DOI: 10.5045/kjh.2010.45.3.145
The Korean Journal of Hematology
Volume 45 · Number 3 · September 2010

Perspective

Freedom to choose a cure: how safe is a deadly cancer?

Vladia Monsurró, Ph.D.

Department of Pathology and Diagnostic, University of Verona Medical School, Verona, Italy

"A 56-year-old woman with advanced, incurable ovarian cancer was invited to be the first patient, in the first dose level, of a phase I trial of a new drug that was being given to patients for the first time. The patient information sheet stated that she was unlikely to benefit from her participation in the trial, and she was told that when phase I trials are initiated, the drug concentration is usually significantly less than the final recommended dose or maximum tolerated dose of the compound. The patient was concerned about not obtaining a tumour response with the lower dose level, and asked if she could delay participation until higher dose cohorts had opened for accrual" [1].

This episode is emblematic and poses, in my opinion, a number of key ethical questions. Are, for example, phase I trials always in the patient's interest? Is the safety requirement that is tested in phase I trials really an advantage for patients? Perhaps, instead of a dose escalation, the best guess approach for cancer patients would be more in their interest? Should it not be the patient who, after being fully informed, decides and tailors the therapy according to a risk evaluation that encompasses his or her specific situation (emotional, familiar, and clinical)? Why shouldn't a patient with an incurable terminal disease be able to choose for himself or herself the level of risk to take in the hope of gaining some benefit?

Maybe patients' voices should be listened to more often and they should, after being appropriately and completely informed about a new trial's risks/benefits, be able to decide, with their doctor's support, the level of risk to which they should be exposed. An interesting study from Manish Agrawal's group showed that for 63% of patients, the most important information for decision making was the fact that phase I drugs killed cancer cells, whereas only 12% considered drug adverse effects as the most useful information. In the same study, more than 90% of patients said they would still participate in a study even if the experimental drug caused serious adverse effects, including a 10% chance of dying [2].

In 1936, the US government instituted the federal registers to record regulations. The main objective was to protect consumers. Nowadays, regulatory agencies are developing and growing in number. Philosophically, the presence of regulatory agencies is very important for protecting consumer and patient health; moreover, in the biomedical scientific field, the presence of a third party committed to defending and protecting patients from biotech economic interests and speculations is of great value.

However, currently, the regulatory steps for clinical approval of a new drug are so numerous that often there is a considerable delay from when the drug is ready to be tested to when the investigational new drug (IND) application is ready to be filed. Furthermore, before the Kefauver Harris Amendment ratification in 1962, the average time from filing an IND application to gaining approval was 7 months. By 1998, it took an average of 7.3 years from the time of filing to the time of approval [3].

In February 1999, during the television show "Take it to the limits," the economist Milton Friedman argued that, while all the regulatory agencies are concerned with the safe usage of new drugs, the delays in the approval process have cost lives. This was proved in 1990 by Louis Lasagna, then chairman of a presidential advisory panel on drug approval, who estimated that thousands of lives were lost each year due to delays in the approval and marketing

of drugs for cancer and AIDS. Subsequently, the FDA introduced on their website an expedited approval of drugs for life-threatening diseases and expanded pre-approval access to drugs for patients with limited treatment options.

The worldwide growth of diversified regulatory agencies has created another phenomenon: the huge discrepancy regarding the possible therapeutic choice for patients, depending mostly on the country they live in. This again limits the power of patient choice. Why, for example, is an adaptive therapy more efficient or more toxic for a German pancreatic cancer patient than for one from Italy? While it is impossible to argue about the importance of the FDA developing effective global risk control on the food industry in order to ensure greater safety for consumers with respect to suspect food on the market, it is definitively more difficult to assess the benefit and the main focus of reducing of all kinds of risks for terminal patients.

Historically, medicine has always improved thanks to clinical experimentation. If we consider most of the key drugs and medical procedures that are successfully used in the clinic nowadays, they would never pass the requirements needed to complete a successful IND application for a regulatory agency like the FDA in the United States in order to allow a phase I clinical trial [4]. As a practical example, let's just think about a bone marrow transplantation procedure to produce new blood cells. This therapy, which uses bone marrow-derived stem cells, was initiated in 1950 by the Nobel Prize winning E. Donnall Thomas's team at the Fred Hutchinson Cancer Research Centre. However, one of the recurrent major and life-threatening complications that occur as a consequence of this widely adopted procedure is graft-versus-host disease (GVHD). GVHD is an inflammatory disease that is unique to allogeneic transplantation.

This type of therapy would never be introduced into clinic practice today, prohibited by the stringent safety criteria adopted in the new phase I studies.

In an era in which medicine is moving toward personalized solutions, where we start to fully appreciate the differences in the unique biological response of every single patient to treatments, we translate this highly innovative vision of the individuality of each single patient and disease to standardized, highly conservative phase I criteria that is the major obstacle to a more effective bench to bedside translational research. The main goal for patients and physicians should be fighting cancer, and almost no adverse effect, including death, should dissuade terminal patients from enrolling in promising phase I trials. This idea and the data obtained by Agrawal's group are in open disagreement with the bureaucratic system that delegates the responsibility of risk decision making to third parties made up of government employees who often have never worked in a clinic or in research, and who lack practical clinical research experience to effectively judge the consequences of a trial. The economist Milton Friedman has claimed that the regulatory process is inherently biased against approval of some worthy drugs, because the adverse effects of wrongfully banning a useful drug are undetectable, whereas the consequences of mistakenly approving a harmful drug are highly publicized. Therefore, the FDA will take actions that will result in the least public condemnation, regardless of the health consequences [5]. This observation underlines once again that safety is probably a more important endpoint for regulatory agencies than it is for patients.

REFERENCES

1. Rosa DD, Harris J, Jayson GC. The best guess approach to phase I trial design. J Clin Oncol 2006;24:206-8.
2. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ. Patients' decision-making process regarding participation in phase I oncology research. J Clin Oncol 2006;24:4479-84.
3. Thomas LG. Regulation and firm size: FDA impacts on innovation. Rand J Econ 1990;21:497-517.
4. Senderowicz AM. Information needed to conduct first-in-human oncology trials in the United States: a view from a former FDA medical reviewer. Clin Cancer Res 2010;16:1719-25.
5. Friedman M, Friedman R. Free to Choose: a personal statement. 1st ed. New York, USA: Harcourt Brace Jovanovich, 1980.