Pergamon

European Journal of Cancer, Vol. 33, Suppl. 2, pp. S11–S13, 1997

Printed in Great Britain
0959–8049/97 $17.00+0.00

PII: S0959-8049(96)00448-0

The Need for Endpoints in Anticancer Drug Trials that will Simplify the Clinical Decision-making Process

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The endpoints relating to antitumour effect which are commonly used are limited in that they give no information about the effect of the treatment on the person with cancer. This is particularly important in those many situations where cure is not a viable option. The use of quality of life as an endpoint may help to overcome this problem, but limitations remain. New endpoints, which simplify the clinical decision-making process in terms of the potential impact of treatment on the individual patient, are now needed. A variety of factors must be considered when evaluating the efficacy of an anticancer agent, including such issues as whether the drug is easy to use. Despite the complications this will present, in terms of the planning and implementing of clinical trials, the long-term benefits to patients and healthcare professionals would fully justify the investment of time and multidisciplinary expertise involved. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: endpoints, clinical trials, clinical decision making
Eur J Cancer, Vol. 33, Suppl. 2, pp. S11–S13, 1997

INTRODUCTION

THE ANTICANCER DRUGS available to oncologists today are not very sophisticated in their actions. A powerful analogy may be drawn between the use of an anticancer drug to kill cancer cells and the use of a bomb to kill someone in the middle of a crowd: just as a bomb kills and maims innocent bystanders, anticancer drugs kill and maim normal cells. The results of this are well-known and problematic side-effects, such as nausea and vomiting, alopecia and the risk of infection. Despite the many advances of recent years, such side-effects remain an important problem. As more agents become available to oncologists, so the clinical decision-making process becomes more complex.

In everyday oncological practice, the clinician must constantly weigh up the risks and benefits associated with the various anticancer agents to decide on the most appropriate agent to prescribe for a particular patient, given a particular set of circumstances. In the clinic, such decisions on intervention (what treatment to use, when to use it and for whom to use it), may be broken down into two separate questions: (1) What can be done for patients in this situation? and (2) What should be done for this patient?

The answers to these questions determine the 'right' treatment decision [1]. Clinicians have a critical need for relevant information to be able to supply these answers. A further key question therefore arises: do the endpoints used currently in drug trials provide oncologists with the knowledge necessary to make such an informed clinical decision? I contend that they provide only incomplete information, and this tends to obfuscate the decision-making process.

Table 1. *Endpoints relating to antitumour activity*

- Cure
- Duration of survival
- Tumour response
- Duration of remission

LIMITED NATURE OF CURRENTLY USED ENDPOINTS

The primary endpoints measured in trials today relate to a drug's antitumour effect (Table 1). Such information is clearly important, but these endpoints are limited in that they give no information about the effect of the treatment on the person with cancer. This is particularly important in those many situations in which cure is not a viable option.

An endpoint often examined, in an attempt to overcome this problem, is quality of life. Exciting work on this is being carried out by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Unit. Nonetheless, the methodological problems associated with the measurement of quality of life remain substantial [2, 3]. The concept remains poorly defined and is multidimensional in nature [2, 3]. The exact range of factors involved has yet to be clearly defined—indeed, there is little clear evidence that health *per se* has much direct impact on quality of life [3]. This creates a clear and fundamental problem when the impact of medical intervention is measured in these terms.

HETEROGENEITY OF THE PATIENT POPULATION

A variety of personal, social, economic and psychological factors must be considered in making the 'right' decision for a

