Translational Study in Cancer Research

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Abstract

Recent progress in molecular biology has led to the identification of numerous molecular targets of cancer chemotherapy, and the strategies for new drug discovery have concentrated on target-based screening. In the development of target-based drugs, translational research is considered to be essential. In this review, the definition of translational research is clearly explained, and the points of misunderstanding of Japanese researchers are discussed and resolved. The primary goal of translational research is to integrate the advanced informations of molecular biology in moving forward from phase I and II trials to phase III trials of target-based drugs.

Definition of “Translational Research” (1)

The concept of translational research addresses what would be an efficient and orderly way of applying the advanced understanding and technology of the field of biology to cancer treatment. The essence of translational research lies in coming to understand the biological features of a cancer so as to translate molecular biological evidence into clinical anticancer strategies. In other words, “translational research” can simply be defined as the process of determining a treatment solely on the basis of molecular biological characteristics.

Up to now, we have classified cancers as arising in the lung, the stomach, the breast or the ovary. There are common molecular characteristics that are active in different histological types of tumors, and these characteristics can directly determine the treatment.

Translational Research in Cancer Diagnosis

Based on the general definition of translational research, there are various ways in which this research can be approached. One area to which it can be applied is diagnosis. Lung cancer has been classified as either small or non-small cell lung cancer based on the selection of treatment modality, and has been histologically classified as squamous cell, adeno, large cell or small cell lung cancer. We can classify lung cancer into as many as two dozen different diseases that attack different molecular targets working in different ways. For example, some cancer cells are p53-mutated and others are of the p53 wild type, some have ras oncogene overexpression and others have overexpressed tyrosine kinases such as EGFR, HER-2/neu, VEGF, etc. Now many new investigational drugs are available in each of these different molecular targets. A better diagnosis based on the knowledge of which molecular markers are present in a tumor may enable physicians to better understand the action of newer treatments.
Translational Research in New Drug Development

Another type of translational research involves using the expression of a particular target as a basis for developing new agents. This type does not intend to develop a drug that is effective against tumors in specific organs, such as lung, colon, gastric, head & neck, breast or ovarian tumors, but rather aims for drugs that can be used in many tumors in different organs. The critical contribution that the translational research can make is to increase the efficiency with which we are able to develop such drugs. Rather than treating 100 patients with some specific tumor type, only 10% of which may have a given target, we can select the appropriate target patient population ahead of time, and thus there will be a very high likelihood of a good outcome.

Globally, researchers are coming to understand translational research as being tightly connected with biology, both as a source of strategies for developing new drugs and in the selection of patients for study.

Molecular Correlative Study and Translational Study

Are there any differences between molecular correlative study and translational study? Many of the techniques and tools that allow us to make distinctions between tumors and normal tissue originated in molecular biology, e.g., the detection of overexpression in new genes and the detection for the mutation of tumor suppressor genes as heavily involved with molecular endpoints. Some types of correlative studies may actually be quite translational because we are assessing whether the drug’s action or toxicity correlates with an effect on the molecular target. Other correlative studies, however, may not be directly tied to the drug’s target action. For example, if we study the effect of the agent on some index of normal organ function such as the development of some cytokines, we are not correlating with the effect on the target in the tumor, but rather with an effect of the agent on the normal host physiology. In addition to studying the molecular effects of new drugs in either tumor specimens or actual biopsies from patients, there is great interest in extending this way of thinking to the development of imaging approaches, so that we would be able to not only perform molecular studies but also be able to image the presence and modulation of molecular targets with radiology or nuclear medicine techniques. Although translational research started with molecular characterization, it will potentially include radiologic and diagnostic approaches as well.

Japanese Definition of Translational Research

There is a great misunderstanding of the definition of “translational research” among Japanese scientists. In Japan, “translational research” is considered to apply to very early clinical trials using treatment skills developed by investigators in a university/research institute, not by a company, using very small numbers of patients, just before the NDA phase I trial. After the NDA phase I trial, the study is no longer called a “translational study”. The term refers to very narrow clinical areas without evidence of molecular events in the background of the treatment modalities. Major strategies of “translational research” in Japan are gene therapy, immunotherapy, chemoprevention and the use of some small molecules to inhibit angiogenesis, which pharmaceutical companies do not want to develop.

Gene Therapy as Translational Research

Gene therapy itself is not necessarily translational research according to our definition. In the case of gene therapy, the genes that one would seek to develop or use in a therapeutic approach are derived from an understanding of what genes are altered in the case of a disease. For example, there are gene therapy approaches that would seek to reintroduce wild-type p53 into tumors. However, the maneuver depends on whether a tumor has wild-type or mutated p53. In this sense we are translating the concept of p53 as important in the clinic. However, if a gene therapy is applied indiscriminately to all types of cancer, it is only an empirical treatment. If patients were selected based on the possession of an abnormal gene that is being attempted to be replaced or corrected, the gene therapy would fit the definition of translation.

Immunotherapy as Translational Research

There has been much debate over many years as to the best approach to stimulate immunity against tumors. Previously, researchers involved in immunotherapy ground up tumors and simply gave them back to the patients they were removed from or to other patients. This is not really translational research. At present, there is an understanding that the tumor antigens can be isolated and grouped as to which are more or less likely to provoke an immune response by collaborating with HLA antigens. Knowledge of this resulted from an understanding of the biology of how antigens are processed. We can now define which peptides in which the antigens have a likelihood of inducing a response when they are presented either as cells or with dendritic cells or in other ways. It can be said that to merely give tumor vaccines without consideration of immune response is not translational. But it is translational to have a selection of antigens based on our understanding of how the immune system operates and which antigens are likely to be or actually are expressed in a tumor, because we are incorporating the biology into the clinical trial design.

