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YEAR IN REVIEW: BASIC SCIENCE

Tumor heterogeneity was the focus of some of the most exciting basic science research in 2018, Robert Benezra, PhD, said on Saturday. Single-cell sequencing studies have allowed researchers to observe that tumor cell clones were present in tissue ducts before invading invasive parenchymal tissue. The basic theme of the findings, said Dr. Benezra, of Memorial-Sloan Kettering Cancer Institute in New York City, was that "changes take place within the duct prior to extravasation." It also has been shown that in some patients, clones of certain mutated cells were "extinguished" following treatment, and that this finding is associated with a good therapeutic outcome. Mutations that persist even after treatment are thought to have adapted to the chemotherapy. Other tumor cells may develop acquired resistance to the chemotherapy through transcriptional reprogramming. The investigators postulated that harsher, more mutagenic chemotherapy regimens may promote even more acquired resistance in certain tumor cell types.

In other research, single-cell RNA sequencing of triple negative breast cancer (TNBC) cells has shown that up-regulation of the glycosphingolipid pathway in those cells is associated with poorer therapeutic outcomes, at least in part because that mutation also was associated with an increase in innate immune cells, which may have protected pro-invasive or tumorigenic lympohcytes within that cell population.

Heterogeneity also characterizes the tumor microenvironment (TME), Dr. Benezra continued. In what he termed a "rather lovely study," Fatima Mechta-Grigoriou and colleagues have found that subsets of TNBC cancer-associated fibroblasts (CAFs) have different genetic signatures that vary across breast cancer subtypes. One of these CAFs (CAF-S1) is associated with immunosuppression. These findings give rise to more questions, such as: "Can one CAF subtype be converted to another, or are these fixed states?" and "How do CAF subtypes compare between primary and metastatic tumors?"

Another feature of the TME is that it may influence tumor response to chemotherapy. TW Miller and colleagues have found that stromal cells may secrete fibroblast growth factor (FGF) 2, which can engage tumor FGF receptors and confer drug resistance on ER+ breast cancer cells. One question to address moving forward, said Dr. Benezra, is whether or not the FGF2 is secreted in response to tumor cell signals, "and if so, what are those...signals that are conferring that ability to resist these therapies?"

In the realm of tumor metabolism, Dr. Benezra described a "very nice" study by Gregory J. Hannon and colleagues showing that asparagine synthesis is crucial to metastatic progression.

In a particularly intriguing finding, reducing dietary asparagine in mouse models was associated with a reduction in lung metastases. Other investigators have found that increasing reactive oxygen species in the tumor environment may

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ISSUE 5 AT A GLANCE

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promote the transition of mesenchymal to epithelial cells. Scavenging the reactive oxygen through the addition of n-acetyl cysteine had the opposite effect. Adding drugs such as auranofin to enhance the formation of reactive oxygen species may have therapeutic value by hastening cell death.

The year also saw some interesting research in the area of metastatic progression, Dr. Benezra said. In an exploration of the well-established observation that metastatic potential is related to chromosomal instability, Samuel F. Bakhoum and colleagues showed that missegregation of chromosomes can elicit a pro-inflammatory response within the tumor environment, induce epithelial-to-mesenchymal transition, and ultimately result in a higher metastatic burden within laboratory animals. Other studies examined the phenomenon of tumor dormancy and the genetics of brain metastases.

"Single-cell sequencing analysis allows for detailed analysis of tumor heterogeneity and tumor evolution, which may inform clinical decisions," Dr. Benezra concluded. "The interplay between the tumor and the microenvironment continues to reveal new basic mechanisms of tumor evolution and diversification, which may provide new targets for intervention." Additionally, "chromosome instability may fuel tumor metastasis by inducing a pro-inflammatory response to cytoplasmic DNA." Finally, he said, "amino acid metabolism may play an important role in protein selection, which drives tumor evolution."

YEAR IN REVIEW: TRANSLATIONAL RESEARCH

In a review of the most significant advances of 2018 in translational research, Andrew Tutt, MD, focused on four areas:

- Improved understanding of immune cell behavior in the tumor microenvironment (TME);
- Lessons gleaned from studies on the genome of metastatic breast cancer and the epigenomic landscape;
- Techniques for improved understanding of the BRCA reports and the "BRCAness" of tumors; and
- Treatment approaches to other lethal scenarios in breast cancer subtypes

The TME can best be thought of as "the party to which immune cells often – but don't always -- get invited," said Dr. Tutt, Head of the Division of Breast Cancer Research, and Director of the Breast Cancer Now Toby Robins Research Centre, the Institute of Cancer Research and Guy's Hospital, King's College, London, United Kingdom. One of the major questions before investigators is, "if very few immune cells are on the guest list, how can we get more of them invited to alter the outcome?" Single-cell sequencing techniques have helped researchers determine not just the cellular milieu within individual patients, but also the inter-patient variability, allowing them to develop a map of the micro-environment.

Such an analysis has shown enormous diversity in the "guest list" – that is, the population of T cells relative to B cells -- within the TME, Dr. Tutt explained. This suggests a diversity of checkpoint receptor expression. For example, there appears to be a much higher volume of T cells and NK cells within the TME compared with normal breast tissue environment, which presents a possible target for therapies that are currently available. Understanding the TME also may be important for designing trials of treatments against the different types of cells. Other research has shown that high levels of the CD8+ class of tumor resident memory cells is associated with higher survival times, compared with patients who have fewer of these cells.

