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The choice of whether to participate in a phase I clinical trial: increasing the awareness of patients with cancer. An exploratory study

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Abstract

***Objective*: In a previous study, we found that patients who were offered the possibility of participation in a clinical trial had unexpressed concerns and fears that prevented them from making free or fully knowledgeable choices about their trial participation. In a selected population of patients who were offered participation in a phase I trial, we prospectively investigated whether a face-to-face discussion about their unexpressed fears might lead to a more conscious decision about whether to accept/refuse participation in the trial.**

***Methods*: After the presentation of the trial, a questionnaire was administered to assess the presence of specific fears. Before the patients decided whether to participate in the trial, they discussed any fears that they had; finally, the impact of the discussion on the patients' choice to participate was evaluated.**

***Results*: The majority (86%) of the patients thought that physicians conduct clinical trials for scientific interest, 13% felt exploited as 'guinea pigs' and 20% believed they were offered participation because they had no further hope for improvement. These existing fears were not elicited during the trial interview because the patients were themselves unaware of having them (28%) and because of fear of the doctors (3%). The possibility of discussing these fears was felt as an opportunity and made patients feel more conscious (92%) and freer (97%) when making their choice.**

***Conclusions*: Recognising and discussing misconceptions and fears, often unexpressed, make patients freer and more aware when facing the choice of whether or not \to participate in a phase I clinical trial.**

Background

During the course of their disease, patients receive the possibility of participating in clinical trials in which they may receive new drugs, which are considered a good opportunity by the physicians. This opportunity is conditional on the decision of the patients.

In a previous study, we found that the majority of patients (85%) who were offered the possibility of participation in a clinical trial agreed to participate, and most (92%) considered this choice as a possibility for new treatment for them and for other patients. The patients chose to participate in an experimental study because they trusted the doctors (76%) and the institution (64%) and because they hoped to have a chance of therapy (78%) [1]. It was found that some patients thought that they would be used as guinea pigs (36%), that proposed participation in a clinical trial was for the sole economic or scientific interest of the physicians (31%), that physicians propose clinical trials even if there are other drugs that could be more effective than the drug used in the clinical trial (28%) and that the proposal to participate in a clinical trial was their last chance of treatment.

Although patients have these concerns, they are not usually discussed during the conversation with the doctor, who is concentrated on explaining the proposed study; furthermore, they are not usually cited in the informed consent, and patients do not request discussion of these concerns [2,3]. Consequently, patients who have neither discussed nor resolved their fears cannot make free or fully knowledgeable choices about whether or not to participate in a clinical trial [4–9]. When discussing trials, the communication between the oncologist and the patient is important to the patient's decision-making process [10,11]. The role of emotions regarding trial participation has rarely been investigated [12,13]. A proposal to participate in a phase I study, in which the potential safety and efficacy of the trial drug are basically

unknown, is even more complex. Moreover, participation in phase I studies is usually proposed following the failure of previous standard and specific treatments for a disease, and patients have fears and many expectations. Indeed, Catt *et al*. found that while most patients offered participation in a phase I study accepted, they did so with optimistic expectations of personal benefit (expectation of some medical benefit, trial the best option available, to maintain hope and to help with research) and gave a low ranking to altruism (to benefit others in the future) as a reason for entering a phase I trial [14].

Doctors have the duty to inform patients fully, discussing the possible lack of effect of the proposed treatment and the potential, sometimes unknown, toxicity of drugs used in phase I studies [15]. In such a complex activity, an educational programme for clinicians may improve communication with patients about phase I clinical trials [16], thereby avoiding poor communication and lack of information and understanding by doctors [17] when discussing participation in phase I studies with patients.

Fears and misconceptions could be different and/or greater in phase I studies. We, therefore, focused this exploratory pilot study on patients who were offered participation in a phase I trial, to identify and evaluate, through questionnaires, their fears and beliefs. Moreover, we prospectively investigated whether openly considering these unexpressed fears through in-depth discussion with the patients could make the patients' choice of whether or not to participate in a phase I clinical trial more informed and less influenced by possible misconceptions. The current study pursued an alternative way of improving communication by having an intervention that works with the patient rather than looking at an intervention that applied to the clinician. This study not only includes the doctors' understanding of the patients' fears and concerns about participating in phase I studies but also the intervention by doctors, who are ready to respond to and overcome the patients' fears and doubts if asked to do so by the patients. We believe that potentially the two approaches could work synergistically to improve the communication and consent process in phase 1 trial participation.

