National Consultative Ethics Committee for Health and Life Sciences

OPINION N° 73
PHASE 1 STUDIES IN CANCEROLOGY

On September 17, 2001, Professor Laurent Degos referred to CCNE regarding ethical issues raised by phase 1 studies involving cancer patients. Physicians must alleviate their patients' pain and suffering, respect their dignity, and give due consideration to their best interests, but must also further therapeutic progress, and these two imperatives do not necessarily coincide. The object pursued by these preliminary but necessary trials, is to evaluate tolerance and toxicity of new drugs, without seeking directly any therapeutic benefit for the participating patient. As a result, information given to patients regarding the uncertainty of any benefit, the possibility of adverse effects, and ensuing risks, often leads to some confusion. More or less consciously, there is a tendency to minimise problems, so that no truly informed consent is achieved. In the circumstances, physicians are torn between conflicting obligations : duty of care, and the advancement of medical research.

All physicians in the field of cancerology are concerned by these issues, as is society as a whole, since the actual purpose of such trials is the common good.

Present status of the problem :

Scientific aspects

- Phase 1 studies are defined as the first trials involving human subjects following experimentation with animals ; they are an essential step before any new molecule is put to use. Their main purpose is not to seek a therapeutic effect, but to assess

toxicity by determining a maximum tolerated dose They also research possible adverse effects in both qualitative and quantitative terms, their duration, their potential reversibility, and their possible connection to pharmacokinetic data. This data is required before proceeding to the first studies of the drug for efficacy (phase 2 trials). Phase 1 trials are organised according to very strict scientific protocols (recognised competence of personnel, approved premises). They entail a process of dose escalation administered to small separate groups. Subjects are generally healthy volunteers. In France, specific legislation (the Huriet-Sérusclat law, n° 88-1138 dated December 20, 1988) governs such trials, and they are described as being "without direct individual benefit".

Since anti-cancer drugs used in cancerology are usually very cytotoxic, they cannot be used on healthy volunteers in phase 1 trials. They are administered to cancer patients for whom therapy is no longer an option, who are sometimes in fact terminally ill. The European Agency for the Evaluation of Medicinal Products (EMEA) in their document 2001, recommended that phase 1 trials should not involve patients who stand a reasonable chance of prolonged symptom-free survival or who may benefit from conventional treatment. However, one of the criteria for eligibility stipulates that probability of survival must be greater than 8-12 weeks. Still, these prognostic evaluations are always much more tentative than is generally thought, and they may be contradicted by events one way or the other.

- The expected therapeutic effect of the molecule being tested is not a decisive criterion for selecting patients in such trials. The strongest tolerated dose is the one which, by a narrow margin between toxicity and efficacy, is the most likely to be effective.

  In phase 1 studies, there has to be a constant increase of dose levels (dose escalation). The classic methodology which requires a minimum of three patients being given that molecule at each level, has only rarely been used in recent years. New dose escalation procedures have been outlined, based on fresh statistical

models and pharmacokinetic methods. Such modifications were designed to determine the toxicity level more rapidly, avoid excessive toxicity risks, and limit the proportion of patients receiving very low doses which are highly unlikely to have any efficacy whatsoever. However, recent experience has shown that, despite progress, it is difficult to achieve simultaneously all three of these objectives. Furthermore, the difficulty of extrapolating toxicologic and pharmacokinetic data from animals to humans, and the variability of toxic effects from one patient to another depending on physiological deterioration, are significant obstacles to defining the best methodology.

- Although the aim of phase 1 studies is not to pursue therapeutic effects, a study of the literature does show that therapeutic benefit may come about. Specialists differ on frequency and importance. Some researchers consider that some benefit may occasionally be gained by almost 15% of patients at the highest doses. Most of them however consider that benefit may occur for only less than 5% of patients, and that only less than 1% benefit substantially. Death may ensue for almost 1%.
- The essential requirements of paediatric oncology research are such that phase 1 trials need to be performed on children suffering from specific cancers, or else to adapt the adult maximum tolerated dose which had already been determined.
- In recent years, non cytotoxic molecules which aim to modify tumour biology or modulate host response, are tested more and more frequently. In this case, the maximum tolerated dose becomes less significant than the biologically effective dose. Despite the fact that effective dose and toxic dose are more often than not very far apart, these trials continue to be regarded, perhaps inappropriately, by the French Agency for the safety of health-related products (AFSSAPS - l'Agence française de sécurité sanitaire des produits de santé), as classic phase 1 trials.
- A particular situation deserves special mention. To obtain a European product marketing authorisation, a phase 1 trial is required, because of perhaps disputable legislation, even though the toxic dose of the molecule has already been established and its efficacy already recognised in the United States. The argument of first administration to humans which justifies the very principle underlying a

phase 1 test, no longer applies in this case, and it could therefore be argued that the patient (for whom serious adverse effects could be avoided) is in fact subject to administrative rather than scientific rules.

