Pergamon

European Journal of Cancer Vol. 33, No. 2, pp. 184–185, 1997

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

PII: S0959-8049(96)00476-5

Point of View

Ethical Issues in Cancer Clinical Trials: A European Perspective

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AS BIOMEDICAL research has changed over the past 30 years, the issue of ethics has grown in importance. Since the 1964 Declaration of Helsinki [1], the international scientific community has focused on ethics in medical research. Every area of biomedical research has its own ethical issues, but as clinical trials have expanded in size and complexity, often involving large numbers of patients, with the aim of rapidly developing new and more effective therapeutic approaches, ethical considerations are critical for several aspects from research design to protection of individual patient's confidentiality and rights.

Convincing, relevant and objectively analysed clinical trials are required to improve the quality of cancer clinical research. In many instances, only small differences in treatment outcome can be shown, but these are medically important because even a rather limited gain in survival becomes highly significant when later applied to all cancer patients, particularly for common cancers. Large-scale studies are necessary to reach such goals [2].

There is a large diversity of clinical trials with different and challenging end points linked to major public health issues; therefore, clinical cancer research requires a multidisciplinary approach and is particularly complex.

Because curative therapy has not been established for many tumour types, there is a need for high quality clinical research alongside routine cancer care to assess effectively new therapeutic proposals including investigational drugs or procedures. However, it is mandatory to establish the ethical basis for adopting such innovations in clinical care, just as there is a necessity for ethics in the design of clinical trials.

This is especially important for clinical cancer research as investigational designs and often highly toxic drugs are likely to expose patients to risk. The ratio of risk to benefit is a daily concern for the research co-ordinators and clinical investigators involved in cancer research. In a sense, the entire field of clinical cancer research can be seen as the continual effort to define the risk and the benefit of new treatments. Trial design seeks to ensure that ethical principles are embodied in all the procedures, and that the rights of trial subjects are protected, while at the same time providing reliable results without delay, with the goal of improved treatment for all cancer patients.

Launching and conducting clinical trials in Europe is a challenge due to the diversity of national laws among Member States. There are no "European" guidelines and procedures for ethical reviews of research protocols, which lead to an unnecessary duplication of ethics reviews between and within Member States, that adds little to the protection of patients. In addition, it delays study initiation as well as the dissemination of results, which can be detrimental to patients waiting for possible therapeutic improvement. These delays may also jeopardise the competitivity of European clinical research. The EORTC, in collaboration with the Ethics Working Party of EFGCP (European Forum on Good Clinical Practice), is attempting to draw the attention of the international community and policy makers by developing research projects to improve the working procedures and the ethical reviews of multinational clinical trials.

Too many ill conceived trials are running and in a number of instances poor data are published. EORTC protocols have the advantage of being peer reviewed and carefully evaluated by a panel of experts throughout the world. EORTC protocols are also submitted to local ethical reviews as required by current regulations and benefit from this double revision. In this respect, EORTC protocols ensure that research is performed in a totally independent way which has obvious ethical implications. Sponsorship and ownership of data are also issues in which ethicists should turn their attention [4, 5].

SPECIFIC ETHICAL PROBLEMS IN CANCER CLINICAL TRIALS

In addition to the ethical principle that each patient participating in a trial must be respected, the clinical research teams must consider the larger community of patients waiting for a possible cure or at least a better and longer survival time.

During the last decade, dramatic changes in the relationship between physicians and their patients have occurred. The reasons have already been analysed [6]. Today, thanks to new screening and diagnostic technologies, doctors often

Received 8 Nov. 1996; accepted 18 Nov. 1996.

know that patients are diseased before patients experience any symptoms of their disease. Consequently, the whole relationship has, to some extent, changed from a traditional patient–doctor relationship to that closer to an opinion seeker and advisor. This situation is especially true when a life-threatening disease such as cancer is involved.

Treatments are often either toxic or mutilating. Sometimes, they are temporarily more harmful than the disease itself, with the ultimate goal of improving the patient status and controlling the evolution of the disease. It is easy to understand that, for patients in the short term, this can be hard to accept, but usually patients agree with the statement that new effective and safe therapeutic approaches are needed. Different treatment options or alternatives are proposed to patients in a clinical cancer trial which increases the level of complexity of their decision.

As a consequence, it is most often relatively easy to convince a patient with very advanced disease to enter a phase I study because the patient is experiencing symptoms and is seeking help, and is, therefore, in a classical patient–physician relationship. The situation is obviously different when a physician is proposing surgery, radiotherapy or chemotherapy to a patient with early stage disease. The informed consent process should take these issues into account. There is a major need to improve the awareness of patients and the public about clinical research and the impact of participation in clinical trials.

ETHICS IN VARIOUS CANCER PROTOCOL DESIGNS

In diseases such as cancer, where many tumours have no curative therapy, a case can be made that participation in a clinical trial is the most ethical approach to helping the patient. This is true both from the standpoint of the individual patient and of society. Furthermore, the best protection for a patient is provided within the framework of a clinical trial with a careful design and consistent management. A large multicentre trial has the benefit of support from many experts in designing the protocol and takes into account all that is known about a specific cancer to that point in time. In a field of rapid change, such as oncology, this is already an advantage. It is a guarantee for the patient that he or she will receive the best therapeutic approach.

Conversely, performing a small size study with inadequate sample size to test difference in treatments is unethical, and there are still too many ill conceived trials in Europe.

Whereas once the concept of an experimental treatment was a desperate and almost serendipitous effort to try something to help a terminally ill patient, who was often unaware of being treated with an experimental agent, now the accepted chain of events of clinical cancer research has a wealth of information available from preclinical and animal studies.

Cancer patients participating in oncology phase I trials are those for whom there is no improvement expected with the currently available therapeutic strategies. Ethically, it is important not to expose patients unnecessarily to excessive toxicity, and it must also be considered that such patients may have experienced side-effects from previous administration of highly toxic drugs. At least, for an individual, psychological benefit should be obtained as a result of their participation in a phase I clinical cancer trial [7]. The major ethical issue in cancer phase II trials lies in unnecessarily exposing patients to ineffective therapies. Ethics are, therefore, embedded in statistical design in order to assure that the number of patients exposed to a therapy is scientifically sound. In phase II trials, designed to demonstrate a therapeutic benefit, the ethical issue is to choose appropriately the respective arms, the stratification criteria and the end point of the study.

It has been shown that patients in randomised controlled clinical trials do better than their counterparts who are not treated within clinical trials [8–10].

ETHICS AND INFORMED CONSENT IN ONCOLOGY CLINICAL RESEARCH

Within Europe, there are various levels of awareness and willingness of cancer patients to discuss these issues openly and many of them may not even be aware of their exact diagnosis and/or the related prognosis. Therefore, the informed consent procedures and contents have to be adapted to these geographical and cultural differences.

The informed consent form should never become an extra source of confusion or worry for the patients. It must not be misleading and thereby increase the risk of misunderstanding on the part of the patient [11].

CONCLUSION

All aspects and phases of cancer clinical trials should be designed and implemented ethically. Respecting ethics while conducting clinical cancer trials requires commitment, expertise and time from all professionals involved in the process [12]. It is important that clinical cancer trials should be done for the right reasons, addressing key end points for major public health issues such as survival, quality of life, health economics and prevention.

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