Materials and methods

We created new questionnaires to evaluate whether the fears and misconceptions assessed in a previous study [1] were also present in patients who are offered participation in phase I studies. Other questionnaires have been used previously to explore factors influencing patients' willingness or decision not to participate in clinical trials. One of the most interesting factors, called 'accept/decline', was recently amended to look at phase 1 trial participation [14] but does not specifically evaluate the four new aspects that the current study was intended to investigate or the outcome of the doctors' intervention. We, therefore, developed new questionnaires capable of evaluating precisely these aspects and the utility of doctors' direct intervention.

The phase I studies proposed were those taking place in our institute; their main aim was to determine the toxicity of treatment and incorporated dose escalation to find the maximum tolerated dose. Out of 11 studies, one was first-in-human, five were phase I b and five were studies with experimental drugs as monotherapy. Study drugs were given orally in three studies, intravenously in six studies and in combination (oral plus intravenous) in two studies. All these studies required pharmacokinetic analysis.

Patients

All consecutive patients with advanced cancer who were offered participation in phase I clinical studies in our institute between 2009 and 2012 and who had never previously participated in a phase I clinical trial were eligible for recruitment to the current study. All patients had stage IV solid tumours, which are most frequently due to breast cancer, lung cancer, ovarian cancer and colon-rectal carcinoma. Patients not included in the clinical trials were offered alternative treatments, if available, or supportive care.

The questionnaires were administered to eligible patients, independent of whether they did or did not decide to take part in the phase I clinical trial that had brought them to our institute.

Questionnaires (Appendix A) and study design

A team including medical oncologists and a medical ethicist developed five questionnaires designed to assess patients' perceptions, fears and prejudices regarding phase I clinical trials. Domains were developed on the basis of the previous study [1]. A validated instrument, the Edmonton Symptom Assessment System (ESAS) scale, was also included.

The patients who came to our outpatient services to talk about their participation in phase I studies completed a routine interview with the referring doctor, in accordance with the usual guidelines of our institute. During this routine interview, the patients were given an explanation of the features of the proposed trial and discussed the expected benefit of the proposed treatment and/or the absence of knowledge about it. They were also consigned a personal information form and a consent form for the phase I trial that had been discussed, which the patient kept for at least 24 h before returning it.

At the end of the interview with the referral doctor, the patients were invited to participate in the current study. They were, therefore, given

- a symptoms' form (the ESAS form), an information sheet and an informed consent form;
- questionnaires A, B and C to fill in immediately and return;

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- questionnaire D to be filled in at home;
- questionnaire E to be filled in after the second interview in which fears and misconceptions were discussed, if present and if the patient so desired.

Questionnaires A, B, C and D were administered at the beginning of the study, and questionnaire E was administered after the second interview.

