ASC0 Breast: DNA-Damaging Therapies Emerging as Possible Triple-Negative Breast Cancer Therapies

By Dave Levitan [2]

Triple-negative breast cancers represent a challenge for patients and clinicians, with poorer prognosis and fewer treatment options than other breast cancer subtypes. Recently, though, there have been suggestions that targeting pathways that repair DNA within tumor cells could provide benefit beyond the currently available treatments.

Joyce O'Shaughnessy, MD, of the Baylor Sammons Cancer Center in Dallas, discussed this ongoing research at the American Society of Clinical Oncology (ASCO) Breast Cancer Symposium in San Francisco. Triple-negative breast cancer refers to those tumors that do not express the genes for estrogen receptor, progesterone receptor, or HER2; this accounts for about 15% of all breast cancers.

"If we have some breast cancers that have some underlying problems with homologous recombination”—generally used by cells to repair DNA strand breaks—“there are two strategies that come to mind immediately about trying to exploit this deficit,” she said. “Perhaps if you really stress the cell, you can overcome the capacity . . . to repair the DNA,” thereby helping to cause cell death and prevent a tumor from continuing to grow.

Though some success has been achieved with DNA-damaging agents like anthracyclines, this sort of cellular stress could best be achieved with high doses of certain chemotherapy agents. Dr. O'Shaughnessy reviewed data from one study she and colleagues conducted of iniparib, an inhibitor of the DNA repair enzyme PARP1. “Iniparib does induce double-strand DNA damage . . . but at currently administered doses, it does not block PARP1 or PARP2,” she said.

In the study, which Dr. O'Shaughnessy presented earlier this year at ASCO's annual meeting in Chicago, 258 patients with metastatic triple-negative breast cancer received gemcitabine and carboplatin, and another 261 patients received those two drugs along with iniparib.

Disappointingly, the study did not meet its primary endpoints for either progression-free survival (PFS) or overall survival (OS), though there were slight nonsignificant benefits with iniparib for both. The iniparib patients had a median PFS of 5.1 months compared with 4.1 months in those who did not receive the drug ($P = .027$, with a prespecified requirement of .01); OS results were 11.8 and 11.1 months, respectively ($P = .28$).

Specifically among patients who received the regimen as a second- or third-line regimen, Dr. O'Shaughnessy said, “there was a hint that we may be enriching here, in some way, these breast cancers that may benefit more from a DNA-damaging strategy.” OS among this subgroup was 10.8 months with iniparib and 8.1 months without.

Even if iniparib or other therapies prove beneficial as DNA-targeting agents for these difficult cancers, identifying patients who need them remains a challenge. John Carpten, PhD, of the Translational Genomics Research Institute in Phoenix, spoke during the same session about efforts to meet this challenge and improve sequencing and characterization of breast tumors.

"We've spent a lot of time over the last couple of decades really teasing out the genetic and molecular alterations and events that govern tumor genesis, and we've learned quite a bit about the pathways and processes,” he said. Studies are ongoing to describe the genomic details of triple-negative breast cancers, and next generation sequencing technologies continue to improve. One finding from a study that has looked at the complete genomes of nine breast tumors is that $TP53$ mutations appear in many cases, and other details are emerging as well.

Dr. O'Shaughnessy also noted that there may be surrogate methods for determining candidates for certain therapies. Basal-like breast cancers, she said, may benefit in particular from DNA-damaging
agents like iniparib. “We are uncovering some important therapeutically actionable concepts and targets across this data set,” Dr. Carpten said. “Undoubtedly, we believe this is likely to become part of clinical assessment to hopefully improve clinical management through deep molecular profiling in these patients.”


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