Blood Test May Detect Recurrence of Cancer

BY DOUG BRUNK

SAN DIEGO — Scientists have developed a new way to track cancer using DNA-based blood tests to monitor individualized biomarkers after treatment of solid tumors, and thereby to detect cancer recurrence, an advance that could further the personalized management of cancer patients.

The method, known as PARE (Personalized Analysis of Rearranged Ends), "is based on next-generation mate-paired analysis of resected tumor DNA to identify individualized tumor-specific rearrangements," Dr. Victor Velculescu and his coauthors said (Sci. Transl. Med. 2010 Feb. 24 [doi:10.1126/scitranslmed.3000702]). "Such alterations are used to develop [polymerase chain reaction]–based quantitative analyses for personalized tumor monitoring of plasma samples or other bodily fluids."

During a press briefing at the annual meeting of the American Association for the Advancement of Science, one of the study's coauthors, Dr. Luis A. Diaz Jr., said that PARE "allows us to measure the amount of cancer DNA in any clinical specimen. As soon as a patient's cancer is identified by biopsy, it can be scanned for gene rearrangements. These rearrangements will then be a template to act as a fingerprint for that individual cancer. This can be applied in a variety of clinical scenarios."

Dr. Velculescu, codirector of the cancer biology program at Johns Hopkins Kimmel Cancer Center in Baltimore, and his associates used six sets of tissue samples obtained from four patients with colorectal cancer and two patients with breast cancer to catalog the number of gene sequences in each patient. They did this by first identifying regions where the number of DNA sequences was more or less than anticipated and where sections of different chromosomes fused together.

The researchers analyzed these regions further to identify DNA sequences that displayed incorrect ordering, orientation, or spacing, and observed that an average of 9 rearrangements was found in each of the six samples (range, 4-17).

"The rearrangements represent the most dramatic form of genetic changes that can occur in the genome," Dr. Velculescu said at the briefing. "If the genome were like a book with many chapters, the rearrangement would be like swapping of two chapters within book, so that both chapters would be out of order. If one could recognize rearrangements accurately, that could potentially be one of the best ways to distinguish cancer cells from normal cells."

Next, they looked for the same changes as shed from tumors into the blood of patients. After amplifying DNA that was found in the blood of two of the colorectal cancer patients, they determined that the tests were robust enough to detect rearranged tumor DNA.

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Major Finding: Identification of individualized tumor-specific rearrangements can be used to assess response to treatment and detect recurrence of solid lesions.

Data Source: Analysis of cancerous and normal tissue samples from four colorectal cancer patients and two breast cancer patients.

Disclosures: Under a licensing agreement between Johns Hopkins University and Genzyme, Dr. Velculescu and two of his coauthors are entitled to a share of royalties received by the university on sales of products related to the research.

For example, the fraction of mutant DNA contained in the blood of one of the colorectal cancer patients was 37% prior to surgery for tumor removal, and it dropped to 14% after surgery. "The mutant DNA fraction decreased further after chemotherapy and subsequent removal of metastatic lesions from the right lobe of the liver," the researchers reported. "However, the fraction of mutant tumor DNA did not reach zero (remaining at 0.3% at day 137), consistent with the fact that this patient had residual metastatic lesions in the remaining left lobe of the liver."

The researchers noted certain limitations of the study, including the chance that some rearranged genetic sequences "could be lost during tumor progression," and that the PARE assay currently costs about $5,000, making it expensive for general clinical use. "This cost is a consequence of the high physical coverage and the inefficiencies associated with stringent mapping of 25-bp sequence data to the human genome," the researchers explained.

"As read quality and length continue to improve, less stringent mapping criteria and lower physical coverage will permit analyses similar to those in this study but with substantially less sequencing effort. Moreover, the cost of massively parallel sequencing, which has decreased substantially over the last 2 years, continues to spiral downwards."

Despite such limitations, Dr. Velculescu and his associates maintain that the potential applications for PARE are "numerous," including the identification of tumor-free surgical margins, the analysis of regional lymph nodes, and the measurement of circulating tumor DNA after surgery, radiation, or chemotherapy. "Short-term monitoring of circulating tumor DNA may be particularly useful in the testing of new drugs, as it could provide an earlier indication of efficacy than possible through conventional diagnostic methods such as computed tomography scanning," they concluded.