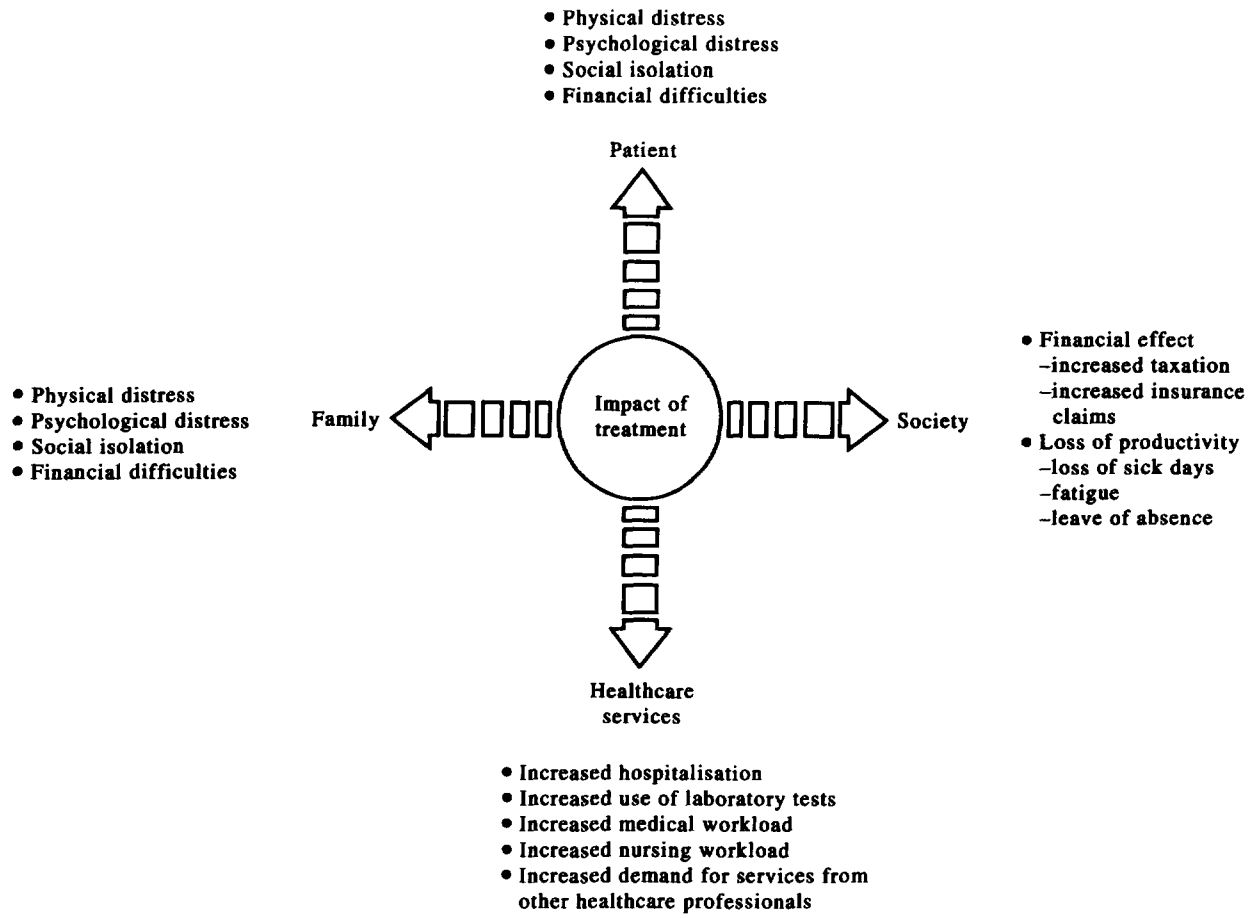

Figure 1. Factors affected by anticancer treatment.

given patient [1]. Yet, a major problem facing clinicians today is a relative lack of knowledge of the patient population. Even the most cursory examination makes it immediately apparent that the patient group is heterogeneous, including people with very different attitudes, values and beliefs about the benefits of cancer treatment. The importance of choosing cancer therapies on the basis of both objective measures of survival and patients' attitudes has been highlighted previously [4]. At one end of the scale is the patient who values life in the short term and is not willing to take the risk of treatment-induced mortality when weighed against the benefit of possible survival in the longer term. This situation may not be as uncommon as some doctors imagine [4]. At the other end of the same scale is the patient who wants treatment at all costs. There is then the broad spectrum of varied perspectives between the two ends of the scale. At present, very little data are available to describe this range of attitudes, and this is a further factor complicating the clinical decision-making process.

