focus on finding the small proportion of patients that might be harmed [by ADT]. Until such a subgroup is definitively identified, we should still generally be offering ADT to men with high-risk disease, as this has been proven repeatedly in randomized trials to improve overall and cancer-specific survival.”

The only randomized prostate cancer trial that has included cardiovascular history is a study of 6 months of ADT plus radiation compared with radiation alone in 206 men with localized but high-risk prostate cancer. After a median follow-up of 7.6 years, the study showed that although men with no or minimal cardiovascular comorbidities (such as controlled hypertension) had improved survival with the addition of ADT, men with moderate to severe cardiovascular comorbidities (such as a heart attack more than 6 months before the start of the trial) did not benefit from the therapy (JAMA 2008;299:289-95). A retrospective analysis of more than 5,000 patients treated with ADT in the neoadjuvant setting also showed that ADT can increase the risk of all-cause mortality in those men with a history of heart attack or coronary artery disease-related heart failure (JAMA 2009;302:866–73). A cohort study of more than 22,000 newly diagnosed prostate cancer patients found that men who took ADT for at least 12 months had a 20% higher risk of serious cardiovascular morbidity than patients not treated with ADT (Cancer 2007;110:1493–500).

Patients with metastatic prostate cancer generally receive ADT as a first-line treatment. ADT, typically in the form of GnRH agonists or sometimes antagonists, is also used to treat some men with localized disease who are at high risk and some with intermediate-risk prostate cancer. These medical forms of ADT suppress serum testosterone levels to below 50 ng/dL.

In 2010, the U.S. Food and Drug Administration issued a warning label for all GnRH agonists because of the potential increased risk of diabetes and CVD, including heart attack, stroke, or sudden cardiac death in men taking these drugs for prostate cancer. The American Heart Association and American Cancer Society also issued an advisory statement on the accumulating evidence ADT–CVD link (Circulation 2010;121:833–40). Since then, no further guidance on cardiovascular risk with ADT has emerged, partly because no consensus exists on the issue, according to Nguyen.

These studies, said Christopher Saigal, M.D., urologist at the David Geffen School of Medicine at the University of California, Los Angeles, have reduced use of ADT for localized prostate cancer and has caused clinicians to move to shorter ADT courses in the neoadjuvant and adjuvant settings. At his institution, D’Amico said, patients are referred to a cardiologist before starting ADT to make sure the patient is evaluated and optimized. “You don’t have to do anything special or extra at this time, since the evidence to date is hypothesis generating, but just to make sure the person is up to date with his cardiologist,” D’Amico said. Saigal added that the general practice is to encourage heart-healthy behaviors such as exercise and a healthy diet, as well as to monitor cholesterol and blood pressure, in men starting ADT.

The potential explanation by which ADT may influence CVD is that testosterone, the predominant androgen in men, synthesized in the testes, promotes muscle mass and can decrease fat mass. Conversely, lower testosterone levels, as occurs with ADT, can result in accumulation of fat and a decrease in muscle. “When fat mass increases, the secretion of adipokines from the adipose tissue contributes to development of insulin resistance,” said endocrinologist Shehzad Basaria, M.D., of Harvard Medical School in Boston, who wrote an editorial accompanying the new study on the Swedish cohort. “So you develop an internal milieu that predisposes you to develop metabolic syndrome, a risk factor for cardiovascular disease.”

The big question, still not addressed, is whether ADT shortens survival in some men treated with ADT. None of the ADT studies were designed to evaluate cardiovascular events as the primary outcome and most of the studies are post-hoc analyses, Basaria said. “Although these analyses are informative, only well-powered studies can answer the question of the role of ADT in causing cardiovascular events,” he said.

According to Basaria, a prospective, randomized trial evaluating cardiovascular events during ADT is needed, and he would like to see a control group of prostate cancer survivors not treated with ADT and who are matched for comorbidities in the experimental group. But Nguyen said he believes it is difficult to execute a prostate cancer patient trial with cardiovascular death as a primary endpoint. “What may be the most practical solution is to stratify patients by cardiovascular comorbidities into ongoing prostate cancer endpoint trials,” he said.

Another route is to understand whether antiandrogens, which in contrast to GnRH agonists that lower serum testosterone systemically, act on the androgen receptor locally at the prostate level. If, as the new study suggested, antiandrogens may indeed lower the risk of cardiovascular events—or at least not increase them—then antiandrogens could become the first-line therapy of choice for men with cardiac comorbidities or even for all prostate cancer patients. A 64-patient phase II single-institution clinical trial (NCT02028988) is exploring the efficacy of enzalutamide plus radiation in men with intermediate-risk localized prostate cancer. “Enzalutamide doesn’t drop serum testosterone, so you may get the benefit of a hormonal therapy but without the cardiovascular risk,” D’Amico said. But, he warned that the efficacy of the regimen first needs to be studied.

For part of a prospective trial, Basaria said he would also like to see mechanistic studies evaluating how ADT influences vascular biology and other measures of cardiovascular health. “These aspects are also important and need to be studied concurrently if we want to come close to a definitive answer.”

