Researchers May Use Cancer Cell Lines To Identify Target Populations Prior to Clinical Trials

In recent years, scientists have used cancer cell lines and tumor samples to decipher why one patient responds to a targeted therapy when another does not. Now several groups are doing the testing first, using their lab results to identify patients who will likely respond before a targeted therapy goes into clinical trials. For one research group, the information is already being used to select patients for an early-phase trial.

If the strategy works, clinical trials can be streamlined by these targeted therapies, requiring fewer patients and less time to show effectiveness. However, not everyone is convinced that an early choice of target populations is the right way to go, noting that it might exclude patients who would derive some benefit even if they do not show a complete response to the new drug.

Proponents say the tests will help effective drugs to get to market that might fail in large trials. For example, there might have been a different outcome for the AstraZeneca’s gefitinib (Iressa), which failed to improve survival in a randomized placebo controlled trial of non–small-cell lung cancer patients but did show a benefit for some groups. It is no longer approved by the FDA for use in new patients.

“If we knew or AstraZeneca had known back then what we know now about subsets, would the world have been different?” asked Daniel A Haber, M.D., Ph.D., director of the Massachusetts General Hospital Cancer Center. “Is there a way to predict ahead of time how the clinical scenario is likely to play out?”

“Clearly if you now look at lung cancer cell lines with mutations, they represent the clinical situation quite well; they are very sensitive to [epidermal growth factor receptor (EGFR) inhibitors like gefitinib and erlotinib]. So if you had known that 10% of lung cancer cell lines are exquisitely sensitive to these inhibitors, you might have used that information in designing the clinical trials.”

Haber’s group and others have looked back at who did and did not respond in the EGFR inhibitor trials. They found that patients with mutations that activate EGFR are highly sensitive to EGFR inhibitors, such as erlotinib (Tarceva). Although the data are valuable, the key question is whether such an approach can be used to identify responsive patients before a drug enters clinical trials.

To find out, Haber’s group turned to MET, a growth factor receptor gene that is active in some epithelial cancers. After screening 40 cancer cell lines, they found one gastric cancer line that was highly sensitive to a low dose of a MET inhibitor. That cell line carried an amplification of the MET gene, a variation that is found in up to 20% of gastric tumors. When the team screened 16 more gastric cancer cell lines, they found four others that had MET amplification, all of which were sensitive to the inhibitor. The cell lines dependence on MET was verified when they saw that RNA interference against MET reduced the cell viability in these lines, suggesting that the response to the drug was due to inhibition of MET itself.

Now they are taking that information into the clinic. The group plans to preferentially enroll gastric cancer patients with MET amplification in a phase I trial of the MET inhibitor PF-02341066. Patients lacking amplified MET will not be excluded from the trial because, as Haber said, “we are making a pretty big assumption based on cell lines.” Besides, this will tell them whether patients whose tumors lack MET amplification will respond, regardless of what the cell screen predicts should happen.

Although the method is not proven useful yet, Haber hopes selecting cell lines will work for other targeted therapies. Researchers can set genetic markers for clinical response by identifying the markers that correspond to the highest reaction in tissue culture cells.

Cell Line Research Spreading

Other scientists are taking a similar approach. At Memorial Sloan-Kettering Cancer Center, medical oncologist David Solit, M.D., and Neal Rosen, M.D., Ph.D., laboratory head in the molecular pharmacology and chemistry program, showed recently that mutations in BRAF, an enzyme that promotes cell proliferation, predict sensitivity to inhibitors of its downstream target, MEK. By contrast, cancer cells that had either normal BRAF or carried an upstream mutation were largely insensitive to the inhibitor.

Like Haber’s group, the Sloan-Kettering physicians want to know whether their in vitro data predict which patients will be sensitive to the drug in clinical trials. However, the group will not preselect patients for their upcoming phase II trial. “We eventually want to do a study where we select the patients in real time, but that is not the first study,” Solit said.

Instead, the trial will be open to all lung cancer and melanoma patients, and the researchers will retrospectively analyze the patients’ tumor samples to determine whether those with a BRAF mutation respond better to the drug. The group opted for an open phase II trial in part because there is no commercial test available for detecting BRAF mutations—making such real-time decision making expensive and time consuming. Also, the cell line work predicts that a few patients without BRAF mutations may derive some limited benefit from the drug, and they would be excluded from a preselected trial.

Are the researchers worried that an unselected population won’t have enough patients with the mutation to test the BRAF hypothesis or show whether the drug is effective? Not in melanoma, where more than half of the tumors have a BRAF mutation. Thus, even a 20-patient phase II
trial would likely show responses, if the cell line prediction is correct. But in lung cancer, where less than 5% of patients have a mutation in BRAF, the chances are high that the benefits will be missed if patients are not selected prior to enrollment.

“If the mutation is found in a high percentage of patients, I think we are unlikely to miss it by just doing a broad phase II,” said Solit.

In a variation on the cell-line-to-patient selection theme, Edwin A. Clark, Ph.D., director of oncology biomarkers in the division of clinical discovery at Bristol-Myers Squibb, is using microarray gene profiling to identify biomarkers that predict response to dasatinib in breast cancer cells. The team has found six genes whose expression is associated with breast cancer patients’ response to the multitargeted kinase inhibitor. None of the six are targets of the kinase inhibitor itself, but some are known to be downstream of one of dasatinib’s targets, the Src kinase. The company plans to initiate a phase II trial for the profile later this year.

To Exclude Patients or Not

It still isn’t clear at what point during drug development and clinical trials to use biomarkers for patient selection, but it will be especially important if only a few patients will respond to a therapy, Solit said. Identifying that group and ensuring that enough of them are included in the early patient trials will be essential, or good drugs could be lost. For example, posttrial analyses have shown that the early trastuzumab (Herceptin) trials could have been negative if patients had not been preselected for Her2/neu expression, even though trastuzumab is now known to be an effective drug in some Her2-positive patients. Solit predicted that patient selection will become even more important as increasingly rare mutations become therapy targets.

On the other hand, restricting patients too early may exclude patients who would have a partial response to the drug or otherwise derive some limited clinical benefit from it. For example, although the patients with the best response to erlotinib appear to be the ones with activating mutations, an equal fraction of the patients have a minor response even though they lack such mutations.

“You are going to throw out some babies with the bath water, but what you want to do is reduce the number,” Clark said. That means testing the drug in patients who don’t fit the predicted profile, either in early trials or after the drug has already proven its value in the target population—maybe even after it has received FDA approval.

In fact, the agency might even require it. “As soon as Herceptin was approved, the first thing the FDA asked is ‘What about Her2-negative patients?’” Clark said. “You need to test a drug in the marker-negative population. But rather than just testing everyone and showing a marginal response, there is a great advantage to honing in early on the patients that are most likely to get the most benefit from therapy and developing the drug for them.”

Haber also argues that you should focus on a target early in the drug’s development. Although some patients who partially respond might be lost with this approach, they are not the goal of targeted therapies.

“There is a mindset [in oncology] of adding drugs and multiplying them and looking for relatively incremental changes. I think if these molecular strategies are really going to fulfill their promise, then we have to change our expectations a little bit: The question is whether treating a smaller number of patients but having a really big impact is what we should be focusing our clinical trials on, rather than the much broader population with relatively minimal effect.”

—Rabiya S. Tuma

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