Eur J Cancer Clin Oncol, Vol. 20, No. 4, pp. 457–462, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Patient Motivation and Informed Consent in a Phase I Study of an Anticancer Agent*

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Abstract—*In order to evaluate the quality of an informed consent procedure (I.C.P.)* 48 *patients with advanced cancer were offered participation in a phase I clinical trial and entered an I.C.P. consisting of three separate conversations. In the first session, the possible risks and benefits of a phase I study were informally explained by the patient's personal physician. The second session was attended by the patient, a relative, a registered nurse and a physician; the third session was held at least* 5 days *after the second. Forty-one patients gave their consent motivated by hope for improvement of their conditions, pressure exerted by relatives and friends, the desire to contribute to the progress of medicine or simply because they felt they had 'no choice'. Encouragement by relatives or friends seems to be a powerful incentive to participate. A period of a few days to consult relatives, friends or trusted physicians as a part of the procedure seems helpful in arriving at a well-considered decision.*

INTRODUCTION

THE ULTIMATE goal of the oncologist caring for patients with advanced incurable malignancies is improving the quality of life by therapeutic interventions, i.e. radiotherapy or palliative chemotherapy. Many patients, however, who still have a reasonable life expectancy and whose physical and psychological conditions are still fair, enter a stage of their disease in which these therapeutic modalities are exhausted. Depending on the scope of the treatment center, these patients may be candidates for participation in a phase I trial of an experimental antitumor agent.

These early clinical trials present special ethical and psychological problems as the purpose of those studies is not only to confirm the antineoplastic properties of the agent known from animal experiments, but also to acquire first experience with administration to humans and to assess the nature and severity of the invariably present toxicity [1, 2]. Last but certainly not least, these trials serve to offer optimal treatment to the individual patient [3]. It has been a major concern of legislators, patients and doctors throughout the world to ensure responsible decision-making in initiating and conducting these studies, but results have been confusing [4, 5].

In addition to responsible design of the protocol and careful selection of the experimental agent to be tested, the informed consent procedure deserves special consideration. It is well known that written informed consent statements in no way ensure that patients understand the risks and benefits of the planned treatment [6–9], and the need for extensive personal talks and explanations offered by the attending physician should be emphasized [10]. It is appropriate to stress the possible benefit to mankind and to scientific knowledge as a counterbalance to the possible toxicity [11]. Evaluation of informed consent procedures are sparse [12–16] and reports concerning informed consent in phase I trials of anticancer drugs do not, to our knowledge, exist.

We therefore explored the motives of patients with advanced cancer to participate or to refuse participation in a phase I clinical trial and evaluated the quality of an informed consent procedure designed for this purpose. Due to the rarity of medicolegal entanglements following

Accepted 31 August 1983.
*The study was supported in part by the Dutch Cancer Foundation (Koningin Wilhelmina Fonds).
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clinical studies in the Netherlands, full emphasis could be placed on informing the patient, disregarding the legal aspects of obtaining informed consent.

MATERIALS AND METHODS

Patients

All patients were considered candidates for a phase I clinical trial of a new antitumor agent, SOAz [17]. All had histologically confirmed malignant disease not amenable to known effective treatment. Each patient had a Karnofsky Performance Status (KPS) of at least 50 and an estimated life expectancy of at least 8 weeks. Bone marrow, liver and renal functions were adequate as determined by standard biochemical tests. Pertinent patient data are summarized in Table 1.

Informed consent procedure (I.C.P.)

The I.C.P. consisted of at least three sessions:

(1) The first information about possible participation in the study was provided by the patient's personal physician, who was not necessarily one of the authors. The patient was informed of the investigational nature of the study and some of the risks and possible benefits were informally explained.

