ETHICAL ASSESSMENT OF GENOME EDITING APPLICATIONS IN ONCOLOGICAL PATIENTS

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Further development of genetic engineering improved the chances to defeat deadly disorders due to discovery of innovative methods of treatment of various diseases, including oncological ones. In doing so, the methods have to go through clinical trials; they are not safe today. In fact, a paradox emerges: the trials are necessary, but they can't be approved in accordance with regulatory requirements, as the risk for the subjects is higher than the benefit. For oncological patients, clinical trials, however, are the last chance for salvation. This requires an additional ethical discussion regarding approval of ethical expertise by the corresponding authorities in these exceptional cases. In this regard, the author of the article provides an ethical assessment of human genome editing applications from the point of view of risk and benefit for a subject and community of subjects, taking into account such ethical principles as 'human priority', 'precautionary principle' and 'principle of responsibility to future generations'.

Keywords: morality, bioethics, ethical principles, genome editing, treatment of cancer patients, the precautionary principle, the principle of responsibility to future generations

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МОРАЛЬНАЯ ОЦЕНКА ПОСЛЕДСТВИЙ ИСПОЛЬЗОВАНИЯ ТЕХНОЛОГИЙ РЕДАКТИРОВАНИЯ ГЕНОМА ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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С развитием генной инженерии появился шанс одержать победу над смертельными болезнями благодаря открытию инновационных методов лечения различных заболеваний, в том числе и онкологических. При этом методы должны пройти клинические испытания, и на сегодняшний день они небезопасны. Возникает парадокс: исследования необходимы, но согласно регулятивным требованиям и предписаниям разрешить их нельзя, так как риск для испытуемых в данный момент выше, чем польза. Однако клинические испытания, например, для онкологических больных являются последним шансом на спасение, и это требует дополнительного этического обсуждения в плане разрешения проведения в этих исключительных случаях этических экспертиз соответствующими инстанциями. В этой связи автор статьи дает нравственную оценку последствий использования технологии редактирования генома человека с позиции пользы/риска для отдельной личности и сообщества индивидов, опираясь при этом на такие этические принципы, как «приоритет человека», «принцип предосторожности», «принцип ответственности перед будущими поколениями».

Ключевые слова: мораль, биоэтика, этические принципы, редактирование генома, лечение онкологических заболеваний, принцип предосторожности, принцип ответственности перед будущими поколениями

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Searching effective methods of treatment of oncological diseases is a strategic task of modern medicine. Traditional methods of struggling with the developing tumor that have been used by physicians for a long time include surgical treatment (complete tumor removal), radiation therapy (tumor radiation), and chemotherapy (use of medicines that inhibit rapid cell division). The methods do not always provide for the desired outcome, as a surgery does not warrant complete tumor removal, whereas radiation therapy and chemotherapy can kill healthy cells and result in decreased immunity and other serious outcomes, including a patient's death. That is why doctors and scientists across the world started seeking alternative methods of treatment. Deepened knowledge of tumor genetic features and rapid development of genetic engineering opened up new horizons to treatment of oncological diseases.

Thus, virotherapy (viral oncolytic therapy) is not an innovative alternative method as it was developed in the second half of the XX century. At that time, however, medicine had to deal with naturally occurring viruses only, that's why the antitumor effect was short and unstable. Moreover, 'the lack of a normal virus-specific immune effect consistently worsened a patient's condition' [1]. It significantly, up to oblivion, inhibited development of virotherapy and only gene engineering opened up new prospects for it, because the majority of developed methods and technologies

focused right on cancer treatment. Today, genome editing is the most perspective method in this regard [2], even though the possibilities of its application are limited, and these ethical and medical discussions raise more questions than they answer.

Technological approaches to human genome editing appeared at the end of the last century. However, the principal achievement included development of CRISPR/Cas system by J. Doudna and E. Charpentier who obtained the 2020 Nobel Prize for that. They examined Cas9 exposure on bacteria and showed that 'any DNA molecule, including human DNA, can be cut at any point' using a certain mechanism. That was a revolutionary discovery. CRISPR/Cas system made it possible 'to introduce point mutations, integrate new genes at certain sites or remove parts of nucleotide sequences, correct or substitute gene fragments' [3].

