Pergamon

European Journal of Cancer Vol. 30A, No. 7, pp. 897–899, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00+0.00

0959-8049(94)E0072-C

Comments and Critique

Is Informed Consent Essential for all Chemotherapy Studies?

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AMONG THE many problems facing clinical oncologists who are dissatisfied with current treatment, the ethical and moral difficulties relating to the introduction of any novel approach raise fundamental issues [1]. The conflict between compassionate but impartial care for the individual, coupled with the natural desire of all clinical oncologists to move the field forward, has attracted increased attention and seems certain to remain contentious for the foreseeable future [2, 3]. Over the past decade or so, the move towards fully informed consent for all participants in cancer studies has become increasingly difficult to resist and is now codified in various guidelines [4]. In our view, this may well result from social changes during this same period, with an increasing emphasis on the strongly voiced argument that each individual's autonomy and right to self-determination must be respected in all areas of life.

Fully informed consent to all medical procedures is an obvious consequence of such a shift in opinion, yet neither lawyers, ethicists nor medical scientists have, to date, agreed precisely what this term actually means. It is generally held to imply a full declaration of the competing treatment options to any patient who has been invited to become a participant in a clinical study, and as a result is of particular relevance to randomised controlled clinical trials. Together with the full description of treatments, there should be an explanation of the possible side-effects of both new and standard therapies. It is also widely assumed that whenever the study is controlled by random allocation, this fact should always be made clear to the patient. Inherent in such an explanation is, of course, the additional implication that the patient will also be made aware of the shortcomings of current treatment, and the essential need for research in order to improve our results.

Patients who undergo treatment within a clinical trial will usually be given a far higher level of information than those who are not, leading to an intolerable ethical position, the 'double standard' [5], by which clinical trialists feel constrained and frustrated in their attempts to improve knowledge, constantly looking over their shoulder at other medical staff, sometimes practising in the same institution, who define their current policies without admitting to current uncertainties.

How full an explanation can reasonably be regarded as sufficient to help the patient to become 'informed'? From the culture of 'doctor knows best', we moved in the 1970s towards a directly opposed dictum 'the patient must make the decision' which might be paraphrased 'the doctor shouldn't be trusted'. Increasing openness, media concern and a gathering army of hungry lawyers provide a cynical but in our view broadly accurate explanation for this altered view, rather than a genuine change of heart within the medical profession. For the most part, we have grudgingly accepted 'informed consent' as an unwelcome but necessary accompaniment to our continued clinical research. Little emphasis has been placed on the patient's responsibilities as a result of the change.

If we are to continue to make progress in clinical research with the aim of providing the very best quality care, patients will need to take their place in the new shared decision-making environment. Playing a major role in this process has significant consequences for them too. Once information has been imparted, it cannot be withdrawn; it will be too late for the patient to decide that faced with unwelcome knowledge, he would have preferred not to have been made aware of the likely prognosis. Facing the dilemmas that doctors continually face about the inadequacies of current treatments does not add to a patient's quality of life at a time of deep psychological trauma. Failure of treatment may also be accompanied by feelings of personal sorrow at having made the 'wrong' decision. Paradoxically, the patient now in need of treatment is of course benefiting from the generosity of previous generations of patients who participated in studies which now guide our practice every day. An excellent example would be the wide acceptance that few patients with breast cancer require mastectomy, a dramatic change of view largely driven by a convincing large-scale randomised study from the U.S.A. [6]. Because of problems relating to informed consent, similar studies proved impossible to complete in the U.K. [7].

Doctors who engage in clinical trials often feel frustrated that others have imposed a set of guidelines as to what the patient must be told, but which appear to bear little relationship to what we ourselves judge to be necessary. Ethics committees, though well intentioned and generally sympathetic, may come to quite different views as to what is acceptable, so that multicentre randomised studies which have contributed so much to patient care may be regarded as acceptable in one district, but ethically

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Received 6 Jan. 1994; accepted 9 Feb. 1994.

inadmissible a few miles away in a neighbouring district. Despite years of discussion about a national ethics committee in the U.K., the idea has got precisely nowhere.

Who needs informed consent? In our view there are four broad categories of trial, or study, in which new treatments need to be tested.