(2) A meeting was then arranged that was attended by the patient, a close relative or trusted friend, a registered nurse and one of the authors. Four statements were specifically made in each case: the drug is experimental and has not been used in humans prior to this study. The objective of the study is to provide data necessary for the progress of cancer therapy; side effects are to be expected. These may be serious though the oncology team will make every effort to prevent serious complications; the effect on the tumor is uncertain. A cure seems highly improbable and every improvement will be regarded as a success; the patient who refuses to participate in the study or who decides to stop his participation during the study will continue to receive the best available treatment for his condition.

(3) The third session was scheduled at least 5 days after the second. It was held, if possible, in the presence of the relative or friend who had attended the previous one. Questions were answered and additional explanations offered as required. If consent was obtained, treatment usually began on the same day. A written informed consent form, which is not required by law in the Netherlands, was not a part of the procedure.

Interviews

The patients admitted into the study between 15 June and 30 September 1981 were asked to cooperate in a study of the Department of Medical Sociology. The purpose of the study, it was told, was to find out how patients valued the treatment and the information provided by the clinicians. Cooperation meant that one interview was held, preferably at the patient's home. The interviews were conducted by a trained observer (WvdH) and took place at least 4 weeks after treatment had begun. They were structured around three topics: (i) How well is the patient informed of the nature of the treatment, i.e. which information provided during the I.C.P. is recalled? Has the patient actually grasped the meaning of this information? (ii) Which motives made the patient participate? What was the influence of relatives and friends in this respect? (iii) Does the patient feel that the treatment adds to the quality of life or would—in retrospect—refusal to participate have been a better choice? We consciously avoided pressing patients into deciding on this issue if they did not seem ready to do so spontaneously.

Table 1. Characteristics of 48 patients entered into the study

Age (yr)	20–30	31–50	51–60	61–72
Patients	3	13	13	19
Duration of disease (months)	0–6	7–12	13–24	>24
Patients	10	15	9	14
Survival (weeks)	1–12	13–24	24–>53	
Patients	22	17	9	
Intensity of prior chemothotherapy*	none	moderate	intensive	
Patients	17	13	18	

*Chemotherapy of moderate intensity was considered: single-agent chemotherapy, adjuvant chemotherapy in head and neck cancer and multiple agent chemotherapy of less than two months duration.

The clinicians' assessment

After completion of the I.C.P. and the start of the experimental treatment all patients were at least once weekly examined at the Outpatient Department by one of the three clinicians responsible for the trial (S.R., N.H.M. and D.Th.S.). In addition to the history and physical examination performed at each visit, the patient and (if present) her or his partner were encouraged to talk about their motives to participate in the trial, and to discuss their subjective responses to the treatment and their prospectives for the future. Notes were taken, but the use of standard questions or written interview protocols was consciously avoided. Patients who seemed reluctant to comment on the topics specified were not pressed to do so. When progressive misconceptions concerning the efficacy of the treatment or the objectives of the study developed, these were not always corrected; it was felt that patients should have occasion to use their individual psychological defense mechanisms to cope with their distressing situation. However, straightforward questions were answered to the best of the knowledge of the clinician involved.

RESULTS

Forty-eight patients, 27 males and 21 females, received information on the investigational drug SOAz and were offered treatment according to the treatment protocol. In forty-one cases informed consent was obtained and treatment was started. Seven patients did not receive SOAz because informed consent could not be obtained or because of preference for an alternative investigational treatment protocol available. Some of their characteristics are summarized in Table 2. There was no significant difference between the groups in terms of age, sex, K.P.S., duration of disease, intensity of prior chemotherapy or survival after the I.C.P.

The I.C.P. required a period of at least 5 days between the second session and the actual start of the treatment, in order to facilitate consultation of friends, relatives or trusted physicians and to provide additional information to any of these, if required. In four cases additional information was sought by children of a patient, twice by a husband or wife; in five cases attending physicians of other departments or hospitals, who had been asked to provide a second opinion, requested further information.