- One finds that phase 1 trials, in particular recent combined medication tests, are sometimes unduly presented to the patient in the guise of "compassion" trials, or else they are called 'phase 1/2 studies'. In this way, thanks to semantic confusion, investigators can avoid the constraints connected to research "without direct individual benefit".

Consent

- As is the case for any biomedical research involving human participants, consent must be obtained. The procedure includes a written notice of information, drafted by the sponsor (academic or industrial) and oral information supplied by the investigating physician to complement and elucidate the written material. According to the 1988 Huriet-Sérusclat law, information must be provided to patients regarding the object, duration, expected benefit, constraints, and predictable risks of the research.
- For phase 1 cancerology trials, the European Agency for the Evaluation of Medicinal Products (EMEA), only requires that "information provided clearly establishes that the object is research, and the patient be warned that no clinical benefit is expected". The formal requirement for consent must not in any way curtail dialogue between investigator and patient and does not in any way preclude inquiry on the significance this information may have for that particular patient in those particular circumstances.
- The quality and veracity of information provided to the patient vary considerably, which may have an effect on the crucial loyalty of the doctor-patient relationship. Neither in France, nor in most other European countries, is there a standard form for the written notice of information for this type of trial. Some protocols abroad (Canada, United-States) provide very clear information, and should lead to reflection regarding the situation in France which can be viewed at the present

time as, to say the least, ambiguous.

CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) (Institutional Review Board)

- In France, CCPPRBs have a threefold mission : verify that the research is sufficiently rigorous; guarantee the rights of subjects participating in the research, and evaluate the validity of the notice of information and of the consent form. Before activating the protocol, sponsors send a letter of intention to AFFSAPS, describing the essential research data, together with the findings issued by the CCPPRB concerned.
- The various CCPPRBs seem to diverge in their approach and attitude when evaluating the notice of information, which reveals some uneasiness about this matter. Certain CCPPRBs emphasise the ambiguity of trials which investigators describe as phase 1/2 to avoid giving information which if explicit, might give reason for rejection. More harmonisation of CCPPRB findings in this respect would be desirable. This could easily be achieved by creating a data base, following the recommendations contained in Senator Huriet's report. (Information report on the proceedings of CCPPRBs. Commission for Social Affairs of the *Sénat*. April 2001).

Problems arising :

The risk/benefit ratio :

Published data reveals that in the course of phase 1 cancerology trials which remain essential, the risk/benefit ratio is clearly in favour of risk, so that such trials are in contradiction with the Helsinki declaration which the writer of the protocol must state that he subscribes to. In its October 2000 version, the declaration affirms "In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject". In the specific framework of cancerology phase 1 trials, the expression "wellbeing of the subject" is an abstraction and does not sufficiently draw attention to possible deterioration of the quality of life of patients. The Declaration also states that research is only justified if the population under study can gain some benefit from it .

The distinction between trials "with" or "without direct benefit" is particular to France. It will need to be removed after adjustment and publication by France, before May 1, 2003, of the required procedures to conform to European Directive 2001/20/CE, dated April 4, 2001. Eliminating the concept "without direct benefit" is a desirable simplification, but could lead to misuse of phase 1 trials and increasing the risk run by patients. The present drafting of the European Directive is ambiguous and could prohibit any kind of phase 1 trial in cancerology, since it states in paragraph 2a of Article 3 that "a clinical trial may be undertaken only if, in particular, the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients".

Selecting patients for inclusion in a trial :

Phase 1 trials are generally offered to patients whose therapeutic options have run out, and who are often terminally ill. Choosing particularly vulnerable patients, sometimes elderly, always in a state of anxiety, sometimes poorly informed about the severity of their condition, is an ethical problem insofar as most of them accept participation in such trials without fully understanding their aims and scope, and in the hope they might benefit in some way from them. In fact, they are willing to consent to any procedure providing even a spark of hope. The situation is particularly agonising in oncopaediatrics when parents are informed of the possibility of a phase 1 trial involving their child and must give consent in his place. They can only resign themselves to experiencing extreme anxiety, or grasping at very meagre hopes of improvement, for which they are requesting a protocol without any knowledge of the possible suffering their child may have to endure as a result.

Indeed, an essential observation is that for terminal phase patients, clinical and biological tolerance and the pharmacokinetic performance of a cytotoxic molecule may vary depending on whether they are used in a less sick patient, or even in one who has had no previous chemotherapy, which raises the issue of the scientific evaluation of the protocol under study.

