Research in oncology: legal and ethical aspects

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Medical research is largely based on the conduct of clinical trials. These trials should be able to respond to relevant questions, and their conclusions should be more broadly applicable to the study's target population, regardless of whether the findings are positive or negative. As this research is conducted in humans, both experimental and observational studies should be subject to controlled conditions and compliant with ethical and legal standards.

There are several basic documents related to the ethical aspects of research in humans:

1. Nuremberg Code [1] (1947): establishes that research in humans must be justified by the expected results and that, in any event, subjects must grant their voluntary consent.

2. Declaration of Helsinki [2] The latest version dates from 2004. It establishes that biomedical research in humans must always be based on animal experimentation results and laboratory findings; that the purposes of the study and the methods used for its conduct must be clear and examined by an independent committee; that studies shall be conducted by persons with the necessary scientific qualifications; that research subjects must grant their consent after being duly informed about the study, and that individual interests shall also prevail over those of science or society. The latest version adds that, at the end of the experiment, all participants must be provided with the treatment that has been found to be most effective, that study results must be published whether they are positive or negative, and that participants must be aware of the investigator's economic interests in the trial.

3. Belmont Report [3] Commissioned by the United States Congress. It contains the basic ethical principles applicable to research in humans and was intended to establish the legal standards applicable to biomedical research.

4. Council of Europe Convention on Human Rights and Biomedicine (Oviedo Convention) [4]: Establishes conditions for conducting research in humans, including a lack of alternative and comparably effective methods, that the risks for participants must be in proportion to the expected benefits, that the project must be approved by the competent authority, and that investigational subjects must grant their consent in writing.

Based on these ethical aspects, all approaches to clinical research is or should be conservative, so the risk of rejecting what could be beneficial (type II or beta error) is greater than the risk of accepting what could be harmful (type I or alpha error).

The conduct of clinical trials is also regulated by different national and international agencies. On a European scale, the responsible body is the European Agency for the Evaluation of Medicinal Products (EMA), but the member States of the European Union are responsible for regulating clinical trials. In Spain, Royal Decree 223/2004 and the Medicinal Product Act (Law 25/1990) are applicable to the conduct of clinical trials, for which the Personal Data Protection Act (Organic Law 15/1999) also has to be considered.

All the above is applicable to all fields of medicine, including oncology. Research in oncology, however, has some specific connotations, such as the poor prognosis of some conditions for which there is no standard treatment of proven efficacy, so it would be desirable to include many patients in clinical trials. On the other hand, many oncological treatments are highly toxic, and this must be considered in their evaluation, considering the quality of life they give to patients. These aspects must be considered in all the developmental phases of a clinical trial:

- *Phase I*: First step in research in humans. In oncology, it is largely conducted in patients and not in healthy volunteers. It provides the approximate toxicity and tolerance profile of the investigational product.
- *Phase II*: Its primary objective is to identify the dose providing the best risk/benefit ratio.
- *Phase III*: Evaluation of safety and efficacy in the theoretical regular conditions of use, considering the possible therapeutic alternatives available at the time.

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- *Phase IV*: It discovers more about efficacy and safety during long-term use of the drug once the marketing authorization is issued.

These phases usually form a sequence, but occasionally, and increasingly in oncology, they tend to overlap. This is ethically and scientifically correct in some situations but occasionally involves subjecting a large number of people to a possible risk without appropriate safety or efficacy data. This could be because most research is sponsored by the pharmaceutical industry, which attempts to reduce the time required to develop new drugs and test them on a more or less wide range of diseases.

Although, as mentioned earlier, it is often desirable for patients to be included in clinical trials due to a lack of effective treatment, we should not lose sight of the ethical aspects referred to at the beginning. In a study conducted in the United States, it was found that only one of every eight phase II clinical studies in oncology continues to a subsequent phase of development [5], for different reasons, even when the drug has had promising results in the initial phases. Many trials do not continue due to a lack of financial support or patient recruitment, which in some cases can only be expected. The promising results of the initial phases of a clinical trial are occasionally used to encourage the use of a drug in unapproved indications, thus avoiding the costs of phase III studies and failing to compare the results with those of other available treatments. This means that some patients are subject to possibly unnecessary risks, whereas the work and time of the team of investigators is wasted, as these studies will never result in changes in clinical practice, which is the ultimate objective pursued by the conduct of a clinical trial.

Another aspect to be considered is that the difficulties involved in conducting a clinical trial mean that most research is in the hands of the pharmaceutical industry. In Spain, this represents more than 80% of all clinical trials. This could generate bias, as clinical investigators often focus on other fields or aspects that are of no interest to industry, finding multiple difficulties for the conduct of independent research. An effort is required to promote independent research, creating cooperative work groups and with the administration providing financial and personal support.

In sum, medical research in general, and particularly in oncology, is essential for scientific progress when it aims to provide future (and often present) benefits for patients. Research should always be conducted in ethical and legal conditions that provide protection for patients, and this must be considered before agreeing to the conduct of a clinical trial. As investigators, we must be quite clear about the direction in which research is steered and the objectives we are pursuing, regardless of the pharmaceutical industry's interests. In this regard, the administration should promote independent research, which is often more significant and has more clinical implications than that sponsored by industry.

References

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