Interviewed patients

All patients asked to cooperate in the study of the department of Medical Sociology were willing to be interviewed. Ten interviews were actually held. One patient was seen in the hospital, the others were talked with in their homes. The diagnoses were: melanoma (4), head and neck cancer (3), lung cancer (1), breast cancer (1) and cancer of the cervix (1). Six patients were male, four were female. In five cases the interview was held in the presence of the patient's partner, who actively participated in the conversation. The interviews were held 1–6 months after the I.C.P. and took an average of 60 min.

Interviews

Eight of the ten interviewed patients were adequately informed. They recalled relevant aspects of the phase I study, including "experimental", "so far only animal studies", "effect uncertain" and "side-effects unknown". Four of these patients, however, apparently lacked complete understanding of the situation since they specifically stated that being the subject of an experiment ("being used as a guinea pig") was inacceptable to them. The two patients who did not recall the information provided during the I.C.P. seemed to believe they received a standard treatment regimen which is known to have unpredictable results.

Five patients stated that hope of improvement of their diseases was the main motive for taking part in the study. Four of these belonged to the group that had only limited understanding of the study objectives. Three patients, all females, stated that their husbands had urged them to go along. Two patients were not able to formulate an

Table 2. Characteristics of the patients whose consent was not obtained.

Patient	Age	Sex	Duration of disease (months)	Survival (weeks)	Pretreatment (chemotherapy)	KPS*
1	62	M	38	14	moderate	70
2	48	M	10	6	none	50
3	48	M	14	1	moderate	50
4	61	F	14	34	intensive	80
5	51	F	9	4	moderate	60
6	65	F	50	52	none	80
7	52	F	8	5	moderate	70

*KPS, Karnofsky performance status.

explicit motivation and had the impression that they were just following a path staked out by their personal physician. "The doctors would not advise this treatment if it were not effective", one of them argued. In all cases relatives and sometimes friends had been of great importance for the decision to participate. In all but two cases the relatives had argued in favor of the experimental treatment option and seemed much less prepared than the patient to enter the terminal stage of the illness.

Two patients believed the treatment to be effective, two others were sure it was not. The remaining six patients were uncertain. Five patients reported what they believed were side-effects of the drug, such as weakness, dizziness and headaches. Three of them expressed hope that these were indications of antitumor activity. No patient spontaneously expressed regret at having participated.

Clinicians' assessment

Patients 1–4 (Table 2) rejected the experimental therapy option. Their motivations can be summarized as follows; patients 2 and 3 objected because of the experimental nature of the drug; patients 1 and 4 refused to have any further chemotherapy but had no particular objections against the investigational nature of the study. Patients 5 and 6 consented to therapy but did not receive it. Both were withdrawn from the study by physicians who had been in charge of previous therapies. Their motivations were the wish to withhold any therapy in patient 5 and preference for an alternative chemotherapeutic protocol in patient 6. Patient 7 decided to refrain from participation because of an unexpectedly rapid deterioration of her condition during the course of the I.C.P. that rendered further treatment impractical.

In all patients who participated in the study the hope for stabilization, improvement or even cure of their diseases was the major motivation. However, during the treatment seven patients specifically stated their interest in taking part in the scientific struggle against cancer. On the other hand, the clinicians felt sure of the nearly complete lack of understanding of the nature of the study in four patients. Four other patients avoided discussions and explicitly asked their physicians to decide. One of these patients later stated his interest in participating in a research project.

The subjective side-effects of the experimental antitumor agent SOAz were thought to be minimal. Two minimal responses were noted and stabilization of disease occurred in five cases. The dose-limiting toxicity of the agent proved to be myelosuppression, which made platelet transfusions necessary in five patients. Extramedullary toxicity was almost completely lacking, resulting in excellent patient tolerance.

