Triple-Negative Breast Cancer in the Post-Genomic Era

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Clearly there is no single therapy for all patients with TNBC, given the molecular heterogeneity of this subtype. However, new insights from further genomic analysis of TNBC suggest approaches to rational clinical trial design, and patients will undoubtedly benefit as we define the most appropriate therapeutic targets in management of this aggressive disease.

The article by Drs. Herold and Anders is an excellent, comprehensive review of the evolving understanding of triple-negative breast cancer (TNBC) as a molecularly heterogeneous entity with several potential treatment approaches.[1] The authors point out that the Perou classification published in 2000 has been refined to include new entities such as the claudin-low subtype.[2] In an effort to define potential therapeutic targets for TNBC, the Pietenpol group performed a comprehensive analysis of genomic data to develop a molecular classification for TNBC. They defined and validated six molecular subtypes based on gene expression data: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and luminal androgen receptor (LAR).[3] Pathway analysis revealed that the BL1 subtype is heavily enriched in cell-cycle and cell-division pathways, that the BL2 subtype involves the growth factor signaling pathway, and that the IM subtype is enriched in immune cell processes. In addition, the M subtype is heavily enriched in pathways involved in cell motility, extracellular matrix (ECM) receptor interaction, and cell differentiation pathways, whereas the MSL subtype adds growth factor signaling pathways. Finally, the LAR subtype is enriched in androgen-regulated pathways. Therapeutic implications suggested by study of key pathways in TNBC cell lines are that the BL1 and BL2 subtypes are more sensitive to cisplatin, the LAR cell line is sensitive to the AR antagonist bicalutamide, and the M and MSL cell lines are more sensitive to dasatinib (an SRC family inhibitor). The subtype findings were validated in The Cancer Genome Atlas (TCGA) dataset and suggest possible clinical trial designs for specific TNBC subsets.[4]

Herold and Anders note that bevacizumab has produced improvement in progression-free survival (PFS) but not overall survival (OS) in the metastatic setting, a finding that led to reversal of the US Food and Drug Administration approval of the breast cancer indication for bevacizumab in 2011. The role of bevacizumab in breast cancer remains controversial, however, as emerging data suggest that patients with the TNBC subtype may benefit from the addition of bevacizumab to chemotherapy. Brufsky et al reported a subgroup analysis of the Regimens In Bevacizumab for Breast ONcology (RIBBON)-2 trial, which showed that TNBC patients had significantly improved PFS ($P = .0006$) and a trend toward improved OS (17.9 months vs 12.6 months; $P = .0534$).[5] In addition, the GeparQuinto trial showed benefit in the TNBC population with the addition of bevacizumab to chemotherapy preoperatively. Of note, the Pietenpol study shows that the MSL subtype is enriched in genes involved in angiogenesis, suggesting that treatment with anti-angiogenesis agents may be beneficial in this subtype. Currently, the greatest limitation to optimal use of bevacizumab is the lack of predictive biomarkers, despite many years of intensive study. As Drs. Herold and Anders point out, the role of bevacizumab in breast cancer remains controversial, however, as emerging data suggest that patients with the TNBC subtype may benefit from the addition of bevacizumab to chemotherapy.

An unexpected finding from the Pietenpol analysis is a subgroup of TNBC that is characterized by androgen receptor (AR) signaling. These tumors are more indolent and behave more like luminal breast cancers. In addition, they are more likely to have a phosphatidylinositol 3-kinase (PI3K) mutation, and in preclinical studies resistance to bicalutamide could be reversed with inhibitors of PI3K or the mammalian target of rapamycin (mTOR).[4] In the clinical setting, Traina et al conducted a phase II study with bicalutamide in AR-positive metastatic breast cancer. They found 12% of TNBCs were AR+ and demonstrated an overall clinical benefit rate of 21% in this heavily pretreated population.[6] Ongoing studies are evaluating abiraterone and enzalutamide in this setting. While there are promising data that poly (ADP-ribose) polymerase (PARP) inhibitors are active in patients with $BRCA1$ or $BRCA2$ mutations (regardless of tumor subtype), it has been more difficult to
demonstrate activity in somatic TNBC. Data from the TCGA project confirmed the loss of \( BRCA1 \) as a basal-like feature, making treatment with a PARP inhibitor an attractive option for TNBC with loss of \( BRCA1 \), however studies to date have not subclassified TNBC in the context of potential response to PARP inhibitor therapy. Pietenpol showed that the BL1 and BL2 subtypes had a higher expression of DNA damage response genes, which suggests that patients with this subtype may benefit from treatment with a PARP inhibitor. One challenge in the field is the drug iniparib; this agent, which showed striking activity in a phase II randomized trial, was later found to exert its DNA damaging effects via alterations in reactive oxygen species, rather than via PARP inhibition. Hence, the value of “true” PARP inhibitors in somatic TNBC remains controversial. There is ongoing interest in the use of iniparib for TNBC, however, as several studies do show activity of iniparib in combination with gemcitabine/carboplatin or irinotecan.[7] 

Herold and Anders highlight new insights from TCGA on somatic mutations and copy number alterations in TNBC. In patients with TNBC, mutations occur commonly in three genes (\( TP53, PIK3CA, PTEN \)), with other genetic mutations occurring less frequently. Focal amplification of the \( cMYC \) gene seems to be a basal-like characteristic.[8] Copy number alterations are common in TNBC, being seen, for example, in \( PARK2 \) (6%), \( RBI \) (5%), \( PTE \) (3%), and \( EGFR \) (5%), and suggesting possible targets for therapy.[9] 

It has long been appreciated that basal-like tumors show a high frequency of \( TP53 \) mutations (\( \geq 80\% \)); the therapeutic relevance of this finding has yet to be appreciated, however, as re-expressing a tumor suppressor gene is not clinically tractable. Herold and Anders discuss the role of checkpoint 1 (Chk1) inhibition in potentiating the cytotoxicity of irinotecan in two \( p53 \)-mutant TNBC lines, and they suggest that certain combinations of targeted therapy and cytotoxic agents may be worthwhile in the context of \( p53 \) loss of function. However a phase II study conducted by Ma of UNC-01 (a nonselective Chk1 inhibitor) with irinotecan in patients with metastatic TNBC showed that UNC-01 did not appear to potentiate the cytotoxic effects of irinotecan.[10] One novel therapy under preclinical investigation for \( p53 \)-mutant breast cancer is the small-molecule compound YK-3-237, a SIRT1 enzyme activator that reduces acetylation of mutant \( p53 \) and exhibits anti-proliferative effects in TNBC cell lines.[11] 

The review by Herold and Anders highlights the enormous efforts that have been made to define potential targets and therapies for TNBC since the identification of molecular subtypes by Perou in 2000. Clearly there is no single therapy for all patients with TNBC, given the molecular heterogeneity of this subtype. However, new insights from further genomic analysis of TNBC suggest approaches to rational clinical trial design, and patients will undoubtedly benefit as we define the most appropriate therapeutic targets in management of this aggressive disease.

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