Few Positives for Triple-Negative Breast Cancer

By Karyn Hede

ost of us learned in primary school that using a double negative is bad grammar. But a disease defined by three negatives, triple-negative breast cancer (TNBC), has somehow sneaked into the oncology lexicon. Now it has a fourth negative: It is not responsive to iniparib, the poly (ADP–ribose) polymerase (PARP) inhibitor that many hoped would improve survival among patients with this recalcitrant disease.

Initial findings about iniparib were encouraging. In January, the New England Journal of Medicine reported results from a trial (BSI-201) that showed clinical responses in metastatic TNBC patients who received iniparib plus chemotherapy: 56% of patients had complete or partial response (stable disease of at least 6 months), compared with 34% (P = 0.01) of those who received chemotherapy alone. But the initial excitement was short-lived. In late January, the drug’s sponsor, Sanofi-Aventis, announced that a phase III trial with 519 patients showed no improvement in overall survival and progression-free survival when iniparib was added to the standard chemotherapy combination of gemcitabine and carboplatin.

“This is a setback in the overall impression that these PARP inhibitors were going to be a total hit in [treating TNBC],” said Edith Perez, M.D., director of the breast program and chair of the clinical study unit at the Mayo Clinic in Jacksonville, Fla.

For lack of a better definition, TNBC has become stand-in terminology for breast cancer tumors that express none of the three key diagnostic markers: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (Her2/neu). That has made it particularly difficult to treat, since many breast cancer drugs target those receptors. TNBC tumors appear and grow quickly between yearly mammography screenings, which makes catching them before they metastasize a challenge.

Furthermore, as Perez said, “The issue is that TNBC is a unique type of breast cancer: It tends to recur early, and the sites of metastasis particularly target the visceral organs and the brain.”

Between 10% and 20% of diagnosed breast carcinomas are triple negative, and the standard course of treatment has been surgery and chemotherapy. Prognosis for TNBC patients is worst in the first 5 years and improves in patients who have a complete response to chemotherapy.

The BRCA1–TNBC link

Since TNBC has few treatment options, researchers are trying to understand the disease’s underlying pathology. “It’s only really recently that the term TNBC came about,” said William Foulkes, Ph.D., a researcher at the program in cancer genetics at McGill University in Montreal and lead author of a 2010 New England Journal of Medicine review of current understanding of TNBC. “But it never really implied anything that is diagnostic in the sense that you think of as breast cancer subtypes. It’s not a pathology-driven diagnostic code.”

In the review, Foulkes and his colleagues describe TNBC as belonging to a “basal cell–type” family of tumors that includes tumors arising from the basal–myoepithelial layer of normal breast. These tumors tend to be larger and higher grade, with no particular subtype. But they point out that the triple-negative phenotype is heterogeneous and therefore should not be thought of as a group.

For example, nearly all tumors arising in patients who carry mutations in the BRCA1 gene have basal-like characteristics and have similar molecular profiles to those of TNBC tumors. Both also have a high degree of chromosomal abnormalities, which led investigators to believe that the PARP inhibitors—which target DNA repair and have been particularly effective in treating tumors arising from patients with hereditary BCRA1 and BRCA2 mutations—might be particularly useful for TNBC patients as well. That has not turned out to be the case.

“The dream that there was a ‘BRCA-ness,’ if you will, to these [TNBC] tumors seems to be at the moment maybe just that,” said Foulkes.

He suggested more careful study of subpopulations of TNBC to determine which are truly defective in DNA repair and therefore perhaps more susceptible to the many PARP inhibitors that are currently under study for various tumor types.

“It seems like [TNBC] is going to be much more complex than people had thought,” said Perez.

She pointed out that promising early-stage clinical trials raised hopes about treating TNBC with epidermal growth factor receptor inhibitors, only to be dashed.

“There was this idea that the epidermal growth factor receptor inhibitors were going to be particularly helpful, and that has not panned out from the small clinical trials that have been done to date with either erlotinib or cetuximab,” she said.

However, the antiangiogenesis agent bevacizumab performed just as well with TNBC patients as other metastatic breast cancer patients in the ECOG-E2100 trial, a phase III randomized trial evaluating the addition of bevacizumab to paclitaxel as first-line therapy in women with metastatic breast cancer.
“We need to be open-minded,” Perez said. “We need a concerted effort nationwide to obtain biopsies, when feasible, from the metastatic sites, because that’s how we will unravel what are the changes that occur that makes these tumors less sensitive to treatments.”

**Risk Factors Begin To Emerge**

Although little is known about the risk factors for TNBC, epidemiological studies suggest that women who develop the disease are more likely to be black and to be diagnosed at an earlier age.

Since by definition TNBC is unresponsive to the sex hormones estrogen and progesterone, the role these hormones may have in the development of TNBC is unknown. But a recent study published in this issue of the Journal reports that women who don’t have children have a 39% decreased risk of developing TNBC compared with women who have children. Furthermore, women who have more than one child have a 50% greater risk of TNBC than those who have only one child. Using data on 155,723 postmenopausal women collected as part of the Women’s Health Initiative, Amanda Phipps, Ph.D., and her colleagues at the Fred Hutchinson Cancer Research Center in Seattle assessed associations between reproductive history, breastfeeding and other factors that affect hormone levels, and later development of subtype-specific breast cancer.

“Going into this study, we had expected that a woman’s reproductive history would be associated with her risk of hormonally responsive breast cancers but not [TNBC],” according to Phipps. Instead, the group found a statistically significant correlation with giving birth, but no correlation with breastfeeding, age at menarche, oral contraceptive use, or any other risk factor studied. The study also confirmed previous research that found a decreased risk of estrogen receptor–positive breast cancer among women who give birth, with the lowest risk among women who had given birth multiple times.

“The mechanisms behind these associations really aren’t clear,” said Phipps. “We do know that the hormonal changes that a woman is exposed to during pregnancy induce changes in the cellular structure and architecture of the breast. Overall, those changes seem to make the breast less susceptible to cancer development in the future, but why those changes don’t translate to reduced risk of [TNBC], we don’t yet know.”

**Newer Agents**

In the short term, the most promising treatment for TNBC may be ixabepilone, a microtubule inhibitor similar to the taxanes. Perez and her colleagues conducted a pooled retrospective analysis of five phase II studies and two phase III trials of metastatic breast cancer patients treated with ixabepilone in various treatment settings. The team recently published the analysis in *Breast Cancer Research and Treatment* (June 2010;121:261–71). Of 2,261 total breast cancer patients, 556 had triple-negative tumors. The most promising results, according to Perez, were in the two phase III trials of ixabepilone plus capecitabine. The median progression-free survival time was statistically significantly longer for triple-negative patients treated with ixabepilone plus capecitabine (4.2 months) than for treatment with capecitabine alone (1.7 months), with no increase in toxicity.

A new formulation of the approved chemotherapy agent irinotecan is also showing some promise. In phase II data presented at the 2010 San Antonio Breast Cancer Symposium, seven of 18 TNBC patients with refractory tumors responded to PEGylated (encased in polyethylene glycol) irinotecan (NKTR-102), a response rate similar to that in non-TNBC patients. The compound formulation of NKTR-102 has shown increased half-life compared with the standard formulation and is in consideration for a larger phase III study, according to Perez.

Looking forward, Perez said, “we need to be innovative in our approach, but for now chemotherapy remains the backbone.”

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