NEWS

Immune Profiling of Tumors May Better Stage Early Cancers

By Gunjan Sinha

When immune cells infiltrate tumors in large numbers, patients do better. Now researchers aim to harness this immune response to predict outcomes.

The Society for Immunotherapy of Cancer (SITC) in Milwaukee is coordinating an international effort to validate Immunoscore, an assay that quantifies this immune response. If added to the current tumor–node–metastasis (TNM) cancer staging system, it may help clinicians decide when to use additional therapy to treat early-stage cancer. Such immune profiling may also help hone immunotherapy by identifying patients more likely to respond.

“Immunoscore will be used if it can be validated,” said Bernard Fox, Ph.D., head of the tumor immunology focus group at Oregon Health and Science University Cancer Institute in Portland and former SITC president.

Researchers led by Jerome Galon, Ph.D., research director in the cancer immunology laboratory at Paris’s French National Institute of Health and Medical Research, proposed that profiling immune cells in and around tumors might help stage cancers after their own studies suggested that it could predict survival. Seventy-three percent of colorectal cancer patients with high densities of immune cells in and around their tumors survived for 5 years, compared with only 30% for patients with low densities (Science 2006;313:1960–4).

Further research showed that quantifying densities of two lymphocyte populations—cytotoxic CD8 T cells and memory T cells expressing CD45RO antigen, CD3 and CD8 T cells, or CD3 and memory CD45RO T cells—both in the tumor core and in the invasive margin of tumors could predict survival of early-stage colorectal cancer patients (J. Clin. Oncol. 2009;27:5944–51 and 2011;29:610–8).

“This [immune profile] was an even stronger predictor of survival than TNM classification,” Galon said.

Multiple studies of several other cancers, including breast, ovarian, and rectal cancer, found similar associations. Evidence that the immune system is an important ally in attacking cancer dates back 50 years, Fox said. But the methods used in existing studies have been wildly inconsistent.

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“From a clinical perspective, most of these studies have not used objective assessment platforms and haven’t been done in large cohorts,” he added.

In 2012, SITC began an international effort to standardize and validate Immunoscore as a potentially new assay to help stage cancers. Validating the assay in colorectal cancer involves partners across at least 14 countries and 5,000 patients and is focused on measuring densities of CD3 and CD8 cells in tumor cores and within invasive margins from tumor samples. The assay expresses immune response as a score from 0 (weak) to 4 (strong). The task force has also teamed up with Definiens, a biotech company in Munich, to automate the assay.

TNM stage I and IIA colon and rectal cancers are often only surgically removed, sparing the patient chemotherapy. But about 13% of colon cancer patients and 20% of rectal cancer patients in these stages relapse within 5 years, according to the National Cancer Institute. Immunoscore might help identify which patients with early-stage disease are more likely to relapse and who might benefit from additional therapy, Galon said. Results from the SITC collaboration are expected next year.

If Immunoscore works in colorectal cancer, it could help stage other cancers as well. However, “it’s been a huge effort to standardize,” Galon said. “Funding has been difficult to obtain.” While clinicians wait for the assay to be validated for colorectal cancer, other researchers are applying the idea to bolster evidence for using it in other cancers.

Joseph Baar, M.D., Ph.D., and colleagues at Case Western Reserve University Medical School in Cleveland, for example, analyzed immune cells in stored breast cancer tissue samples from women with triple-negative, HER2-positive disease. But instead of using immunohistochemistry to quantify specific T-cell populations, the researchers used standard hematoxylin–eosin staining to study tumor-infiltrating lymphocytes (TILs). Unpublished data show that the presence of many TILs is associated with better long-term survival. Heavily infiltrated tumors treated with chemotherapy die off more, Baar
said. He plans to continue studying TILs in breast cancer patients and their relationship to outcomes in clinical trials.

Still other researchers are using the idea of Immunoscore to help parse people who might better respond to immunotherapy. At the University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Antoni Ribas, M.D. Ph.D., director of tumor immunology, and Paul Tumeh, M.D., assistant professor of dermatology, applied Immunoscore to predict how well metastatic melanoma patients respond to pembrolizumab. (Pembrolizumab is an anti–PD-1 [programmed death 1] antibody checkpoint inhibitor that the U.S. Food and Drug Administration approved to treat inoperable or metastatic melanoma.) Using samples from 46 patients with metastatic melanoma obtained before and during therapy, researchers found that in patients who responded to pembrolizumab, CD8 cell proliferation inside tumors associated with tumor shrinkage. Also, samples obtained before treatment from patients who responded showed more CD8 cells as well as cells expressing PD-1 and its ligand, PD-L1, at the invasive tumor margins and inside tumors (Nature 2014;515:568–71).