Thus, CRISPR/Cas9 gave hope for salvation to millions of people. We have already succeeded in treatment of certain types of cancer by now. Physicians managed to obtain immune cells of a patient and alter their genetic defects that would not allow them to struggle with tumor antigens [4]. According to Stadtmauer E, this may be evidence of safe genome editing [4], as only necessary cells, but not the entire human genome, are edited in this case. Thus, apparent safety is not real safety, that is why there is no reason to discuss early integration of CRISP-technology due to opposite opinions of scientists [5]. Thus, He Jiankui, a Chinese scientist, used the CRISPR/Cas9 system to conduct clinical trials with human embryos. The fact was made available to the public and had serious disputing resonance. In spite of certain success, gene editing could result in DNA errors: according to genetic scientists, there is a risk that the errors will be inherited. In this regard, such world-famous journals as Nature and Science refused to publish the results obtained by Chinese scientists referring to non-compliance with ethical and legal standards of the trial and lack of uniformity regarding the borders of using the genome editing technology [6].

Nevertheless, clinical trials are required to introduce any technology; it is impossible to assess its safety without them. So, the 'ethical risk' is inevitable in case with CRISPR/Cas9 as well, which calls for ethical assessment on the part of benefit/risk for the subjects.

Every person tries to live longer. When coming across such a restriction as a deadly disease, the person thinks of experimental methods of treatment and possibility to participate in clinical trials with some advantages and shortcomings. The principal advantage for the participants includes access to novel medications and technologies, which are currently inaccessible to other oncological patients. There is a chance that they will be effective and that the patient can prolong his life. Moreover, the level of control over such a patient is much higher than that during standard therapy. This would certainly have an effect on taking a decision. The altruistic factor is important here as well. It is associated with contribution to the trial by the patient which makes our knowledge of oncological diseases deeper and more expanded, saving lives of others in the future.

The benefit of CRISPR/Cas9 system is doubtful for sceptics only, as previously incurable diseases will turn into curable ones owing to correction of genes. This can have negative, and probably irreversible impacts, as correction of certain gene mutations can affect occurrence of others (just like with the Chinese scientist's experiment); the genetic perspective is not always known. The technology of genome editing can be successful for some patients and useless for others. Nevertheless, the trials are necessary and many oncological patients agree to use the chance. But is it ethical in relation to them? Can we mention a voluntary, rational and weighed solution in this very case?

In this regard, ethical assessment of using the method of human genome editing should be performed from the perspective of a certain personality who has a right to live and from that of the society of people considering potential risks and benefits, as any human genome transformation can result in both positive and negative consequences with different modalities. In this case, according to Jonas G, the rule 'of advantage of unfavorable prognosis over favorable one' should be applied on a constant basis. Thus, we need to be 'more attentive to the prophecies of disasters than to the prophecies of welfare' [7]. It is obvious that modified genes are inherited, and the human genetic pool can be altered. Two ethical issues that arise are as follows: the issue of the right to experiment with human beings of the future and the issue of how and to which extent genetic control over a human of the future can be implemented. They are now subject to the ethical 'do no harm' restriction and regulated by the 'precautionary principle', which is synonym to the rule by Jonas G. According to Yudin BG, the principle should be applied when safety of a new biomedical technology is doubtful. The last one can be used only when scientists can provide solid arguments in favor of benefit over possible risks [8]. In case with genome editing technology, no such risks are available yet. Moreover, the consequences can be unpredictable for the future genetic pool and concern 'the roots of the entire human enterprise' [7]. Thus, global mistakes and failures must be excluded. Following pragmatic purposes, however, a human being re-estimates his own mind, and his attempts to submit and control over own evolution are overconfident. That is why the moral attitude 'to preserve the legacy of prior evolution' is still pressing because the heritance is not that bad for the people of today.

