Review Article

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Post-trial access to treatment for patients participating in clinical trials

Abstract

Clinical trials are the mainstay for bringing out newer and better drugs to serve the mankind. By virtue of participating in a clinical trial, a patient receives access to the newer drugs/therapies, but nothing is generally being offered to them once their participation in the study comes to an end. Though the issue of post-trial access to treatment by patients participating in a clinical trial is debatable, there is no compelling justification either for or against it. We examined a case study in order to evaluate the applicability of post-trial access to treatment for patients participating in clinical trials. The provision of post-trial access to treatment should also keep into consideration the compassionate use of drugs on humanitarian grounds, especially in cases of trial drugs that have offered significant benefit to the trial patients and whose termination would lead to deterioration in patient's overall condition. In the present era of personalized medicine, the incorporation of genetic testing into clinical practice further authenticates the rationale of compassionate use of drugs and post-trial access to treatment.

Key words: Clinical trials, medication, post-trial access

INTRODUCTION

Clinical trials are the mainstay for bringing out newer and better drugs to serve the mankind. It is the most expensive and time consuming component of the new drug development process. In today's scientific era, research is taking a major stride in all streams and newer and better drugs are being introduced to cure ailments, which are difficult to treat. Although the conduct of clinical trials in any country is governed by a set of well-defined guidelines, it is still looked upon as an area of humanitarian concern at times. As the patients remain the cornerstone for every clinical research project, the focus of all the clinical research guidelines is towards protecting the rights, safety and well-being of study subjects. By virtue of participating in a clinical trial, a patient receives access to the newer drugs/therapies but usually very little is being offered to them once their participation in the study comes to an end.[1]

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The issue of post-trial access to treatment for patients participating in clinical trials has always posed a state of ethical dilemma having strong justification for and against it. On one hand, it seems fair to offer post-trial access to treatment to patients participating in clinical trials, but on the other hand it appears to be a factor posing undue influence or coercion for participation or continuing participation in a clinical trial.

The Medicines for Human Use Regulations 2004 states that in applying for an Ethics Committee opinion, the sponsor of the trial should supply details of "the plan for treatment or care of subjects once their participation in the trial has

ended."[2] This statement is based upon the World Medical Association Declaration of Helsinki adopted by the World Medical Association in June 1964 (and ratified by Brazil) as a "statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects."[3] In addition, it also states that "at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." Further, the Helsinki declaration includes the statement "in advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process" under the post-trial provisions section. A report by Emanuel, 2013 has also suggested that "participants and their communities should receive fair benefits from participating in research. Benefits can take many forms, including but not limited to access to interventions proven safe and effective in the research."[4]

ETHICAL CONSIDERATIONS FOR POST-TRIAL ACCESS TO TREATMENT

- A patient who takes on the inconvenience and potential risks of a medical research study should have access to the best proven prophylactic, diagnostic, and therapeutic methods that result from the study
- The need to protect the rights, safety and well-being of trial subjects should extend beyond the study duration, especially for those who have responded to study therapy
- Depriving a trial subject who have responded well to study therapy from the post-trial access would defeat the basic principle of medical ethics
- Before undertaking a study, the physician should ensure that all patients entered into the study has access, after their participation, to any available prophylactic, diagnostic or therapeutic methods that the study identifies as the most effective and appropriate for such patients
- When obtaining the patient's consent to enter the study, the physician must explain the treatment options after the study and how they relate to the patient's condition
- Arrangements for the continuation of treatment beyond the study must be described in the study protocol.

FAIRNESS CONSIDERATIONS AGAINST POST-TRIAL ACCESS TO TREATMENT

- Cost of any trial with more exacting standards is too high which in turn would limit the number of new clinical trials
- Laying obligations on trialists will discourage trialists, and funders, and shift the burden away from governments
- All patients in the trial are better off than they would normally be, and are no worse after the trial than they were before
- This long-term benefit would be unfair to countries or populations who were not "lucky" enough to host the trial
- Setting high standards would exclude patients who would have taken part at the lower standard, who cannot take part now because the trial has to be cancelled on cost grounds.

In order to evaluate the applicability of post-trial access to treatment, we examined a case study and the observations are listed below:

Case study

Mrs. SB, a 61-year-old female presented to us in 2003 with the complaints of cough with expectoration, shortness of breath and weight loss of 3 months duration. She was nonsmoker, normotensive, had diabetes as well as cardio-vascular disease. She was investigated and found to have adenocarcinoma of lung. Staging workup revealed bone metastasis and she was offered standard platinum based doublet therapy of gemcitabine and carboplatin. She was responding well to the treatment as was evidenced by chest computed tomography (CT) scan done after three cycles of chemotherapy. In the subsequent fourth and fifth cycle of treatment, her tolerance to chemotherapy was poor. During the fourth cycle of chemotherapy, she had developed Grade 4 neutropenia and she had to be given granulocyte colony stimulating factor (GCSF) support and subsequent cycle of chemotherapy was delayed by 1 week. Subsequently, in the fifth cycle of chemotherapy, she developed febrile neutropenia and Grade 4 thrombocytopenia despite standard dose reduction. She required hospitalization for supportive care and required blood product support, antibiotics and GCSF support. As she was tolerating the chemotherapy poorly, she showed a desire to withdraw from it.