Regardless of gene therapy, immunotherapy and other strategies, translational research ideas should exist throughout preclinical, phase I and phase II studies of a new treatment before and after the initiation of an NDA trial.
Collaboration of Preclinical and Clinical Investigators

The formation of a multidisciplinary team is essential for molecular target design. This team should be built around a particular biologic opportunity. For example, if one has the choice of a given enzyme that is overexpressed on a growth-survival pathway, the team that would address the enzyme as a target would include a basic science team, an animal studies team, a pathology team and a clinician. These scientists should develop clinical trials based on an effort to modulate the effect of that target. There would thus be continued interaction among the different groups, and ultimately there would be a number of agents who might possibly affect the target being studied by the group.

Collaboration with Pharmaceutical Companies

Many of the candidates for target-based drugs originate in a pharmaceutical company. Academic researchers should try to decrease the risk to companies of participating in such scientific studies. Certainly such studies may be costly and may entail the diversion of a compound that may otherwise be on track for government approval. The academic researchers view their activities as increasing the attractiveness to companies of having such studies to be part of the development process for the compounds.

GLP Standard

Without collaborating with a pharmaceutical company, it is quite difficult to obtain the treatment maneuvers in accordance with the GLP standard. The properties of the substance, of the molecule, or the vector or the gene-delivery agent should very carefully and precisely be defined. If the substances are not produced under GLP and GMP manufacturing conditions, it is possible that what is prepared for one clinical trial may be different from what is prepared for another clinical trial, and that other batches will also differ from each other. In such a situation we will not have the necessary correspondence between the clinical trials that come from different centers. The essence of a phase I clinical trial is a dose, route, and schedule that will be as practicable in one place as in another. If this correspondence is not present, there is no point to performing trials in different places, as the results will not be comparable. The believability of different clinical trial outcomes rest on having a fairly uniform approach to obtaining test substances.

Paradigm Shift for the Development of New Anticancer Development

Previously, anticancer drugs have been selected to go into a clinical trial based on the number of *in vitro* and *in vivo* (animal) models that were effected by the drug. In the development of molecular target drugs, it is critically important whether or not the models that are effected actually express or are relevant to the target. Phase I studies aim to assess pharmacology and toxicity. In molecular target-based drugs, we must also assess the effect of the drugs on a target, either in tumor tissue or in peripheral blood lymphocytes, and incorporate these findings into the decision-making process regarding how we go into phase II study. The key difference with phase I study of cytotoxic drugs is not only the ability to deliver a safe dose and schedule, but also the delivery of a safe dose and schedule with significant effects on the molecular targets. If we could select the target well enough, then we could design a phase III study intelligently, even if we do not have enough data from a phase II study.

Clinical Trial Design of Molecular Target Drugs Incorporating Translational Research

During clinical phase I trials, some degree of translational research has been scheduled, and the idea that we would incorporate molecular target assessment in phase I trials has to be judged on the basis of the degree of evidence that the target is related to the effect of the drug. If the target assessment is difficult in terms of obtaining specimens or because of a biopsy or tests that are potentially dangerous to the patient, the assessment is not recommended until the dose reaches the level that is recommended for phase II study. At this point, in a very focused way, we address in a relatively small number of patients whether or not the dose is actually modulating the target. Usually in a phase I clinical trial we accrue 6 patients at the recommended phase II dose level. With target-based drugs, the number of patients at the recommended phase II level may be increased to 12 or 20 for the purpose of seeing whether the target is affected and what the statistical confidence of the target effect is. At this point we must decide whether the trial should go forward (a 'GO') or not (a 'NO GO'). For example, if a number of patients were treated at the recommended phase II dose and the study did not have enough statistical power to determine whether the treatment is effective at that dose, how should it be determined whether this study is a 'GO' or a 'NO GO'? If the target is going to be affected in different patients with enough certainty and there is no toxicity, the decision would be "GO". On the other hand, if there is no effect on the target, the decision should be "NO GO". In a case in which we have not observed much efficacy, but we do have clear evidence of a target effect, either the originating company or the research institute would have to make a decision based on their understanding of the target. It is reasonable to conduct broader phase II studies such as a phase I/II or randomized phase II study, but not a phase III study, under such circumstances. The purpose of this broader phase II study is to gather evidence that these findings are likely going to translate into a favorable outcome. In this phase II study, the dose for which there is evidence that the molecular target can be affected should be used. The statistical power of that type of design is usually not sufficient for registry, but it should be sufficient to tell us that we have a therapy that is going at least as well as standard
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therapy. If the study is conducted properly, the arm that is showing a favorable response can be opened up to become a large phase II study of the effect in particular diseases, such as renal, pancreatic, lung or other cancers. The outcome of such a study, if it is a favorable outcome that is markedly different from the historical controls, may actually be a basis for registration.

To approach, we need to use the molecular target effect obtained by translational research in making the registrational studies decision to go from phase I to phase II, and then use a randomized phase II design to gather evidence that is likely to translate into a favorable outcome (2, 3).

Translational Study in Phase III Trials

It may not be practical or possible to obtain the translational endpoints in a large-scale phase III trial, for reasons ranging from the number of patients to the cost and the logistics. The primary goal of the translational outcome is to provide information for making the decision to go forward to a phase III trial.

References