

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Individualizing Cancer Chemotherapy

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H&O Could you describe the basic concepts behind individualizing cancer chemotherapy?

HM Clinical experience has demonstrated that the majority of patients receiving treatment for cancer do not derive benefit from the drugs administered and, more often than not, do experience toxicity. Very few therapies for metastatic disease are associated with a response rate of greater than 50%, yet a substantial number of such patients experience side effects.

The fact that some patients benefit from certain drugs and some do not, and that some patients experience more toxicity than others given the same drugs, indicates that there are differences among patients that lead to these variations. However, we need to administer the therapy in order to know whether a patient will respond, and whether a patient will experience toxicity.

In addition, there are often several agents that appear to be equally effective for the treatment of many solid tumors. We are no longer bound to administer a particular drug regardless of how a patient might respond. Rather, if it were possible to identify a group of patients who are not likely to derive a benefit from therapy A, then therapy B could be given instead. Ideally, it would be possible to determine in advance whether therapy A, B, or C was the best treatment choice for that patient subgroup.

The basic concept that there are differences in the way patients respond to drugs is relatively simple. The challenging aspect is finding the objective means of prospectively identifying these differences so that they can be incorporated into treatment decisions.

H&O What were the initial studies conducted in this field?

HM The initial efforts to individualize cancer chemotherapy have focused on toxicity. Often, the toxicity associated with a certain agent is prevalent and dramatic, and key candidate genes to pursue are known. For example, the topoisomerase-1 inhibitor irinotecan (Camptosar, Pfizer) is known to cause severe neutropenia and is known to be inactivated by the UGT1A1 enzyme, the gene for which contains a genetic polymorphism. It was logical to wonder whether the genetic variation is responsible, at least in part, for the toxicity. Studies found that at higher dose levels of irinotecan, patients with a particular genetic abnormality of seven repeats in a row in the promoter region have a much higher risk of severe toxicity.

This finding led the US Food and Drug Administration to initiate changes to the package insert for irinotecan and to approve a test for *UGT1A1*. Currently, investigators are exploring when patients should be tested (all patients, only those receiving more than a threshold mg/m², etc), but the regulatory framework for how to use the information now exists.

H&O In what other settings is this approach being pursued?

HM The model initiated with the research of *UGT1A1*, in which the genes that might be responsible for a severe, dose-limiting toxicity phenotype are known, is being pursued in a number of different cancer settings. Almost every approved cancer drug is associated with the same inherent difficulty: the agent benefits some patients but not all, and some patients experience toxicity and some do not, and the reason why is not known.

Studies are ongoing for the majority of cytotoxic chemotherapy agents in which large patient cohorts are being accumulated and candidate genes are being evaluated in the DNA of those patients. Drugs being studied in this type of setting include the taxanes, gemcitabine (Gemzar, Lilly) and other antimetabolites, some of the

classic alkylator agents, such as cyclophosphamide and melphalan, and others.

Because there is often a range of options for treating any given cancer, it is logical to pursue this research in many different settings. While it may be ideal to optimize efficacy, it is also essential to tailor treatment for the minimal amount of toxicity. If it is possible to minimize toxicity while maintaining efficacy, then a treatment approach can be considered acceptable.

H&O Is the *UGT1A1* test being incorporated into clinical practice broadly?

HM The test is available to any physician and can be ordered through standard testing facilities. As with many diagnostic tests, we do not know everything there is to know about how to use the results of the test. A variety of responses to the availability of the *UGT1A1* test have been observed. Some oncologists have not incorporated it into their practice because they consider their current approach to be sufficient and not in need of change. Others changed their practice not in response to the data but rather out of concern that not conducting *UGT1A1* testing would result in medicolegal liability problems. Finally, many oncologists are now using the *UGT1A1* test because they believe it will lead to safer therapy for their patients.

H&O With so much focus on novel agents in the oncology research arena, are these studies leading to renewed interest in chemotherapeutic agents?

HM This is a very useful point. Being able to give any drug more safely is an advancement, and particularly for those for which a fair amount of clinical experience and familiarity already exists. Most likely, studies of genotype-guided chemotherapy will lead to some rediscovery of older drugs.

There are few dramatic success stories in oncology, and one of the most dramatic is with childhood acute lymphoblastic leukemia (ALL). Data from the Children's Oncology Group and St. Jude Children's Research Hospital demonstrate dramatic improvements in survival among children with ALL. In the 1960s, the 5-year survival rate was 21%; today, it is over 90%. This improvement has taken place in the absence of any new drugs during the past 30 years. Rather, survival has improved as a result of learning how to use the available agents better. Many new drugs hold much promise for improving outcomes among cancer patients. However, from a practical standpoint, if we want to be able to help patients today, we also need to optimize our current therapy.