- *Information leaflet*: This leaflet explained the aims of the study; the patients were also informed that the themes to be discussed could be upsetting and were, therefore, asked whether or not they would want to discuss them.
- *Informed consent*: The patients had to have signed an informed consent in order to participate in the study.
- *Personal information form*: The patients filled in a form collecting their personal information.
- *ESAS questionnaire*: The ESAS scale, in its Italian version [18], was a simple method of documenting the patients' state of health at the time they were given the other forms and questionnaires.
- *Questionnaire A* (Appendix A): *misconception/fears regarding phase I studies*—this questionnaire contained six questions with yes/no answers; the first four questions evaluated possible misconceptions/fears regarding participation in a clinical trial, whereas the last two questions investigated whether the patients thought it was useful to discuss these issues during the interviews presenting the phase I studies and whether discussing the issues with the doctors could increase their own awareness and, thereby, help them in the final decision of whether or not to participate in the study.
- *Questionnaire B* (Appendix A): *discussion with physician about their fears*—this questionnaire contained eight questions with yes/no answers and one multiple choice question. The first eight questions investigated which of the themes evaluated in questionnaire A (scientific interest, economic interest, being treated as guinea pigs and last hope of a treatment) had already been discussed during the presentation of the phase I study, which had not been discussed and which would have been useful to discuss. The multiple choice question was aimed at determining the reason why the patients themselves had not asked to discuss the issues in which they were interested.
- *Questionnaire C* (Appendix A): *prejudices regarding experimental study*—this questionnaire contained four questions with yes/no answers, one multiple choice question and three questions with open answers and investigated fears and prejudices regarding clinical trials.
- *Questionnaire D* (Appendix A): *patients' reflections at home*—during the second interview, the possible impact of the previous questionnaires on the patients was evaluated through the use of questionnaire D, and the patients were asked whether they would like a further discussion on the proposed trial participation. Patients who asked for a more detailed discussion were subsequently given questionnaire E to evaluate the impact of the discussion and the clarifications they had been offered during the second interview. The questionnaire contained one question with a yes/no answer and four questions with yes/no/don't know choices of answer and was used to evaluate whether the fact of having explicitly considered and brought to the surface possible fears and misconceptions, through compilation of the questionnaires during the first interview, had *per se* raised a desire in the patients to think about the phase I study they had been offered and any fears, and discuss them with their family (or anyone else) and whether all this had been of help in increasing their awareness when making their final decision on whether or not to participate.
- *Questionnaire E* (Appendix A): *impact of the discussion*—this questionnaire contained three questions with yes/no/don't know answers and evaluated three items, whether, after having received further explanations about the issues, (i) they had greater awareness of their fears and misconceptions and, therefore, of whether or not to participate in the phase I trial; (ii) they would change their idea about whether or not to participate in the phase I clinical trial; and (iii) they were making a freer choice of whether or not to participate in the clinical trial.

This study was approved by our ethical committee in the European Institute of Oncology.

Statistical analysis

This was an exploratory study; however, we estimated the sample size based on the following: considering an accrual rate of about two patients per week and a 10% dropout or nonresponder rate, we calculated that a two-sided Fisher's exact test at the 5% significance level requires a sample size of at least 100 patients in order to achieve an 80% power for the comparison of the frequency distributions of the answers of the patients who participated in phase I clinical trials versus the patients who did not participate.

Patients' characteristics were summarised as counts and percentages for categorical variables and by mean, median, minimum and maximum values for continuous data. Frequency distribution of positive (e.g. 'yes') or otherwise

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specified answers to questionnaires A to E was tabulated as counts and percentages. Associations between patients' characteristics and answers were tested using the Mann–Whitney test for continuous variables or Fishers' exact test for the categorical ones. The McNemar test was used for testing the association between relevant items. The willingness to participate in a clinical trial (the patient signed the informed consent) was analysed by a logistic regression analysis, and the resulting univariate odds ratios were tabulated with 95% confidence intervals. All tests were two-tailed and considered statistically significant at the 5% level. Between-items correlation for the ESAS scale was estimated by Pearson's r^2 coefficient.

Results

A total of 106 patients were offered enrolment in this study, and 106 participated (Table 1). Overall, 69 patients (65%) signed the informed consent showing their willingness to participate in the proposed clinical trial, 18 (17%) refused to enter the phase I trial and 19 (18%) were not eligible (Table 2).

Personal information form

This form was completed by 106 patients. The patients' mean age was 58 years. Eighty-eight per cent came from north Italy (Table 2).

Questionnaire A

All 106 patients filled in questionnaire A with four (3.8%) missing answers to the sixth question. Eighty-six per cent of the patients considered that the main reason they were offered participation in a phase I clinical trial was for the doctors' scientific interest. Thirteen per cent of the patients would feel that they were being treated as guinea pigs if they decided to participate. Most patients (80%) did not think that they were offered enrolment because it was the last hope of treatment, whereas 20% did believe this was the case.

Questionnaire B

All 106 patients filled in questionnaire B with 13 (12%) missing answers to the third question. The patients were interested in tackling issues during the interviews in which they were offered participation in phase I trials.

When asked why they had not requested discussion of these issues that interested them during the first interview, 33% replied that they themselves were not aware of having these fears/prejudices, 2% stated that they were afraid of their doctors and 1% said that it was to please their doctors. Of the 41 patients who replied 'other', 85% had found their interview thorough.