At that point of time, we were actively recruiting patients for Iressa Survival Evaluation in Lung Cancer (ISEL) trial "a double blind, placebo controlled, parallel group, multicenter, randomized phase III survival study comparing ZD 1839 (Iressa, 250 mg tablet) plus best supportive care versus placebo plus best supportive care in patients with advanced non-small cell lung cancer (NSCLC) who had received one or two prior chemotherapy regimens and were refractory or intolerant to their most recent regimen." Although discussing the further treatment options, we gave her

the option of participation in the ISEL trial. She agreed to participate in the trial, tolerated the treatment well and her disease stabilized on the treatment. ISEL study results were negative and Iressa failed to significantly prolong the survival in comparison to placebo in the overall population or in patients with adenocarcinoma. The placebo-controlled phase III study investigated the effect on survival of gefitinib as second-line or third-line treatment for patients with locally advanced or metastatic NSCLC. Treatment with gefitinib was not associated with significant improvement in survival. There was pronounced heterogeneity in survival outcomes between groups of patients, with some evidence of benefit among never-smokers and patients of Asian origin.[5,6] Unblinding of study was done and the patient SB was found to be on Iressa arm, responding well to treatment. We were in the ethical dilemma to continue or discontinue the study drug. In the interest of the study subject, we decided to continue the medicine off trial with the available generic gefitinib. After due discussion with the sponsors of the study and the ethical dilemma in this case, another roll on clinical trial was proposed to allow the patient to get the drug Iressa and the study was entitled "multicenter, open label, extension study of treatment with gefitinib (Iressa) for patients completing other gefitinib clinical studies who may benefit from gefitinib treatment". By the time this new study was getting Institutional Review Board (IRB) and regulatory approval, we started the patient on generic gefitinib, which was available in our country after due discussion and consent of the patient. Once the study got regulatory and IRB approval, the patient was restarted on the drug Iressa after due consent. Her disease status was partial response until October 2008 and periodic evaluation CT scan chest done in May 2009 showed complete disappearance of the tumor with no radiological evidence of disease. Patient continued on tablet gefitinib with periodic evaluations with CT scan of the chest. CT scan chest and abdomen done in April 2013 was suggestive of metastases in liver. A CT-guided biopsy was positive for adenocarcinoma consistent with primary from lung. A mutational analysis done on the liver tissue revealed epidermal growth factor receptor mutation on exon 19. The patient has hence been shifted on tablet erlotinib since April 2013.

Putting things in perspective, we have moved a long way in achieving the goal of personalized therapy on NSCLC. As early as year 2000, all lung cancer patients were only classified into two groups and were either small cell or NSCLC and treated accordingly. However, in the current era, "one size fits all" does not cater to the specific requirements of patients in terms of their treatment.[7-9] The issue of genetic testing and personalized medicine can offer great help and clarity in action to all the stakeholders involved in the trial process. If the genetic makeup is investigated beforehand, it can save the patient from unnecessary toxicities, delayed chemotherapy, and financial costs, make the treatment roadmap clearer for the clinician and reduces the extra costs involved in providing the trial medicines even when the trial is over. Based on the molecular tests, if a particular patient is figured out to benefit from a trial drug, then the issue of post-trial access to treatment should also keep into consideration the compassionate use of drugs. This should be specially promoted and more so on humanitarian grounds in case a patient has been found to have significant health benefits from the trial drug. In the near future, the advent of advanced specific treatment strategies for individual patients may completely change the scenario of lung cancer treatment and change it from an incurable disease to a curable condition. Thus, if individual genetic testing can be amalgamated into routine clinical practice especially in this era of personalized medicine, it further authenticates the requirement of compassionate use of drugs and use of post-trial access to treatment.

CONCLUSION

Though the issue of post-trial access to treatment for patients participating in a clinical trial is debatable, there is no compelling justification either for or against it. As clinical trials moves in a phase wise manner with stringent inclusion/exclusion criteria, a patient is in more than minimal risk while on study. Hence, the issue of post-trial access to treatment should be carefully evaluated on case to case basis depending upon the therapeutic area as well as severity of the condition. In my opinion, the provision of post-trial access to treatment should be limited to compassionate use of drugs on humanitarian grounds, especially in cases of trial drugs that has offered significant benefit to the trial patients and whose termination would lead to deterioration in patient's overall condition. However, the issue should be discussed in greater details among the stakeholders to evolve a uniform consensus about it. Furthermore, the case of post-trial access to treatment and compassionate use of drugs gets further strengthened if the results of genetic testing are available in today's clinical practice involving the use of personalized medicine.

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