1. *Unrandomised study of a promising new agent*

This is the early introduction of a new agent within phase I or II trials; the patient is likely to have recurrent disease and is no longer suitable for conventional active treatment. It is clear that such studies do not have therapeutic intent as their major aim, although a worthwhile clinical response is sometimes achieved.

2. *Randomised study of 'new' versus 'established' treatment*

These studies typically have an obvious distinction between the two study arms, e.g. introduction of chemotherapy for the first time in a solid tumour previously treated by other means (generally surgery or radiotherapy). A good example would be the use of chemotherapy for non-small cell lung cancer, high-grade brain tumours or colorectal cancer.

3. *Highly refined studies investigating a technical difference between the two arms of treatment*

These are concerned with more sophisticated aspects of chemotherapy or other treatment, in tumour sites where such treatment (generally complex) is well established, e.g. primary bone tumours or acute leukaemia, in which the question posed might relate to a three- versus six-drug regimen, or to aspects of timing of one or more agents in relation to other components of the primary therapy.

4. *Trials of supportive care*

These might include, for example, randomised studies of antibiotic prophylaxis during periods of predictable neutropenia following intensive chemotherapy.

In group 1, there is rarely an ethical difficulty. Clearly the agent in question is not normally part of standard treatment, and none would dispute the need to explain this to the patient. There are no established treatment alternatives, the patient cannot be expected to gain from participation, and may have to face the possibility of side effects which could be severe. This point would be emphasised by all doctors involved in such trials. However, the altruism of patients in wishing to benefit future generations who will suffer from similar diseases must not be underestimated, and should encourage doctors to discuss these issues openly. As a result some patients will refuse, but some will agree; a body of response data soon builds up, the new cytotoxic agent may eventually find a role and the patient's desire to give either informed refusal or informed consent will have been respected.

The other types of study are not so easy. Group 2, for example, includes the vast bulk of current adjuvant chemotherapy studies in which a relatively new form of treatment is randomly offered to half the patients — adjuvant chemotherapy in brain tumours, head and neck squamous carcinomas, non-small cell lung, cervix and colorectal cancers are all currently under study in this way. Typically, the drugs employed are well established rather than novel, but have yet to be proven as unequivocally beneficial for the particular site in question or at the early ('adjuvant') stage of treatment. All the patients in such studies are treated to the highest conventional standards (itself a benefit of being a participant in a controlled clinical trial, of course), but half also receive a new treatment. The convention nowadays is that all patients, in both arms of the study, should be 'fully informed', and many brave souls will know just how difficult this can be. With our lengthy explanations, we inevitably introduce additional levels of anxiety on top of the already considerable pressure of facing the diagnosis and recognising the uncertainity of the future [8]. As most of us know all too well, the sense of shock and isolation may last many months for patients who have just been diagnosed.

Presenting *randomised* treatment options poses particular difficulty. First, one has to explain, to all patients of a defined therapeutic group, the potential advantages and disadvantages of the new treatment (generally chemotherapy at the present time) although only half will eventually receive it. The discussion is, in a technical sense, quite unnecessary for half the patients, a waste of their time and the doctor's, and an additional burden to all. Patients being treated for exactly the same condition in the clinic next door are not informed in this way as the non-trialist physician (who presumably chooses not to participate because he knows the answer) has no obligation so to do. Secondly, patients informed about potential benefits of chemotherapy, but then randomised to the control group, often feel 'let down', and far less confident that they are geniunely receiving the highest standard of care which they have every right to expect. Thirdly, it is often difficult for the doctor to reassure such patients that the 'new' treatment truly remains unproven; one finds oneself furiously back-pedalling about the possible advantages (those same potential benefits one had been 'selling' shortly beforehand), probably stressing the side-effects of treatment a little more! One does this of course, in an attempt to support the patient and re-establish a doctor–patient relationship which is now under considerable strain. There is a subconscious and often poorly perceived assumption that 'new' must equate with 'better', not only by the patient but also on the part of the medical profession, despite the lessons of history.

In many situations it would be far better to follow the Zelen recommendation [9] and regard the control group as essentially receiving conventional treatment (and therefore needing no additional explanation). We fully recognise that the 'treatment' group should be treated differently, and at the very least, informed that their treatment will, with their consent, include a promising but as yet unproven departure from the currently accepted standard of care.