There should not be any illusions about specific enrolment difficulties in phase 1 cancerology trials. Lengthening the period of inclusion can be in itself, because of the possible deterioration in the health status of enrolled patients, the cause of evaluation difficulties and unethical situations for dying patients; furthermore, the fact that it is difficult to enrol a sufficient number of patients may mean that their participation turns out to be futile, which is an ethical problem in itself.

Informed consent and prior written information

Recent publications in English on this matter are fairly abundant. All agree that providing information (written or oral) which is deceitful, voluntarily incomplete, distorted, or incomprehensible, is unacceptable.

As for the French information and consent documents seen by CCNE, both industrial and academic, they are very heterogeneous. Their disparity reflects in part, as is the case for the CCPPRBs, the extreme uneasiness of investigators. There is indeed a major conflict of interest between the need to find cancer patients to explore tolerance to new molecules in phase 1 and the duty to "take care" of a patient. There is clearly a moral dilemma when a physician, plays two roles alternately – carer and investigator – as he seeks to improve treatment for future patients. For that matter, should the investigator and attending physician be the same person ? To some people, it seems inconceivable that a doctor could include a terminal patient if there is no hope whatsoever that some benefit could ensue for that patient. Faced with this dilemma, some cancerologists refuse to perform phase 1 trials. Others resort to calling their research phase 1/2. Providing a patient being enrolled for a phase 1 trial with the sincere information that there is a risk of considerable toxicity, that no benefit can be expected, and that the only alternative is palliative care, is not an easy thing to do. As a result, the information provided can be incomplete to avoid rejection of the trial, so that the relationship of mutual trust is damaged. This relationship can also be tainted by a form of moral pressure rooted in the patient's wish to maintain good relations with his doctor. Oral information, more problematical in this case than in any other, must be based on dialogue and exchange.

The issue of whether consent is truly independent must remain a constant concern. The fundamental motivation of patients is generally not altruism but hope that a new therapeutic approach can relieve despair. Consenting to being of use for research never drives out the intimate hope that some personal benefit is still a possibility. The greatest difficulty is in neither extinguishing that hope nor bring it into being unjustifiably. The concept of collective usefulness, of which many patients are well aware, can only become acceptable if there is forthright information given regarding phase 1 trials, and if there is at least a reasonable possibility that the molecules being tested have an efficacious effect on the patient's ailment. As for the patient, if at all possible, his role should be more than purely passive, and he should participate more actively in the research.

The essential ethical problem arising out of phase 1 studies is to ensure that the decision to include a patient is the result of genuine mutual understanding between doctor and patient. The situation here is always lacking in symmetry, and it would be utopian to imagine that patient and doctor can arrive at a common thought process. For that very reason, it is important that the dialogue should bring in the important notion of a third party, i.e. medical research.

Finally, the question of compensation cannot be eluded, but nor can it be solved. Phase 1 trials on healthy volunteers are generally compensated. With cancer patients, absence of compensation is connected to their patient status, and is therefore the source of considerable ambiguity. However, any attempt to assimilate the two situations would raise probably insuperable ethical quandaries.

Such problems have preoccupied CCNE for quite some time.

As early as in Opinion n°2, dated October 9, 1984 (Opinion on the testing of new treatments on humans. Considerations and proposals), CCNE noted that the "*physician faces two ethical requirements, as follows:*

- *in the interest of the patient, he/she must administer what current medical science considers to be the best treatment; and,*
- *the well-being of the community demands that the treatment administered contribute to an improvement of therapy"*.

A European Commission report on basic bioethic principles states that "*The vulnerable*

are those whose autonomy or dignity or integrity are capable of being threatened.". If one considers the potential fragility of patients whose life is ending and to whom a phase 1 trial is offered, everything should be done, as stated in this report, to maintain *"not merely non interference with the autonomy, dignity or integrity of beings, but also that they receive assistance to enable them to realise their potential»*.

Conclusions

CCNE is not questioning the actual concept of phase 1 trials in general. They are essential to evaluate tolerance for any new molecule which it is hoped could become medication. However, their practice in cancerology, for patients for whom no further therapeutic options are available, and who are particularly vulnerable, raise major issues regarding information and consent.

Physicians must avoid ambiguity and clearly state that phase 1 trials do not aim to provide individual patients with any benefit, and are intended to provide collective benefit, even though the first alternative cannot be excluded. Misrepresentation is not the object here, nor is it annihilation of any hope for the future. However, such strict regard for rectitude must take into account the patient's capacity to discriminate. In Opinion n° 58, CCNE underlined that – "duty to inform does not imply that information is given harshly and abruptly". Trust must be founded on the feeling that the patient never becomes simply an instrument for a doctor whose main concern is clinical research. This pact of mutual trust is the only way of reducing the ethical tensions rightfully inspired by phase 1 trials.

