Prospects for Identifying Molecular Alterations for the Treatment of Refractory Residual Disease

Although neoadjuvant chemotherapy (NAC) can induce a pathologic complete response (pCR) in 30% of patients with triple-negative breast cancer (TNBC), those who manifest residual disease at surgical resection may expect worse outcomes and, at present, do not have targeted therapeutic options. Presenter Justin Balko, PharmD, PhD, demonstrated that molecular analysis of tumor tissue from such patients may be used to identify the genetic alterations responsible for disease recurrence and to help individualize treatment with available medications.

“We hypothesized that profiling residual TNBCs after neoadjuvant chemotherapy would identify molecularly targetable lesions in the chemotherapy-resistant component of the tumor and, furthermore, that these persistent tumor cells should mirror micro-metastases, which ultimately recur in such patients.”

For more than 100 TNBC patients with residual disease, Balko and colleagues developed sophisticated molecular profiles and employed deep sequencing to examine and compare 182 oncogenes and tumor suppressors known to be present in human cancers. This sequencing strategy showed that approximately 90% of tumors exhibited individual aberrations that, depending on the pathway affected, could be targeted for treatment by p13K/mTOR inhibitors, DNA-repair targeting agents, RAF/MEK inhibitors, cell cycle/mitotic spindle inhibitors, and/or targeted RTK inhibitors.

“We already knew that triple-negative breast cancer is driven by a diverse group of genetic alterations,” said Balko. “So, in one way, we fell further down this rabbit hole, but we also found some things that could be promising therapeutically.”

Original observations included the discovery that amplification of the anti-apoptosis gene MCL1 occurs in 56% of TNBC, often along with MYC amplification, which was identified in 33% of tumors. Identification of the novel JAK2 gene, associated with cell proliferation, was found to be amplified in about 10% of patients and associated with poor survival; JAK inhibitors are currently under development for inflammatory disease.

Balko concluded, “Efforts to determine whether lesions present in the residual disease mirror those in the recurrence, and whether they are selected during neoadjuvant treatment, are underway.”
Chemotherapy for Patients With Local and Regional Recurrences

Surgery and radiation therapy represent the standard of care for the treatment of isolated local or regional recurrence (ILRR) of breast cancer, but whether chemotherapy can also help these patients is not known from any established body of data. Results from the global CALOR (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer) trial provide clear evidence that adjuvant chemotherapy is warranted, at least for ER-negative recurrences.

CALOR, noted presenter Stefan Aebi, MD, “is the first randomized controlled study that shows that adjuvant chemotherapy works in these patients.” He reported that recruitment for the study proved difficult, in part due to oncologists’ own beliefs about treatment in such cases and to the changing landscape of chemotherapy. The international trial closed with a modest number: 162 patients. Only patients with local recurrences were sought, excluding those with distant metastases or supraclavicular lymph nodes.

The patients randomized for CALOR represented, as expected, a heterogeneous group in terms of prior treatment, which meant that those who entered the chemotherapy arm of the study also received individualized treatment regimens. (Each patient’s treating oncologist determined the chemotherapy regimen based on prior treatment.)

Results proved positive overall and especially so for ER-positive disease. At 5-year follow-up, disease-free survival rates were 69% for women who received adjuvant chemotherapy versus 57% for those who did not (P = .045). Overall survival at 5 years was similar, at 88% for patients who received chemotherapy versus 76% for those who did not (P = .02).

“The benefit was larger for patients with ER-negative recurrence,” said Dr Aebi, noting that the CALOR group can offer a positive recommendation for adjuvant chemotherapy in such cases while, for ER-positive disease, the data is not fully mature.

Dr Aebi noted that further data will be available concerning the pattern of locoregional recurrences and the impact of chemotherapy on second ILRR at Poster P6-07-06 (revised abstract below), presented by Irene Wapnir, MD, which may be viewed at SABCS on Saturday morning.