Ignoring the technology safety for the benefit of an individual, we form the lottery effect based on the 'non-reliable' 'or-or' principle, though as per art. 3 'Human priority' of Strasburg Additional protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research as of 2005, 'the interests and welfare of a subject participating in the trial prevail over the interests of science or society' [9]. The same provision is set in the Model Law 'On protection of human rights and dignity in biomedical trials in member states of the CIS': 'it is acceptable to conduct human biomedical trials if direct benefit is obtained' [10]. Thus, it is not allowed to conduct the trials that provide primary benefit to other people or contribute mainly to progress in science.

Let us consider the situation on the part of benefit for an individual: it is not obvious, but it can occur so. Thus, the principle of 'human priority', principle of humanism that gives the human the status of absolute value, comes into collision with the principle of 'responsibility to future generations', which raises the following question: 'Can I participate in a lottery that affects interests of other people?'. The point is that close genetic intermingling in a human community enables to draw a conclusion that it is practically 'impossible to avoid not influencing the destiny of other people by my actions' [7]. Going big in case of a clinical trial which is the last hope for an oncological patient, the subject indirectly counts upon something that belongs to somebody else. It means that personal interests prevail over public interests, which is primarily based on his comprehension of ethics and feeling/not feeling such an emotion as guilt. Can we consider the decision ethically justified?

Arguing about potential risks for the entire community of individuals, we mentioned the 'no-harm' principle, which is universal and global, and in the case with genome editing its particularization is not possible yet. In the opinion of Apresyan RG, this principle 'is of an objective and impersonal nature', similar to any other ethical requirement [11]. Though it is valid for everyone, it can't grasp the entire richness of real-life

situations, ignoring the right of an individual to a life and his possibly only chance to prolong this life even at the expense of such risk. Moreover, the same Additional protocol states as follows: 'a human trial can be conducted only when there is no effective alternative to this method' [9], which is true at the terminal phase of an oncological disease. So, the principle of 'responsibility to future generations' is a doubtful critical point for a common man who takes the decision.

The principle often results in regulative moral prohibitions adding to the 'precautionary' principle. At the same time, the principle initiates many actions extending beyond the 'here and now' ethics but having an ethical justification while mentioning welfare of a human being in the future. However, everyone of us has moral obligations and responsibility to people we contact and interact with; we expect the same from those around us because of our idea of a moral obligation. This is how the golden rule of ethics is applied in its primitive sense. It is not applicable to the future generations due to the lack of reciprocity. In case of an immoral deed, a person waits for conviction or at least pretension on the part of the recipient of these actions. The 'non-existing' future can't lay any claims, because it has no rights at this very moment. In this regard, the following questions arise: 'What has the future done for me? Does it observe my rights?' [7].

It is obvious that ethics is about reciprocity. It is manifested through the social 'human-human' relations, that's why the 'human being-future human being' linking goes beyond the range. There are cases when ethical activities are a priori unresponsive, for instance, ethics of care towards own children. Such ethical features as unselfishness and altruism are always manifested in this case and the principle of responsibility to future generations acquires the status of 'obligation to the offspring'.

Nevertheless, the question remains open: human genome editing can't be introduced without clinical trials. It is not safe today. The way out is a trial with voluntary participation by people with untreatable diagnosis. The thesis is immoral as it is, because in accordance with the Additional protocol, human benefit from conducted trials and experiments should significantly outweigh the risks and negative effects. Does it mean that the destiny of a patient with terminal illness is predetermined? How can the patient accept and morally agree with the prohibition of clinical trials based on responsibility to the future on a rational basis, if his life is determined here and now, this being the only chance? On the other hand, taking into account the lack of the 'right to suicide' in a human being, the lottery is far from being immoral, as a number of oncological patients and patients with inherited diseases is exponentially increasing. That is why in case with the person of the future, the immoralism can be substantiated from an ethical point of view. In fact, the 'moral luck' is always associated with an 'ethical risk': absolute moral prohibitions of deontology do not operate on the constant basis when it is about the life of an individual. So, in this case those who take a decision about the use of genome editing should refer to the utilitarian and pragmatic practice.

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