Table 1. Frequency distribution of questionnaires answers

		N (%)
Questionnaire A		Total number of points = 106
A.1	Economic advantage	None
A.2	Scientific interest	89 (85.6)
A.3	Treated as a guinea pig	13 (12.8)
A.4	Last hope	21 (20.4)
A.5	It is useful to discuss the issues	79 (74.5)
A.6	Discussing help to be more aware	85 (80.1)
Questionnaire B		Total number of points = 106
B.1	Economic advantage	4 (4.1)
	Scientific interests	75 (72.8)
	Feeling like a guinea pig	23 (22.6)
	Last hope	27 (26.7)
B.2	Economic advantage	8 (8.4)
	Scientific interests	62 (66.0)
	Feeling like a guinea pig	20 (21.3)
	Last hope	33 (35.5)
B.3	Not aware of having these fears/prejudices	35 (33)
	I wasn't aware at the time of having these fears/concerns	18 (28.1)
	Afraid of their doctors	2 (2)
	Embarrassed	1 (1)
	Didn't want doctors think poorly of me	2 (2)
	Want to please their doctors	1 (1)
Questionnaire C		Total number of points = 106
C.1	Already participated in a previous clinical trial	15 (14.9)
C.2	Did you have fears/prejudices about the clinical trial?	2 (13.3)
C.3	Did you discuss them with your doctor?	2 (15.4)
C.4	Greater than those now	2 (5.9)
	Less than those now	2 (5.9)
	The same	6 (17.7)
	Any concerns about phase I trial	24 (70.6)
Questionnaire D		Total number of points = 76
D.1	More informed after discussion	49 (64)
	Discussing them with doctors, friends, family and on the Internet	28/49 (57)
	Reflecting alone	5/49 (10)
D.2	More conscious	44 (91.7)
D.3	Decision change	3 (4.1)
D.4	Freer choice	39 (90.7)
D.5	Anxiety by more knowledge	14 (32.6)
Questionnaire E		Total number of points = 67
E.1	More knowledgeable	63 (94.0)
E.2	Would you change your previous decision?	3 (4.6)
E.3	Freer choice	64 (97.0)

Questionnaire C

All 106 patients filled in questionnaire C. The maximum number of missing answers was five (5%) to the first question. Eighty-five per cent of the patients had never previously participated in any type of clinical experimentation

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(phase II or III), whereas 15% had already discussed potential participation in a phase II or III trial. Of the 15 patients who had already been offered participation in a clinical study, 13 (87%) had not had fears/prejudices with regard to the proposed phase I clinical trial.

There was no statistically significant association between the willingness to participate and the previous participation in a clinical trial (OR = 0.80, $p = 0.79$) (Table 3).

Questionnaire D

Seventy-six patients filled in questionnaire D. The fact of having, during the preceding interview, mentioned the possible fears that can be raised by a proposal to participate in a clinical trial led 64% of the patients to reflect/inform themselves about these issues (Table 1). Ninety-one per cent of the patients stated that they were more conscious of the choice of whether or not to participate in the trial, making their choice freer.

Table 2. Patients characteristics (total 106 patients)

Continuous variables	Mean ± SD, min–max
Age (years)	58.2 ± 8.9, 39–75
ESAS questionnaire	Mean (median), min–max
Pain	1.78 (1.00), 0–9
Fatigue	1.94 (1.00), 0–10
Nausea	0.25 (0.00), 0–5
Depression	1.04 (0.00), 0–10
Anxiety	1.75 (0.00), 0–10
Drowsiness	1.24 (0.00), 0–8
Loss of appetite	0.86 (0.00), 0–10
Malaise	0.99 (0.00), 0–10
Difficulty in breathing	0.90 (0.00), 0–10
Cough	0.97 (0.00), 0–10
Categorical variables	*N* (%)
Gender	
Female	58 (54.7)
Male	48 (45.3)
Geographic distribution	
North	89 (88.1)
Centre	7 (6.9)
South	5 (5.0)
Education	
Primary school	20 (19.2)
Middle school	33 (32.4)
Higher school	11 (10.8)
University degree	15 (14.7)
Has a job	46 (43.8)
Any children	85 (81.0)
Live with the children	50 (58.8)
Live with a spouse/partner	91 (86.7)
Look anybody apart from children	10 (9.5)
Had relatives with a tumour	86 (81.9)
Took part in any clinical trials	
No	83 (96.5)
Don't know	3 (3.5)
Distance from this institute	
≥100 km	64 (61.5)
<100 km	40 (38.5)
Distance-based participation decision (yes)	9 (8.6)

SD, standard deviation; ESAS, Edmonton Symptom Assessment System.