At the briefing, Dr. Diaz, an oncologist at Johns Hopkins, said that PACE could be used to help clinicians determine who is cured or not cured after surgical resection. "Currently, as physicians we can't tell a patient after breast, colon, or lung cancer surgery whether or not they've been cured," he commented. "A fraction of these patients will be cured by surgery alone, but many will have residual disease. We hope that PARE will be able to discriminate between those individuals that are cured and those that are not cured by detecting residual disease at first surgery. This approach would thereby spare cured individuals from unnecessary and potentially toxic and harmful chemotherapy." ■

Brain Irradiation Does Not Reduce Mortality in NSCLC

BY PATRICE WENDLING

CHICAGO — Prophylactic brain irradiation significantly reduces the likelihood of brain metastases in patients with non–small cell lung cancer, but offers no survival advantage and produces temporary declines in memory.

The lack of survival benefit runs contrary to a 5% improvement in survival observed with prophylactic cranial irradiation (PCI) in small cell lung cancer, in which the rate of brain metastasis is higher and PCI use is fairly common.

Among the 340 patients in the current phase III study, PCI significantly decreased the incidence of central nervous system metastases at 1 year, from 18% with observation alone after definitive lung therapy to 7.7%.

However, disease-free survival was 56.4% with PCI and 51.2% with observation; the overall survival rate was 75.6% and 76.9%, respectively.

There was significantly greater deterioration in both immediate and delayed recall in the PCI arm, compared with the observation arm, Dr. Benjamin Movsas reported on behalf of the Radiation Therapy Oncology Group (RTOG) 0214 study investigators at the annual meeting of the American Society for Radiation Oncology.

Immediate recall on the Hopkins Verbal Learning Test deteriorated 45% in the PCI arm vs. 13% in the observation arm at 3 months, improving to 19% vs. 5% at 6 months and 26% vs. 7% at 12 months.

The overall survival rate was 75.6% with PCI and 76.9% without PCI.

DR. MOVSAS

All patients had stage III non–small cell lung cancer, and had completed a combination of chest radiation, chemotherapy, and/or surgery without progression. PCI was administered for about 10 minutes on 5 consecutive days for 3 weeks, totaling 30 Gy of radiation in 2-Gy units.

Prior studies in small cell lung cancer evaluated neurocognitive function in relatively small numbers of patients, from which it was concluded that there was no clear evidence of neurocognitive impairment with PCI, said Dr. Movsas, chair of radiation oncology at the Henry Ford Health System in Detroit.

However, a more recent randomized "sister" study of PCI in small cell lung cancer that was presented at the same meeting showed a significant increase in neurocognitive decline at 1 year in the higher-dose PCI arm, compared with the lower-dose PCI arm, he said.

Dr. Minesh Mehta, who was invited to discuss the RTOG 0214 study, remarked that the memory data were most intriguing, particularly the suggestion of recovery over time. A recent study also showed a similar biphasic pattern of memory recovery in patients who were treated with whole-brain radiation therapy, implicating an "early responding" cell population (J. Clin. Oncol. 2007;25:1260-6).

These declines in memory were "subtle" and occurred early, but also appeared to recover over time. Notably, PCI's effect on memory did not translate into sustained lower quality of life at any of the time points evaluated, said Dr. Mehta, an oncology professor at the University of Wisconsin in Madison.

Both investigators suggested that the current findings support the use of neuroprotective strategies in radiation patients. That could potentially include agents such as donepezil (Aricept) or radiation-sparing techniques, including sparing the hippocampus, which is involved in memory and is the site of only about 3% of brain metastases, Dr. Movsas said in an interview. RTOG 0614 (a phase III study) is testing the ability of memantine (Namenda) to reduce cognitive dysfunction from whole-beam radiation therapy.

Dr. Mehta noted that target accrual for the current study was 1,058 patients, but that it was forced to close early because of low accrual, resulting in a 50% loss of data on memory outcomes. He went on to note that the study population represents just 0.1% of the more than 50,000 stage IIIA/B non–small cell lung cancer patients who are diagnosed annually. Possible reasons for the low accrual could be lack of interest or faith in PCI for non–small cell lung cancer, concern about its toxicity, or lack of access by radiation oncologists to patients after thoracic radiotherapy.

"It is a severe indictment of the whole field," he said. ■

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