NEED TO MEASURE A BROAD RANGE OF FACTORS

Anticancer treatments impact on a variety of different factors which may be classified under four main headings (Figure 1):

- Factors affecting the patient.
- Factors affecting the family.
- Those affecting healthcare services.
- Those affecting society as a whole.

I believe that in order to reduce the complexity of the clinical decision-making process, trials should be measuring the impact of treatment (which is often negative) on these factors.

Negative impact on the patient

The impact of anticancer treatment on the patient is the most important parameter that should be measured. There are several overlapping aspects to this, beginning with physical distress (i.e. side-effects) and psychological stress, such as anxiety, depression or problems with body image. The measurement of the psychological impact of treatment is a problem in cancer research, as most of the instruments used to measure psychological symptoms are designed for the assessment of psychiatric patients, not for use with 'normal' people under the stress of cancer treatment [2].

Either physical or psychological stress, or both, may impact on patients' ability to interact with their social support network, thereby leading to social isolation, and it is known that the strength of social support is an important determinant of how a patient will cope with a cancer experience. Anticancer treatments may also create financial difficulties for patients as a result of hospital stays, the high cost of medication or loss of work. The appropriate measurement of costs incurred by the patient is a specific issue in the economic evaluation of cancer treatments [5].

Negative impact on the family

Cancer is not only a disease of the individual, it is a disease affecting the whole family, and there is an intimate link

between the way the patient copes with cancer and the way the family copes with it. Thus, families may experience negative impacts similar to those felt by the patient, including the financial impacts. It is important to recognise that the psychosocial stresses of coping with cancer in a family member may produce physical symptoms.

Negative impact on healthcare services

Perhaps the most significant effect of anticancer treatments on healthcare services is its impact on medical and nursing workload. Arguably, for example, two drugs might be equal in terms of efficacy, yet they may be different in terms of the complexity of their delivery, the monitoring for side-effects and the prevention and management of those side-effects. Information is needed that would enable identification of those agents that are simple to deliver and monitor, thereby giving doctors and nurses more time to spend on other, equally important, aspects of care.

Negative impact on society

Anticancer treatments have an important impact on society in terms of the financial demands they impose; loss of productivity is a key aspect of this issue. Economic evaluation is an area in which healthcare professionals will need to be proactive in the future. This is particularly true in the case of cancer, as the costs per case are usually high and the expected treatment benefits are still small for many patients [5]. In all countries, healthcare professionals are being increasingly called to account for the financial costs of treatment, and it is vital, therefore, that evidence is available to justify actions. Straightforward survival and clinical outcomes are integral to the question of how best to allocate resources for healthcare, but they are insufficient in themselves. Instead, the financial and other costs of the treatment in question must be compared with the broader benefits that the treatment offers [6]. In my view, it is critical that such economic evaluations of cancer care are performed by professionals with a broad insight into the complexity of the issues involved, not by auditors focusing on only a very limited aspect of costs.

CONCLUSION

I propose that new endpoints be developed for use in clinical trials, focusing particularly on:

- Patient and family well-being.
- Patient attitudes towards treatment.
- Economic cost.

By measuring endpoints in these areas, data more directly relevant to clinicians making treatment decisions will be gathered than is the case at present, thereby reducing the complexity of this decision-making process.

I fully acknowledge that such intended 'simplification' would, in fact, create considerable complications in terms of planning and implementing trials. Indeed, I regard the design of clinical trials to be one of the most difficult aspects of oncology today. Nonetheless, it is imperative that the search is immediately started for ways to determine both the quantitative and qualitative impacts of treatment within as many areas as possible. In particular, more information about the meaning of the cancer experience for patients and their relatives is needed to streamline the process of choosing an agent or agents to prescribe for any given patient in any given situation.

To achieve these aims, expertise from many different sources is required. Thus, the planning and implementation of clinical trials must be multidisciplinary, with physicians, nurses, psychologists and health economists all having a role. Major investment of time and resources will be required. However, the benefits accrued from this approach will be very significant. Healthcare professionals will benefit because they have the information that justifies their interventions to society at large, and because their day-to-day decisions are made easier. Patients will benefit because errors of judgement are less likely to occur.

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