“Patients who responded had T cells in exactly the areas that Galon has described,” Ribas said. “If we found T cells in the invasive margin and expression of PD-1 and PD-L1 in the same area, that told us that a war had started but that the cancer was winning because it had triggered a brake on the immune system. When we release the brake, patients have objective durable responses.” He added that researchers will use Immunoscore more broadly as they learn what to look for.

A biomarker that could predict response to immunotherapy would be a boon to clinical research. Fox, for example, is collaborating with several drug and technology companies to develop methods to immunoprofile tumors and find predictive biomarkers. Part of the limitation has been technology. Immune profiling must be able to quantify not only the numbers of cells within defined areas but also their relationships in a standard and reproducible manner, Fox said.

“That part of the picture is going to be a lot more complex than just CD3 and CD8,” he said. Research in colon cancers already shows a broad spectrum of immune cells whose numbers either increase or decrease, he added. “I think that’s just the start of what you are going to see in many cancers.”

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What Drives Diffusion of New Cancer Therapies?

By Charlie Schmidt

A recent investigation showed that docetaxel treatment for advanced prostate cancer jumped sharply on the basis of preliminary evidence, years before the publication of phase III data and the U.S. Food and Drug Administration’s approval for the indication in 2004. Apart from revealing prescribing trends for docetaxel in prostate cancer, this study, published in JNCI last December (doi:10.1093/jnci/dju412), makes an interesting case study for how new cancer treatments diffuse into clinical practice.

Understanding that process is crucial because patients can benefit from new therapies only if they have access to them. Investigators who study diffusion comb through a variety of data sources, including medical claims data and patient information contained in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program. For the new docetaxel study, researchers relied chiefly on NCI’s SEER–Medicare linked database, which combines national cancer registry data with medical claims data for the Medicare population.

**Limited Alternatives Favor Uptake**

Study coauthor Dawn Hershman, M.D., an oncologist at Columbia University Medical Center in New York said docetaxel was poised for rapid uptake because the other treatment alternatives were so limited. Results from the investigation show that uses began rising during the late 1990s, when the only other approved therapy for advanced prostate cancer was mitoxantrone. That drug offered palliative relief but no survival benefit. FDA had already approved docetaxel for one type of solid tumor—metastatic breast cancer, in 1996—so clinicians were experienced with the drug and its side-effect profile. When phase I and II study results reported at meetings and in peer-reviewed journals suggested it could also work for metastatic prostate cancer, medical science quickly embraced docetaxel for this new indication.

“The drug was showing activity in multiple diseases, so it got out there quickly,” said Howard Scher, M.D., chief of the Genitourinary Oncology Service at New York’s Memorial Sloan–Kettering Cancer Center. “The first publications in prostate cancer appeared in 1997, and 2 years later there were 22 published papers.”

Rena Conti, Ph.D., is a health economist who studies the uptake and diffusion of new cancer therapies. She said docetaxel’s trajectory in advanced prostate cancer follows an established pattern: The single most important determinant governing the rate of diffusion for a new treatment, her research shows, is its benefits compared with those of competing therapies.

“If a new drug has little activity and high toxicity, then clinicians won’t be motivated to use it,” she said.

Scher emphasized that when other options are limited, clinicians face pressure to pursue promising leads—even without definitive clinical evidence. For docetaxel, early positive signals were borne out in phase III data showing a 20% survival advantage in metastatic prostate cancer. Yet Hershman warned that promising leads can also falter in larger studies. This is what happened when phase III trials failed to confirm survival benefits reported earlier for bevacizumab in breast cancer, she pointed out, leading FDA to drop its accelerated approval for that indication in 2011.

According to Conti, other driving factors in diffusion include marketing and promotion—both to clinicians and patients via direct-to-consumer advertising—and especially mortality rates associated with the cancer targeted by a new treatment.

“If a new drug treats a disease with very high mortality, then the probability...