In Vitro Study: A Novel and Rational Approach to Triple-Negative Disease

Histone deacetylase (HDAC) inhibitors, cytostatic agents that have been shown to delimit proliferation of tumor cells in culture, may have a future in targeted therapeutics for the treatment of triple-negative breast cancer. Kapil Bhalla, MD, presented aspects of his ongoing research program that has shown, in vitro, how exposure to an HDAC inhibitor indirectly impairs the ability of triple-negative cells to repair damaged DNA and, at the same time, sensitizes them to 2 agents — a PARP inhibitor and cisplatin — that have clinical activity in some patients with breast cancer.

Prospects for HDAC inhibitors arose around the likelihood that heat shock protein 90 (hsp90), the highly conserved and abundant cell chaperone, is involved in carcinogenesis. Dr Bhalla and colleagues previously reported that treatment with an HDAC inhibitor renders hsp90 inactive, thus impeding the DNA damage response that involves the ATR–BRCA1–Chk1 signaling pathway. HDAC inhibition thus creates an environment within cells not dissimilar to that seen in breast cancer cells with BRCA1 mutations.

“These studies support the rationale of testing the efficacy of a treatment regimen that includes a PARP inhibitor combined with a pan-HDAC inhibitor and cisplatin against triple-negative breast cancers,” said Dr Bhalla.

In addition, Dr Bhalla and colleagues also investigated whether pan-HDAC inhibitors vorinostat or panobinostat could sensitize triple-negative breast cancer cells to PARP inhibition. They found that either agent together with ARP inhibitor ABT888 was a lethal combination to triple-negative cells, whether or not the cells contained the BRCA1 mutation.

“If you have a patient with triple-negative breast cancer who does not have a BRCA1 mutation, you could consider a clinical trial using an HDAC inhibitor in combination with a PARP inhibitor and cisplatin,” Dr Bhalla concluded.
Hypofractionated Radiotherapy: START Results at 10 Years

Hypofractionated radiation to treat early breast cancer is safe and effective, according to 10-year results of the Standardization of Breast Radiotherapy Trials (START).

“Long-term follow-up confirms that a lower total dose of radiation in fewer, slightly larger fractions, delivered over a shorter treatment time, is at least as safe and effective as standard 5-week schedules of curative radiotherapy in women with early breast cancer,” said John Yarnold, MD.

Results reported yesterday at SABCS 2012 are consistent with previous results from the START trial, which included 2 arms based on length of treatment schedules, and following more than 4500 patients. The shorter, 3-week, 15-fraction schedule of hypofractionated radiation has become the standard of care in the United Kingdom and its use is expanding to other countries.

In START A, researchers compared 50 Gy of postsurgery radiotherapy (25 fractions for 5 weeks) versus 41.6 Gy or 39 Gy (13 fractions for 5 weeks). START B tested 50 Gy (25 fractions for 5 weeks) versus 40 Gy (15 fractions for 3 weeks). In both trials, there were no statistically significant differences in the rates of locoregional relapse between the treatment arms. Concerning moderate to marked adverse tissue effect in the conserved breast — which included breast induration, shrinkage, edema, and telangiectasia — 10-year data for START A showed similar rates for the 50-Gy and 41.6-Gy schedules, with slightly lower rates in 39 Gy. Similarly, for START B, significantly fewer cases of moderate or marked adverse effects in the conserved breast were found in the 40-Gy versus the 50-Gy arms.

The study authors concluded that breast cancer and dose-limiting normal tissues respond similarly to fraction size, with no advantage for the smaller traditional 2-Gy fractions, so that patients can be safely and effectively treated to a lower total dose with fewer fractions than the standard 50-Gy/25-F regimen.

TARGIT vs Conventional Radiotherapy: 10 Years On

Although breast cancer is frequently multicentric, the fact that most recurrences originate near the primary tumor suggest that highly targeted radiotherapy might either be more effective over the long-term or might spare patients a small but significant risk of cardiac or other adverse events that occur with conventional radiation treatment.

An ongoing randomized, phase 3, radiology trial, TARGIT-A (Targeted Intra-operative Radiotherapy) compares outcomes in patients who undergo breast-conserving surgery followed by either whole breast external beam radiotherapy (EBRT) or a risk-adaptive approach that deploys, via a mobile unit utilized either during lumpectomy surgery or shortly thereafter, a single high dose of targeted radiotherapy to the tumor bed. The first patients were randomized in 2000, and to date the trial has enrolled 3451 women from 10 countries aged 45 years or older with invasive ductal carcinoma.

