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The era of personalized medicine: back to basics

Lisa Hutchinson and Vincent T DeVita Jr

As *Nature Clinical Practice Oncology* celebrates its fourth anniversary, few would disagree that during this time we have witnessed extraordinary molecular advances that have changed the way oncologists treat patients with cancer. Proof of principle for the effectiveness of targeted therapy has been provided by the use of imatinib in patients with chronic myelogenous leukemia. Not every tumor has the primary target in each cancer cell, hence the interest in identifying those patients who would benefit from a targeted treatment. This is personalized medicine and we have some good examples of how beneficial it can be. In 2004, for example, pivotal trials demonstrated that patients with non-small-cell lung cancer who harbored *EGFR* mutations responded better to molecularly targeted agents than patients without such mutations. Recent data indicate that *KRAS* mutations are an independent, negative, predictive marker for response to the anti-EGFR agents cetuximab and panitumumab in patients with metastatic colorectal cancer. Indeed, clinical resistance to cetuximab in colorectal cancer patients who have *KRAS* mutations has led to the approval of this drug to treat those patients without *KRAS* mutations.

To understand some of the problems associated with the predictive biomarker field in relation to the use of targeted therapies, we have to go back to basics. For the true potential of a predictive marker to be assessed, the underlying pharmacokinetic parameters of the drug need to be better defined. For instance, drug doses defined in early trials may be suboptimal. Phase I trials determine the maximum tolerated dose of a drug and that dose is used for future testing of the agent. Yet, in many cases, these drug dosages could be too high in the subset of patients with the specific target. These issues pose a particular problem because many targeted agents have limited efficacy when used alone, but produce impressive responses when used in combination with other treatment modalities, or in the adjuvant rather than metastatic setting.

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A design flaw exists in adjuvant studies already underway using targeted treatments in combination with chemotherapy. In colorectal studies using cetuximab and panitumumab, randomization did not take into account the *KRAS* status of each patient. It is impossible to be sure exactly how many patients have mutated *KRAS*. The outcome of these trials and the approval of both antibodies by the FDA nonetheless will depend on the overall impact in a mixed population even though a strong positive effect might have been masked by a small subset of patients without *KRAS* mutations. Since the latest information points to the ineffectiveness of EGFR inhibitors in patients with *KRAS* mutations, should this information not be enough to approve the use of these drugs in the adjuvant situation or do we have to repeat these studies and delay the application of these new therapies in patients who most need them?

The same logic applies to the design of early trials of these agents. If an agent modulates a target in preclinical models and the expected downstream effect induced by target interaction is observed, perhaps this provides sufficient evidence to test the agent in a clinical trial, even in the absence of demonstrated efficacy in preclinical models, provided there is enough information to determine a safe starting dose. We have new information that is already proving useful to personalized medicine and we need to be able to use it optimally. If we wish to replicate past advances in the field of cancer medicine over the next few years, we must ensure that these issues are addressed and integrated into the design of future trials.

L Hutchinson is the Editor and VT DeVita Jr is the Editor-in-Chief of Nature Clinical Practice Oncology.

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