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Personalized Devices Predict Cancer Drug Sensitivity In Vivo

By Vijay Shankar Balakrishnan

On April 22, 2015, Science Translational Medicine published two papers under one theme: testing cancer drugs in vivo and in situ. Both papers reported on patient-friendly devices that can predict patients’ sensitivity or susceptibility to
chemotherapeutic agents, before surgery and the start of a systemic therapy regimen. The devices could change how clinicians treat cancers, improving efficacy and decreasing cost while creating opportunities to improve current drug discovery, testing, and trial practices.

One unnamed device designed by Oliver Jonas, Ph.D., and colleagues from the group of Robert Langer, Ph.D., at the Massachusetts Institute of Technology in Cambridge, Mass., is an implantable microdevice that leaks out microdoses of drugs to test both efficacy and patient sensitivity (Sci. Trans. Med. 2015;7:284ra57). “You can use it to test a patient for a range of available drugs and pick the one that works best,” Jonas said.

A second device is a hand-held injectable CIVO developed by Richard Klinghoffer, Ph.D., and colleagues at Presage Biosciences in collaboration with James Olson, Ph.D., and colleagues at Fred Hutchinson Cancer Research Center, all in Seattle. The CIVO device, the size of a pen flashlight, also delivers microdoses of drugs into various tumor sites for testing (Sci. Trans. Med. 2015;7:284ra58). “[Our] approach enables drug developers to analyze and compare multiple drugs and drug combinations in a single living tumor while [they are] still in the patient,” Klinghoffer said.

Problems Addressed

In current practice, testing drug efficacy for a bunch of drugs at a time in live patients is not possible, since physicians test the tumor’s sensitivity to available drugs in a lab dish, after surgically removing it. Through this process, the tumor loses its microenvironment, namely, the associated stromal, immune, and inflammatory cells, whereby it becomes capable of resisting the tested drugs, thus also reducing the rate of patient survival (Sci. Trans. Med. 2015;7:1–4).

Both devices test drug efficacy in vivo, thus preserving a tumor’s integrity. In a foolproof way, this approach can be used for many types of cancers, which could lead to personalized cancer medicine that other existing modes cannot deliver precisely, both Jonas and Klinghoffer said.

Only 7% of the anticancer agents that succeed in preclinical studies make it to phase III trials and secure U.S. Food and Drug Administration approval (Nat. Rev. Clin. Oncol. 2011;8:189–90). If proven in clinical trials, these devices could make new drug development cheaper, the cost of which as of December 2014 can exceed $2.6 billion (Cancer Discov. 2014) by speeding up phase zero and I trials (Cancer J. 2008;14:133–7).

“[Our] approach enables drug developers to analyze and compare multiple drugs and drug combinations in a single living tumor while [they are] still in the patient.”

Implant or Inject

The implantable device is a cylinder 820 μm in diameter and 4–5 mm long, containing 30 reservoirs. “It is smaller than a grain of rice,” Jonas said. The device is made of biodegradable, stiff and crystalline plastic used in artificial joints.

Using a 19-mm biopsy needle or smaller, Jonas’ team placed the device that carried one or a combination of 16 drugs, in the non-necrotic periphery of tumors in mice carrying grafts of human skin, prostate, and triple-negative breast cancers. While in tumor, the drugs seep out of the device and spread 200–300 μm around the tumor, yielding a bioavailability similar to that of systemic therapy.

After leaving the device in the tumor for 1 day, the team removed it along with a portion of tumor tissue using a coring needle, for immunohistochemical (IHC) analyses. The antibodies used during IHC analyses stained different biomarkers that assess the drugs’ action. On the basis of the IHC analyses, the researchers ranked how drugs affected different tumors in situ.

Presage, however, used CIVO to screen 97 approved oncology agents, taking a different approach. Klinghoffer and team used their device with eight needles, arranged in a circle to inject multiple columns of drugs into the tumor. The device thus can reach and deliver drugs into deeper regions of a tumor. “This makes it possible to assess drug effects with multiple biomarkers and in multiple regions along the injection axis to capture the heterogeneity of response within the tumor,” Klinghoffer said.

The team measured drug effects first in mice carrying grafts of human lymphoma. One to three days after injecting drugs into tumors, the team surgically removed the tumors for IHC analysis. Beyond ranking drug effects, here, the researchers screened the signaling pathways that a drug inactivates to elicit the therapeutic response or resistance. For instance, the team found one of those 97 agents had the ability to kill a tumor through the mTOR (mammalian target of rapamycin) pathway in a chemotherapy-resistant setting.

The Outlook

Owing to their differences in design and usability, both the devices have their own advantages and disadvantages. Unlike the CIVO, the implantable device is tiny and can be easily placed into patient tumors without need for an external pump to supply the drugs. “We believe we can reach most tumors, even deeper ones [within the body], [by] using existing biopsy procedures that are already routinely used in clinical practice,” Jonas said. “This means our assay may be more easily integrated with current clinical procedures, and the smaller size likely means it will be easier on patients,” he added. The team is also working toward testing more than 100 drugs in a single tumor.