Follow-up results, still accumulating, are suggestive. Compared with conventional EBRT, TARGIT results indicate a trend towards reduced mortality, largely due to differences in cardiac events and second cancers, though the numbers of such events were small. There was little difference in the numbers of deaths due to breast cancer, explained Jayant Vaidya, MD, PhD, who with colleagues designed the original technique in the late 1990s. He added that other factors — age, tumor size, grade, lymphovascular invasion, lymph node status, and HER2 status — had no measureable influence on differences between TARGIT and EBRT.
Revised Abstract

Patterns of locoregional failure in the CALOR (Chemotheraphy as Adjuvant for Locally Recurrent Breast Cancer) trial


Introduction: The risk of developing distant metastasis is elevated in patients (pts) who experience isolated locoregional recurrences (ILRR) after initial breast cancer treatment. Surgical resection of ILRR, radiation therapy (RT), and adjuvant hormonal therapy are common practice strategies. However, the role of chemotherapy (C) is unknown. Pts with complete excision of an ILRR were randomly assigned to C or no C. We report treatments, estrogen (ER) and progesterone receptor (PR) status in primary tumors and ILRR, incidence of second-ILRR failure events, and deaths.

Methods: 162 pts were enrolled in IBCSG 27-02, BIG 1-02, NSABP B-37. RT was recommended but not required if a completion/salvage mastectomy was performed after an ipsilateral breast tumor recurrence. Hormonal therapy was required for ER+ and/or PR+ tumors and anti-HER2 therapy was given at investigator discretion. Stratification criteria were hormone receptor status of recurrence, site of recurrence (breast, mastectomy scar/chest, regional lymph nodes), and use of prior C.

Results: Primary surgery was breast conserving: 98 (60%) and mastectomy: 64 (40%). Types of nodal surgery for primary cancer included sentinel node resection: 20 (12%), axillary node (AN) sampling: 37 (23%), AN dissection: 88 (54%), more extensive nodal surgery: 6 (4%), and no nodal surgery: 8 (5%). The sites of first ILRR were breast: 88 (54%), mastectomy scar/chest wall: 53 (33%), and regional lymph nodes: 21 (13%), and were similarly distributed by treatment arms. Of the 98 pts who originally had a lumpectomy, 92 (94%) received RT. Among these 92, ILRR were in-breast: 83 (90%), chest wall: 1 (1%), and regional node: 8 (9%). Salvage mastectomy was performed in 76/98 (78%) with prior lumpectomy. Of the other 22 pts, 16 had repeat lumpectomies, 5 had AN resection, and 1 had a chest wall resection. Of the 64 who originally had mastectomy, 52 (81%) recurred in the scar/chest wall, 12 (19%) in the regional nodes and 15 pts (23%) received post-mastectomy RT, 4 of whom had regional nodal recurrences. Of the 143 pts who had ER status reported for the primary tumor, 21 (15%) had a different ER status reported for the ILRR (table). PR expression was discordant in 35 (26%) of the patients with known values.

<table>
<thead>
<tr>
<th>Estrogen Receptor Status</th>
<th>ILRR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>Positive</td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>Tot. known</td>
<td>56</td>
<td>87</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>

Average time from surgery for ILRR to surgery for second ILRR was 1.6 yrs (range: 0.08 -4.8). The average pt age for second LRR was 58.9 yrs versus 54.6 yrs for those who developed distant failures. At median follow-up of 4.9 yrs, 15 pts developed a second ILRR (10 local, 5 regional), 7 (47%) of whom have died. Of the 37 (23%) pts who developed a distant failure 19 (51%) have died.

Conclusions: Similar to the effect observed in distant failure rates, a second ILRR following multimodality therapy for an ILRR is a strong prognostic indicator of subsequent death in this population.

Funding: NCI PHS grants U10-CA-37377, -69974, -12027, -69651, 44066, and CA-75362.