Challenges of Chemosensitivity Testing

□□ *Commentary on Ugurel et al., p. 5454*

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One of the major goals in cancer therapeutics is to increase efficacy and reduce toxicity by tailoring therapy to individual patients. It is well known that tumors and patients are heterogeneous, and with every therapeutic approach, whether immunotherapy, chemotherapy, or antivascular strategy, patient response can be extremely variable, ranging from progression to complete responses. Understanding the principles by which some patients respond to specific therapies whereas others do not is a daunting goal, but may lead to improved patient selection as well as new therapeutic strategies. Differences in response can be due to either genomic variability between individuals or heterogeneity between tumors, or both. Chemosensitivity and resistance studies, in which autologous viable tumor is evaluated for susceptibility to specific agents *in vitro*, test the latter hypothesis that differences in response to combination chemotherapy can be predicted by studying direct effects on that individual patient's tumor. Ugurel et al. tested tumor biopsies from patients with metastatic melanoma and selected drug combinations based on *in vitro* sensitivity testing (1).

Although numerous studies have addressed chemosensitivity testing in other cancers, studies in melanoma have been limited. Melanoma is indeed an important cancer to address because the number of deaths due to melanoma is increasing, victimizing patients of all ages (2). Standard therapeutic approaches have modest effects on advanced melanoma. In addition, patients with metastatic melanoma often have tumors that are accessible for biopsy, making an approach that uses autologous tumor especially feasible.

Although chemosensitivity testing is an intuitively attractive concept, sensitivity *in vitro* does not necessarily predict responses *in vivo*. This is possibly due to the limitations of tumor cell culture, absence of other host-derived cells in the assay that may influence responsiveness, and genomic differences that may affect the metabolism of specific compounds (3). For example, *in vitro* growth of tumor may allow for artificial selection of specific tumor subpopulations depending on culture conditions, thereby limiting ultimate correlation with clinical response. In addition, stromal elements may not be fully represented in the culture but, *in vivo*, may produce in the tumor microenvironment growth factors that influence the sensitivity of a tumor to a specific agent (4). Chemotherapy may also have effects on tumor vasculature, which would not be recognized by assays that focus only on tumors. Finally, chemosensitivity testing does not take into account toxicity on normal tissues. If a given combination is highly effective, but also more toxic, the therapeutic index may not be greater for a specific drug or combination despite *in vitro* test results.

Nonetheless, as technology improves, *in vitro* chemosensitivity testing of tumor may be clinically useful, but this will need to be shown in randomized studies comparing this approach to standard treatment strategies. Indeed, an American Society of Clinical Oncology–sponsored study (5) concluded that evidence for the usefulness of chemosensitivity testing was limited and testing should only be done as part of a clinical trial.

Conducting large randomized studies, however, will first require a reliable assay. The major contribution of this study by Ugurel et al. (1) is that the investigators showed in a multiinstitutional trial that tumor samples could be shipped to a central laboratory where sensitivity assays on tumors from the majority of patients could be done with interpretable results. Importantly, test results were available within 7 days, thereby making coordination with patient therapy feasible.

Whereas there was a trend toward predicting patient outcome for those with "sensitive" tumors compared with "resistant" tumors, this was based on an arbitrary cutoff. Other more classic factors such as performance status and lactate dehydrogenase levels were actually better predictors of patient outcome. In addition, because all patients received sensitivity-directed chemotherapy, it is not clear how this would have compared with a standard regimen. As noted by the investigators, the relevance of this approach will need to be determined by a prospective randomized study comparing patients treated with this strategy to those treated with a standard regimen in the absence of *in vitro* testing information.

Future approaches will rely on understanding the molecular differences between tumors and patients. For example, differences in responses to immunotherapy may be dependent on polymorphisms within specific immune receptors or cytokines. In addition, response to targeted therapies may be highly dependent on the specific mutations present in tumors and the pathways that are up-regulated (6). Therefore, improvement of this approach in guiding therapy through *in vitro* testing may rely on incorporating global evaluations of genomic polymorphisms and molecular profiling of tumors, which might be done even faster than the viability assays.

As more clinical agents that target distinct pathways are available, more and more effort will need to be dedicated towards understanding how to rationally combine agents. This will require mechanistic insight into the effects of conventional chemotherapy and novel agents not only on tumor but also on

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stroma, immune cells, and tumor vasculature. Tailoring optimal combinations to specific patients may require a combination of *in vitro* assays on viable tumor and molecular analysis of patient samples.

While challenging, it is an important goal to determine optimal chemotherapy combinations for individual patients to enhance patient response, avoid unnecessary toxicities, and gain insights that may lead to improved treatment strategies. Ugurel and colleagues have shown that, although complicated, it is feasible to do individualized therapy testing in a multi-institutional setting. We look forward to their follow-up randomized clinical trial that will determine the clinical relevance of this particular assay on individualized therapy.

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