Questionnaire E

Sixty-seven patients filled in questionnaire E. Ninety-four per cent of the patients were more knowledgeable of their choice of whether or not to participate in the clinical trial, 95% did not change their idea regarding their choice and 97% of them stated that being more knowledgeable made their choice '*freer*'.

ESAS scale (Appendix A)

One hundred and three patients filled in the ESAS form. At the time of compiling the questionnaires, most of the patients were in a good general condition and did not complain of pain, fatigue, nausea, depression, anxiety, drowsiness, malaise, loss of appetite, difficulty in breathing or cough. Overall, the grade of intensity of symptoms did not exceed a mean of 1.94 (fatigue) on a scale from 1 to 10 (Table 2). ESAS items correlations ranged from a minimum of $r^2 = 0.006$ ($p = 0.43$) between anxiety and drowsiness to a maximum of $r^2 = 0.469$ ($p < 0.001$) between drowsiness and fatigue.

Discussion

In this exploratory study, we founded that concerns were rarely discussed during the interview with the doctor and are also rarely mentioned in informed consent forms. This could have the consequence that patients, not having discussed and clarified these issues, could be influenced by them when making their decision on whether or not to participate in the proposed study, without being able to decide on the objective reality of the study itself and, in the final analysis, without being able to make either a free or an informed decision [19].

At any time a person is given a questionnaire that requires second thoughts, anxiety may emerge and issues may become apparent, not because they did not exist before but, as described in our report, often the patients were not aware of them previously. Furthermore, in order to make the choice of whether or not to participate in a phase I study in a more informed fashion, specific discussions (referred to as secondary intervention) on the issues that emerged were undertaken as a result of the interview by the physician.

When patients face a proposal to participate in a phase I study, their fears and misconceptions could be different and/or greater than those regarding participation in phase II/III trials, because the potential safety and efficacy of the trial treatments are largely unknown [20,21]. Moreover, participation in phase I studies is usually proposed following the failure of previous standard therapy and/or unavailability of specific treatments. Phase I studies are difficult to propose because the potential participants are in a stage of their life in

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Table 3. Univariate analysis of willingness to participate in a phase I trial

	Odds ratio (95% CI)	*p*-value
Patients' characteristics		
Age (years)	0.96 (0.90, 1.02)	0.18
Gender		
Female	Ref	
Male	1.53 (0.54, 4.35)	0.42
Geographic distribution		
South	Ref	
North	1.65 (0.14, 19.3)	0.92
Centre	Not estimable	—
Education		
Primary school	Ref	
Middle school	2.50 (0.50, 12.5)	0.37
Higher school	1.55 (0.41, 5.89)	0.99
University degree	1.53 (0.29, 7.94)	0.97
Has a job		
No	Ref	
Yes	2.31 (0.74, 7.20)	0.15
Any children		
No	Ref	
Yes	1.04 (0.26, 4.19)	0.96
Live with a spouse/partner		
No	Ref	
Yes	0.92 (0.18, 4.78)	0.92
Look anybody apart from children		
No	Ref	
Yes	0.49 (0.11, 2.20)	0.35
Had relatives with a tumour		
No	Ref	
Yes	0.93 (0.23, 3.74)	0.92
Distance from this institute		
≥100 km	Ref	
<100 km	1.35 (0.45, 4.04)	0.59
Distance-based participation decision		
No	Ref	
Yes	0.79 (0.15, 4.27)	0.78
Answers to Questionnaire A		
Scientific interest		
Yes	Ref	
No	1.24 (0.24, 6.33)	0.79
Treated as a guinea pig		
Yes	Ref	
No	20.7 (4.70, 90.6)	**<0.001**
Last hope		
Yes	Ref	
No	5.80 (1.85, 18.2)	**0.003**
Answers to Questionnaire C		
Have you already participated in a CT?		
Yes	Ref	
No	0.80 (0.16, 4.07)	0.79

CI, confidence interval; Ref, reference category; CT, clinical trial.
Values in bold are statistically significant.

which every standard, known treatment has failed, and patients often feel the need to embrace any opportunity they are offered. The treating physician must be certain that the patients who decided to participate in phase I studies have understood their disease state, their prognosis, the possible influence of the trial on the patients' quality of life and the existence of options, such as supportive care [17]. In such a complex activity, an educational programme for physicians may improve communication with patients [16].

