisitely sensitive to platinum-based chemotherapy regimens [1, 2]. There is little controversy over the use of chemotherapy for patients with stage III or IV seminoma or for stage II seminoma with abdominal node mass greater than 10 cm in diameter. However, for smaller volume stage II disease, the results of a relatively short course of retroperitoneal radiotherapy are very good [3]. A retrospective study at the Royal Marsden Hospital (RMH) demonstrated an increased recurrence rate after radiotherapy for retroperitoneal node masses more than 5 cm in diameter [4] and we have thus used initial combination chemotherapy in the management of patients with RMH stage IIC, III and IV tumours as well as for primary mediastinal seminomas (Table 1).

Our early experience of 34 patients with advanced metastatic seminoma treated with single-agent carboplatin suggested that this formed an effective and non-toxic treatment [5]. We have now extended this experience to a total of 70 patients treated between 1982 and 1990, and have analysed the impact of post-chemotherapy irradiation.

Patients and methods

Patients referred to the Testicular Tumour Unit at the Royal Marsden Hospital between 1982 and 1990 with a diagnosis of

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