DISCUSSION

A patient with advanced cancer confronted with the option of participating in a phase I clinical study of a new antitumor agent faces an extremely difficult choice. The chances of a cure are neglegibly small but some temporary improvement may be gained. On the other hand, the discomforts of chemotherapy are often painfully familiar to the patient and potentially serious side-effects are to be expected. Frequent visits to the Outpatient Department of the hospital and often some period of hospitalization are unavoidable. Therefore a clear understanding of the issues involved is essential for the patient and his relatives, and also for the investigator, who is dependent upon motivated and co-operative subjects to satisfactorily complete his follow-up.

The simple hope for improvement of their conditions, however, does not seem to be the only major motive for patients to participate. Half of the patients in this study gave their consent because of other reasons. By continuing to receive medical attention and some form of treatment they were able to cope with their incurable diseases and deny or postpone more easily the realization of impending death. This mechanism seems to be even more important in relatives of the patient, who constitute a powerful source of motivation. In the interviewed group alone, three women admitted frankly that they had had no serious interest in the phase I study, but that their husbands had urged them to go along, "to grab their last chance", as it was frequently put.

The wish to contribute to the progress of medicine was in no case the main motive for participation. However, seven patients spontaneously stated their interest in this respect and in fact four of them readily agreed to hospitalization for a few additional days for pharmacokinetic studies that were purely investigational in nature and of no personal benefit to them. One patient with a head and neck tumor that proved unresponsive to the investigational agent contacted us several weeks after the completion of the follow-up period to inform us that he was still alive and to inquire if a visit to the clinic would be of any additional scientific interest.

In most cases the I.C.P. seemed satisfactory in informing the patients and their relatives. Only 10% of the subjects clearly lacked an understanding of the situation. In two cases this could be ascribed to limited intelligence and in the third

case the patient's insight was probably impaired by central nervous system metastases of his melanoma. A fourth patient and her family had heard about the ongoing trial from acquaintances and were absolutely convinced that SOAz would cure her breast cancer. Repeated long conversations were not able to modify these expectations to a significant extent. Evidently these four patients may be classified as 'vulnerable' patients, who are able to consent but hardly to be adequately informed. It is therefore questionable if they should be included in a phase I study of an anticancer agent. On the other hand, all four readily agreed to participate at the first session of the I.C.P., at a time when their ability to understand could not be adequately assessed. It seemed unfair to exclude them from the study at a later stage because of their supposedly impaired judgement.

The interviews held with ten of the 48 patients of this study suggest that many of the apparently adequately informed patients have in fact a quite different perception of their position than one should expect on the basis of the information recalled. Unrealistic expectations were sometimes present and, more importantly, the concept of being the subject of an experiment seemed to be repressed. In half of the 'well-informed' patients a dissociation between the recalled facts and their insight into the objectives of the treatment seemed to exist that may be explained by their individual use of psychological defense mechanisms to cope with their distressing situation. In our opinion every effort should be made during the I.C.P. to inform the patient and to improve his/her understanding; after concluding the procedure, however, complete and realistic understanding should not necessarily be pursued at all times, since in many cases this might add to distress without serving a purpose.

We believe that adding a few days to the I.C.P. in order to consult relatives and trusted physicians constitutes an important improvement to the procedure. Of seven patients who did not give their informed consent, five decided not to participate during this period. All of them had seemed positive during the second session. A total of 11 communications between the clinicians and third parties took place between the second and third sessions, contributing to the information of relatives or physicians who could not be present during the second sessions of the I.C.P.s. This may have been one factor explaining the rather low rate of 'drop-outs' of this study (only one out of 41 patients). Another explanation may, of course, be the excellent patient tolerance of the agent tested.

The question of necessity of a written informed consent statement remains unsolved [10]. We believe that in a country not requiring such a document by law a signed form is not helpful in clarifying the situation to the patient. A well-defined informed consent procedure, including extensive explanations by the investigators and ample time to consult with relatives and other physicians, should be part of the trial protocol. It is conceivable that a written explanation of the study-objectives and treatment alternatives in understandable language might lead to further improvement of patient's understanding [16], especially if taken home after the second session to aid in consultations with relatives and doctors.

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