Evidence for Ethnic Differences in Cancer Drug Metabolism and Deposition: Potential Relevance for Clinical Trials and Practice

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For several reasons, there has been increasing interest by the pharmaceutical industry in the conduct of cancer trials across international borders and in multiple countries. First, the rapidly growing global economy has resulted in an ever-expanding market for anti-neoplastic agents. Second, the increase in the number of products requiring evaluation, including phase 3 randomized trials, necessitates larger patient populations willing to participate in such studies. And third, it is recognized that the costs of conducting clinical trials in developing countries may be substantially less than that associated with trials run exclusively in North America and Western Europe.

While a number of benefits of this basic approach to oncologic drug development can be cited, including the ability to rapidly evaluate the potential clinical utility of an increasing number of anti-neoplastic agents in the pharmaceutical industry pipeline, an important assumption of this strategy has been called into question.

In the conduct of clinical trials, there has been limited appreciation or concern for possible unique differences between populations (genetic and environmental) within the regions of the world participating in such studies that might influence outcomes.

For example, well or poorly characterized genetic variations among relatively homogeneous ethnic groups (e.g., Asian vs. European Caucasian) may result in clinically relevant differences in the metabolism (activation or inactivation) of cytotoxic agents, increasing or decreasing the relative biological activity of a drug. In theory, such alterations in activity of an agent could lead to greater or reduced therapeutic efficacy or toxicity.

Important evidence for the potential impact of such differences has been provided by the reported experience with combination chemotherapy in the management of extensive stage small cell lung cancer. A phase 3 randomized trial conducted in Japan that compared cisplatin plus either etoposide or irinotecan revealed an improvement in survival associated with the irinotecan-containing regimen [1]. However, a very similar study conducted in the United States failed to confirm the superiority of this regimen [2]. In fact, in the United States cooperative group study, the irinotecan program was revealed to cause substantially more gastrointestinal toxicity than observed with the etoposide-containing regimen. It was speculated that the striking differences in the outcome of these two studies (efficacy and toxicity) may have been related to genetic differences in the metabolism of irinotecan.

Another study directly compared differences in the distribution of alleles of genes known to influence DNA
repair or paclitaxel disposition between Japanese and United States patients participating in a lung cancer trial including the regimen of carboplatin plus paclitaxel [3]. The analysis revealed significant differences between the two geographical locations, as well as their clinically relevant impact on both measures of efficacy and toxicity.

The novel oral fluoropyrimidine derivative S-1 has been widely used in Japan and the other Asian countries for a number of clinical indications, and recently reported Japanese data have revealed the non-inferiority of the combination of carboplatin plus S-1 when compared to carboplatin plus paclitaxel in the treatment of advanced non-small cell lung cancer [4]. Based on the previous discussion, is it reasonable to conclude a similar outcome (efficacy and toxicity) will be observed if this treatment regimen was delivered to a non-Asian patient population?

In this issue of Oncology, investigators report the results of a phase 1 trial in the United States designed to test the toxicity profile of a regimen of S-1 when combined with oxaliplatin and bevacizumab [5]. One aim of the strategy was the development of a regimen potentially acceptable for future testing in the management of gastrointestinal malignancies.

Of interest, the dose-limiting side effects observed in this trial were mucositis and diarrhea, while in the early phase studies of S-1 in Japan, bone marrow suppression was the major toxicity. These data, although limited in the total experience reported and non-randomized, support the idea that the side effect profile of S-1-containing regimens in the non-Asian population may be substantially different from that previously reported in large-scale trials conducted in Japan and other Asian countries.

This provocative experience also supports the general clinical relevance of the evolving field of pharmacogenomics. In addition, the data highlight the importance of conducting phase 1 studies to define both optimal dose and schedule within specific ethnic groups that may be receiving treatment in the research setting, as well as having such knowledge for patients managed in the non-investigative practice of clinical oncology.

References