This study included patients who declined to enter a phase I protocol and those who accepted. Most (65.1%) of the patients agreed to participate in the proposed phase I clinical trial. We found that, during the interview routinely performed to propose participation in a phase I trial, 75% of the patients did not mention fears/prejudices, but, subsequently, filling in the questionnaires, they discovered fears and prejudices that they had but avoided discussing during the previous interview. The various reasons for this behaviour included the patients' unawareness of their own fears, being afraid of the physician's opinion or a strong desire to please their physician.

How clinicians feel or cope with talking about patients' fears with them is an important issue as it is well known that physicians often find such conversations challenging. Clinicians often worry that they will upset patients by introducing such topics or that it will unduly prolong a consultation when the time available is limited [22,23]. In this study, we did not use specific questionnaires to evaluate how physicians felt, but we believe that clinicians can feel helped by having a method that, through the administration of questionnaires, aids their discovery of patients' fears with regard to participation in phase I studies and consequently discussion of these fears, promoting better informed choices. It has been shown that patients wish to be more involved in medical decision-making [24]. Lars *et al*. tested psychometric instruments and found that satisfaction with physicians was increased directly by patients' involvement and indirectly through decreased decisional conflict [25].

Asking questions on issues that a patient may never have considered or discussing fears/prejudices that a patient might not have thought about could have ethical implications given the possibility that physicians may introduce such fears to patients. However, when we tell a patient he has a tumour, when we explain the side effects of a standard treatment and when we inform him that the treatment we are proposing may not be effective, we are creating fears, doubts and concerns. The patient signs an informed consent form containing extensive details on what could happen, including the possibility of death from toxicity or side effects.

Are we physicians the cause of fears? Doubts, fears and obstacles are inherent in the treatment of the patient with cancer. We, however, believe that it is the doctor's duty not to stop at the surface because of concern of creating new fears, but that all the patients' possible feelings should be explored thoroughly in order to allow the patients to discuss issues that they themselves were often not aware of, as shown in our pilot study. The method using questionnaires to investigate patients'

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potential fears/prejudices concerning participation in clinical studies can help doctors to understand what is important to discuss and can help patients have the courage to ask.

Indeed, in our study, once aware of their fears, most of the patients (80%) believed that discussing these issues could help them to make a freer choice, and almost all of them went through a subsequent interview. One of the major concerns elicited in this interview was the reason why doctors propose experimental trials: most of the patients (85.6%) believed that doctors propose such trials for their own scientific interest and would like to discuss this aspect (66%).

An open discussion about this unexpressed concern allowed considerations that a scientific motivation, which is a feature of clinical research, is not necessarily a negative aspect (i.e. 'corruption' by scientific interest putting the patient on a lower scale) but could rather encourage doctors to be more useful and scientifically informed for the sake of their patients [26–30].

After having discovered their own fears and discussed them, most of the patients obtained more information about the features of a phase I trial, looking for the additional information from physicians, family and the Internet and also reflected on the issues. Becoming aware about the fears led patients to think more and better about the proposed treatment and to be more conscious about their choice (91%). Of major interest, in 4% of cases, the patients' choice (yes/no) of whether to participate in a phase I clinical trial was changed.

Many of these issues (more knowledgeable and freer choice; see questionnaire E in Appendix *A*) were discussed further during the second interview, which was planned and requested for all patients enrolled in our study. The response rate to questionnaire E was lower than that to the other questionnaires because most of the patients who came for the second interview were those who wanted or could participate in a phase I study (patients who would not have participated in the phase I study for logistic reasons, such as living a long way from the institute or starting another treatment elsewhere, were unlikely to return for this interview).

Our results show existing fears that are not elicited during initial phase I trial interviews that can be a barrier to a fully conscious participation in phase I trials. Associating a proposal to participate in a phase I study with questionnaires to tackle patients' unexpressed prejudices and fears can improve doctors' discussions of the proposed trials and help patients to be more conscious of their own concerns and, therefore, freer in their final choice. This exploratory work could be taken forward by expanding this experience in a multicentre study to confirm these findings and to cover a larger spectrum of fears and prejudices concerning participation in phase I trials due to different cultures and different patient/physician relationship.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

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