The basic principle of phase 1 trials, i.e. separating tolerance and efficacy in the evaluation of a new molecule, cannot be viewed with indifference by anyone, least of all investigators. In order to increase the chances of obtaining some kind of therapeutic benefit for the patient, some modifications to rules and procedures as outlined below should be considered. Obtaining consent must not be a blind for the difficulty of preserving a patient's best interests while keeping intact the scrupulousness and the scientific value of phase 1 trials. Clinical research must never lead to disregarding that

the human being involved has a right not only to respect for his integrity, but also to dignity and above all to the consideration owed to someone whose autonomy of judgment is under threat because of his position of frailty.

Medical progress has often found its source on risk/benefit ratios initially lacking symmetry, to the detriment of benefit. Managing this contradiction is only possible if the absolute and enduring need for the availability of new molecules, a concept which is shared by patients, their next of kin, and by society, is associated with awareness of that asymmetry. Every patient must be able to understand that innovative therapy has always been based on such trials enlisting other patients, and is never the sole result of animal testing. In this circumstance, the rights of the individual cannot be at variance with the duty of solidarity. Society taken as a whole must be aware that the demands of research may sometimes need to show partiality towards the interests of the community. However, this awareness must never be allowed to abolish the major obligation to totally respect those persons who, precisely because of their illness, are able to help their fellow human beings.

Recommendations :

1. In the scientific field, the authorities should encourage and view as a priority the development of research seeking to modify the methodology of phase 1 cancerology trials, despite difficulties emphasised above, so that the risk of toxicity can be reduced, and both toxicity and efficacy can be researched jointly.
2. On the side of regulatory measures, for scientific and ethical reasons, it would be preferable not to demand systematic determination of the toxic dose for new non-cytotoxic molecules which could perhaps initially be administered to healthy volunteers.
3. Procedures for European registration of molecules that have already been tested and used abroad should be simplified, and take into account phase 1 trials previously completed so as not to repeat them to no purpose.
4. A national model, or even a European one, for notices of information and consent

forms, containing all the mandatory items, should be drafted and given to investigators to help them promote good practices. In the written material and during discussion with the patient, the doctor should provide information on the kind of toxic event sought after; mention of modest hopes of benefit must not conceal uncertainties, nor the fact that the trial's major objective is to investigate tolerance of a new substance. The word 'treatment' should be avoided. Signing the consent form should take place several days after handing over the notice of information, and after the investigator has replied to any new or reiterated queries.

In the paediatric sphere, methods for offering options and obtaining consent raise particularly crucial issues, and no effort must be spared to ensure that parents are never made to feel guilty about any decision they may have taken.

Improving the process of imparting information should not be limited to documents mentioned and patients concerned by these trials. CCNE has previously recognised the essential role of intermediary played by support groups who in fact could be urged to take more interest in this difficult problem. Society as a whole should be made aware of the reality and necessity of drug trials generally, and more particularly of those evaluating tolerance to a new molecule.

5. Selection of patients for enrolment is an ethical issue of the utmost importance. Preference should be given to patients who have arrived at the end of their therapeutic options, but not actually at the end of their lives, so as to bypass for this type of study these particularly vulnerable people who are often willing to submit to phase 1 trials without any clear understanding of their object and scope. Choosing patients whose tumour would seem to have, according to experimental data, some chance of being affected by the new molecule, would be desirable. It would also be desirable that, insofar as this is at all possible, that patients participating in phase 1 trials, could also benefit from them. For that to happen, phase 1 trials would need to be carried out with the greatest possible celerity, so that a phase 2 trial on efficacy could be offered very soon thereafter.
6. Enrolment in a trial confers special responsibility on not just the physician, but also on the entire healthcaring team who must be fully committed to the trial and

ready to ensure that the patient has understood the importance of what is at stake. The role of the patient's family in this situation is not an easy one, and this factor should not be neglected. Such a situation reaches its peak in oncopaediatrics; the family's consent decision in these circumstances is particularly excruciating .

7. The patient's quality of life must always enter into the equation, and should never in any circumstances be compromised by depriving him of any palliative care he is entitled to receive. It is a fact that the logic of such trials implies a risk that quality of life can be perceptibly prejudiced by a series of disagreeable side effects to which remedy must be provided with attentive efficacy. CCNE draws attention to the obvious possibility of drug interaction causing interference at a time and phase of the disease when analgesics play a prominent role, but that a palliative approach tailored to the needs of the patient must remain ever a priority and never take second place behind the requirements of phase 1 trial procedures.

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