H&O Are genotype-guided studies also evaluating markers of response, in addition to toxicity?

HM Yes. There have been a number of studies with large cohorts of patients in which objective measures of response, time to progression, and survival have been included. Many of these studies are conducted by the National Cancer Institute cooperative groups. In particular, the Cancer and Leukemia Group B has pioneered the integration of blood sampling into clinical trials, enabling investigators to analyze data from hundreds, sometimes thousands, of patients who have been prospectively treated in order to assess whether these genetic variants are associated with efficacy. Many of the small anecdotal studies in the literature can now be replaced by these large objective studies, as they provide a less biased and more useful result of whether DNA or other markers are useful for predicting outcome.

There are data in the setting of non-small cell lung cancer regarding the association between excision repair genes and response to platinum agents. These data are leading to prospective studies evaluating whether genetic variation in these repair genes is truly predictive of response. If so, then gene-guided therapy selection studies for lung cancer will be designed.

Benjamin Tan and colleagues presented a study at the American Society of Clinical Oncology's 2006 Gastrointestinal Cancers Symposium in which DNA was used to select whether patients with rectal cancer would receive 5-fluorouracil (5-FU) plus radiation alone or with additional chemotherapy. Patients with a "good-risk" genotype received standard 5-FU plus radiation, while those with a "poor-risk" genotype received additional chemotherapy. This study found, firstly, that patients were accepting of this approach, and secondly, that laboratory medicine facilities can conduct such analyses in a timely manner. Finally, the data indicated that efficacy was improved in this setting by using DNA-based therapy selection. This finding needs to be proven in a prospective randomized trial, but this study should provide enough clinical evidence to justify a large national study that can determine whether genotype-guided therapy does in fact lead to better outcomes.

H&O Are there any potential drawbacks to incorporating genotype testing into chemotherapy treatment planning?

HM Genetics is only one way of capturing a patient's variability, and there are other variables that are not genetic but are clinically relevant. Therefore, we need to

look at genetics as one way of understanding a patient in a more sophisticated manner, but not the only way. There will be drugs and clinical situations for which DNA is insufficient for making a therapy selection.

Also, the data obtained from DNA testing hold to the same principle as any blood or imaging test: the results reflect a probability of a certain response or toxicity level. None of these tests is 100% predictive; rather, a test might reveal a patient to have, say, a 60% chance of responding instead of a 20% chance.

With these considerations in mind, careful decisions need to be made regarding the right therapy for a particular patient. Some patients will want to remain on a certain therapy regardless of the risk. Others will want genotype-guided testing used in the decision-making process. It is important to not be dogmatic about this approach, and to remember that it is only one component of the decision.

H&O Does genotype ever change as a result of therapy?

HM In normal tissues, the so-called germline tissues, DNA does not appear to change (except in the case of a bone marrow transplantation, for example). Tumors are different, as they have the ability to acquire genetic variation. A tumor present in a patient prior to chemotherapy does have a potentially different DNA profile from the tumor remaining after chemotherapy is completed. This change should come as no surprise, since some tumor cells are obviously able to escape radiation or chemotherapy; the avoidance of tumor cell apoptosis may be due to a genetic change.

H&O Could you give your short- and long-term vision of cancer chemotherapy individualization?

HM We are seeing examples of toxicity avoidance today; there are tests being used currently, and many more are

likely to become available over the next year. DNA-based tests for tamoxifen (Nolvadex, AstraZeneca) efficacy may be available in the next several years. Clinicians can expect a few tests to be added each year. These gradual additions should lead us to the realization that the genetic revolution is not a distant reality, but is happening today. Genotype-guided therapy may not be common for every chemotherapy drug yet, but it is possible and it is happening now.

I think that the time when every newly diagnosed patient automatically undergoes DNA or other sophisticated testing in order to guide treatment decisions is at least a decade away. The main remaining step in this advancement is medical evidence. Without evidence that these tests are key to optimizing therapy, they will not be incorporated into clinical practice. These studies take time to accrue and conduct. However, the findings will not be limited to choosing chemotherapy. There are DNA markers for response to antiemetics, to palliative therapies, to colony-stimulating factors, and other areas of oncology care. Both supportive care elements and anti-tumor efficacy will be improved by the development of genotype testing.

Suggested Reading

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