Pre-randomisation, i.e. randomisation before consent, is an inevitable part of this approach, and we would certainly defend its use: ethical, because it protects patients who may not wish to participate in a trial of unproven treatment which could have side-effects, yet also of help to those who, arguably, do not 'need' to know that they are participating in a study at all. Paternalistic? Yes, a little — and a good thing too.

We are not suggesting that a single method should be employed. Part of the skill required of doctors is that they learn to provide information at the level required by individual patients [10, 11]. These skills need to be extended to the decision-making process. It will be immediately obvious that no less than full disclosure will be appropriate for some patients, whilst many others would prefer the decision to be made on their behalf by the doctor. A group in the middle will value a discussion as to the amount of involvement they would like to have regarding their management. Unfortunately very little research has been carried out in this area to help us determine whether it is possible to elicit what individual patients would really like to receive. We know that giving information is of

positive value [12], but should it be expected (or regarded as desirable) that as a result of this process the patient be solely responsible for arriving at a treatment decision? Since this question applies both within and without research protocols, the currently accepted informed consent process could be seen to be a somewhat pathetic and superficial response to the dilemma.

In the third group, there may be even stronger reasons for avoiding full discussion of the treatment options. The differences on offer are likely to be relatively minor, yet the anxiety engendered by the discussion considerable. Patients in fear of their lives do not, for the most part, want or need to know that treatment regimens, while sometimes effective, are by no means fully established, and may be unsuccessful despite the harrowing side-effects; they are often just embarking on a lengthy course of treatment, and uncertainties of outcome, although often understood by all parties at this early stage, are possibly better left unexplored. It is in this group, perhaps, where the doctor should reveal as much or as little about the trial details as he/she feels appropriate — rather than being bound by an 'ethical' imperative which insists on full and total disclosure for all. This point has been recently argued by Souhami and one of us (JST), and recognises the needless cruelty that uniform insistence on fully informed consent can impose upon many of our vulnerable patients [11].

The same general principles apply in the fourth group. Do patients really need to know that a formal randomised comparison is being made between one group of antibiotics and another, and that they are expected to agree to random allocation? These very same patients may well, of course, have been through one (or more) random allocations already! How many random choices can we reasonably expect patients to take on board, understand, and calmly accept? Not long ago, in one of the shabbiest episodes in British medical journalism, an outstanding and innovative medical scientist was pilloried by the press after disclosure that, in a study attempting to assess the value of breast cancer counselling, half the patients had not received it and had not therefore known that it was available [13]. At the time of the study, not only had it not been unequivocally proven to be beneficial, it was only made available because the the clinical researcher had raised private funding for its provision! Expensive services such as this should always be properly evaluated before becoming the new standard of care.

Patients certainly wish for, and deserve, better cancer treatment than that which we currently have on offer. The constraints of universal 'informed consent' can obstruct the doctor–patient partnership and inhibit both good doctoring (the pastoral aspects of care, if you like) as well as making essential research more difficult. In the lofty interests of helping the patient towards a well-informed insightful judgement we seem to have thrown out common sense somewhere along the line; it is high time we gave it back its rightful place.

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European Journal of Cancer Vol. 30A, No. 7, pp. 899–900, 1994

0959–8049/94 $7.00+0.00

Aggressive Superficial Bladder Cancer

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ABOUT 80% of bladder cancer is superficial at presentation, being confined to the epithelium (Ta) or invading the lamina propria (T1) [1]. The term "superficial" is a pragmatic one implying that there is a good chance of the disease being controlled by transurethral means alone. However, 15–20% of these patients will eventually progress to the muscle invasive form of bladder cancer from which the majority will die. Identifying such patients in advance is an important part of good management. Patients with T1 disease which displays the severest form of dysplasia (G3) comprise only 6–23% of superficial lesions [2] and yet account for 60% of those who progress [3]. The notion that these patients should be "regarded as a separate group in need of special treatment" [4] is one which will receive widespread sympathy. There, unfortunately, the concensus will cease for there are widely varying opinions on what form the "special treatment" should take [5]. At one extreme are a few urologists who favour early radical surgery whilst at the other there are those who would manage T1 G3 disease with transurethral resection (TUR) alone. In between are surgeons who would give some form of adjuvant therapy, usually intravesical chemotherapy or BCG, or less commonly radiotherapy.

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Received 17 Mar. 1994; accepted 28 Mar. 1994