Jonas noted that the present study did not address the problem of tumor heterogeneity, wherein different cells in a tumor exhibit distinctive morphologic, genetic, and pathologic features. However, he said that the team has already started testing either by using one drug in multiple reservoirs on the same device or by implanting several identical microdevices into different
regions of the same tumor. The researchers are also working toward integrating real-time readouts, avoiding a complicated biopsy step.

Keith Flaherty, M.D., at the Massachusetts General Hospital Cancer Center in Boston, said the number of drugs in combination that Jonas and team chose to test the synergistic effects is much smaller than the number of available approved drugs. “Sixteen drug combinations is actually a fairly limited investigation,” Flaherty said. He added, “Taking hormone receptor–negative breast cancer as an example: There are eight or so chemotherapy drugs used in standard practice in another six targeted therapies available. So, there is room in the device to accommodate this repertoire of drugs.”

The CIVO device by Klinghoffer and colleagues is not implantable and can reach only superficial tumors such as lymphomas, sarcomas, breast cancers, head and neck cancers, melanomas, and superficial metastases, but not deeper-seated tumor types such as those of colon and pancreas. “Further engineering, potentially an adaptation to fit an endoscope, is required to expand [these] clinical indications,” Klinghoffer said. However, Flaherty said, “[The device with only] eight ports does place a significant limit on the number of single drugs in combination drug effects that can be explored in any given tumor/patient.”

Klinghoffer said their team is set to show that their device has negative predictive value in human clinics, that is, CIVO will determine whether a tumor is already resistant to a drug or drug combination in a human patient. Although they have shown that the device can predict drug response in both positive and negative directions in mouse models, Klinghoffer said, “our planned studies in humans are the logical extension of that work.”

Unlike Jonas and team, Presage has tested CIVO in pet dogs and run a pilot test in humans. Thus, CIVO’s usability in the clinic differs substantially from the implantable device; however, both advance towards approval from the U.S. Food and Drug Administration. To the question on the status of clinical trials, Jonas said, “We are very close to beginning the first clinical trial, which should begin this summer.” Klinghoffer said, “Presage is evaluating its CIVO platform in a first-in-human study in collaboration with the Seattle Cancer Care Alliance and the Fred Hutchinson Cancer Research Center, with funding support from the National Cancer Institute.”

To Wrap Up
Raoul Charles Coombes M.B., Ph.D., at the Imperial College in London, wrote in a perspective accompanying the two papers that the devices need to jump several hurdles up before they become fully usable in clinics. According to him, both papers have validated the device with only a few biomarkers such as Ki67. Now they need to test many others. The teams may also have to refine their devices to demonstrate their effectiveness against many more cancer types.

“These devices could become for cytotoxic drugs what genetic profiling is for targeted therapy,” said Christoph Lengauer, Ph.D., MBA. He is the chief scientific officer of Blueprint Medicines in Cambridge as well as cofounder of Sagely Health, a startup that helps cancer patients identify their best treatment options. According to him, the devices have demonstrated a “major selling point,” that is, “the possibility to test drug sensitivity of cancer cells within the context of the tumor microenvironment”. To him, this proof of concept studies indicate that both devices may work for approved medications, and he is curious about the future. “It will be interesting to see how well suited they are for experimental drugs where [pharmacokinetics] and [pharmacodynamics] are still investigational,” he said. However, he added that the drug response profiles these devices generate could help to stratify patient populations to match with efficacious medicines and provide better tailored therapy options.

Both devices try to answer the same questions taking different paths, so “it is probably too early to say at this point whether either one or both will ultimately be successful in clinical practice,” Jonas said. To Klinghoffer, any approach that works toward getting effective treatments to patients in reality is the important point to consider: “We believe that the most important model for understanding cancer drug response is the human patient, and technologies that make this possible will fundamentally change the way cancer drugs are developed and tested.”

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Little Progress in How to Advise Women With Dense Breasts
By Judy Peres

Lawmakers around the country are rushing to enact laws that require providers to notify women if their screening mammograms find dense breast tissue. Meanwhile, clinicians remain at a loss concerning how to counsel such women.

As of early August 2015, nearly half the states have laws requiring health professionals to report mammographic density data to patients. Some also require that the report include information on supplemental screening tests. But although ultrasonography and magnetic resonance imaging (MRI) can detect cancers that mammography missed, many questions remain unanswered, including the effect on morbidity and mortality, cost-effectiveness, and insurance coverage.

The problem is widespread, since up to half of all women reporting for screening mammograms have breasts classified as extremely or heterogeneously dense. The problem is especially common for women in their 40s. Dense breasts (those with a high proportion of fibroglandular, as opposed to fatty, tissue) can hide small cancers. Mammographic density is also an independent risk factor for breast cancer, especially advanced cancer.

For 40 years, researchers have worked to understand and refine that risk, but progress has been slow. In May, Karla Kerlikowske, M.D., of the San Francisco Veterans Affairs Medical Center and the University of California–San Francisco, and colleagues reported the results of a prospective cohort study. They found that not all women with dense breasts...