Defining "who wears what and who dances with whom" – that is, what markers are present on the immune cells and what they do – is also an important focus of research, Dr. Tutt said. "This gets us beyond a guest list to who sat with who, who danced with who, and, as we all know, at any good party, learning about who came with one person and left with another might give you particularly good information along the course of treatment."

The role of tissue-infiltrating lymphocytes (TILs) also has come under close scrutiny. Much has been learned about their type, location, and genetic expression, Dr. Tutt pointed out. Variability in the 3-dimensional organization of cells and drug targets in tumors and lymphoid tissue with different types of TILs may have significant prognostic implications and "will likely affect prediction of drug benefit" in future clinical trials," as well as offering new biomarkers for correlative biology. He cited the example of neoadjuvant chemotherapy (NACT) in the treatment of triple-negative breast cancer: a "cold" tumor with few TILs portends a poorer response to NACT and a less favorable prognosis overall.

Building on this knowledge, neoadjuvant oncolytic virotherapy prior to surgery presents another promising avenue of clinical research: in mouse models, it has been shown to sensitize triple-negative breast cancer (TNBC) cells to oncolytic viruses, which infect and replicate within the breast cancer cells, leading to immunogenic cell death. The investigators concluded that pre-surgical exposure of "cold" tumors to a viral stimulus might lead to a better response to checkpoint inhibitors.

In the realm of genomics and epigenetics, particularly with respect to metastatic tumors, mutations in genes ESR1, ERBB2, and NF1 were associated with greater resistance to endocrine therapy, compared with tumor cells that did not have those mutations, Dr. Tutt added. Such alterations were shown to occur in 22% of tumors, and were associated with a shorter duration of therapeutic response. All in all, SABCS featured a "tsunami" of data on the identification of mutations and the use of therapeutic agents targeted to those mutations. Most of the differences were seen in ER-positive tumor cells, with metastatic lesions showing an even higher concentration of mutations than the primary tumors.

Current research is confirming that the "genomic landscape of metastatic breast cancer is different than that of early-stage breast cancer," although these are not the only factors that determine response or resistance to treatment. The epigenetic landscape also is important, Dr. Tutt noted.

The clinical utility of these findings has been studied in a series of "basket" trials, which group together tumors that come from different organs but have similar mutations. In a study of tumors with HER2 and HER3 mutations, a tyrosine kinase inhibitor (neratinib) elicited "meaningful" responses from breast cancer patients with missense mutations in the kinase domains.

For clinicians and patients alike, the stress of a breast cancer diagnosis may be increased by a BRCA genetic report that comes back with findings of "variations of unknown significance" (VUS). Dr. Tutt discussed a number of approaches to resolving the uncertainties in these BRCA genetic reports.

Dr. Tutt concluded his presentation with a short discussion of other synthetic lethal scenarios in different breast cancer subtypes, besides their BRCA status. For example, a defining feature of lobular breast cancer is a loss of function of E-cadherin, a cell adhesion molecule that plays a key role in the contact between tumor cells. This loss of E-cadherin "creates a distinctive invasive phenotype and a particular tropism for metastasis," Dr. Tutt explained. However, it may also make the cancer cells vulnerable to certain therapeutic agents. Already, it has been shown that E-cadherin-poor cells produce the enzyme ROS1 kinase. Proof-of-concept studies are now under way to examine the effect of the ROS1 inhibitors foretinib and crizotinib on the activity of cells from advanced, treatment-resistant lobular carcinoma.

YEAR IN REVIEW: EARLY-STAGE BREAST CANCER

Saturday morning's Year in Review session continued with a discussion about early-stage breast cancer and the evolving paradigms in care, presented by Dr. Priyanka Sharma, from the University of Kansas Medical Center in Westwood.

2018 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) GUIDELINES

This year, ASTRO updated evidence-based guidelines about the use of hypofractionated whole breast irradiation (HF-WBI) therapy. "Evidence supporting oncological safety of HF-WBI has grown substantially, but adoption of HF-WBI among appropriate patients remains low," Dr. Sharma said.

Based on 2011 guidelines, HF-WBI was restricted to women ≥50 years old with T1-2 N0 disease. But the new guidelines recommend offering HF-WBI to patients regardless of tumor grade, hormone receptor (HR) status, and HER2 status.

The new guidelines strongly recommend a dose of 40 Gy of HF-WBI given in 15 fractions or 42.5 Gy in 16 fractions for women with invasive breast cancer with or without inclusion of the low axilla.

KATHERINE TRIAL: CLINICALLY MEANINGFUL PRACTICE-CHANGING RESULTS

Dr. Sharma reviewed findings from the phase III KATHERINE trial, which compared ado-trastuzumab emtansine (T-DM1) to trastuzumab as adjuvant therapy in patients with HER2+ early-stage breast cancer with residual invasive disease after receiving neoadjuvant chemotherapy and trastuzumab.

The study showed that T-DM1 reduced risk for invasive recurrence or death by 40%. Clinically meaningful improvements were also seen in secondary endpoints of disease-free survival and distant recurrence-free interval.

"T-DM1 is a new standard of care for residual disease," Dr. Sharma said.

ADJUVANT OVARIAN FUNCTION SUPPRESSION IN EARLY BREAST CANCER

Dr. Sharma presented information from the combined analysis of the TEXT and SOFT studies, which looked at exemestane or tamoxifen used in combination with ovarian function suppression (OFS).

Data confirmed statistically significant improvements in disease outcomes with exemestane versus tamoxifen used in combination with OFS. Adjuvant exemestane and OFS, compared with tamoxifen and OFS, showed improvements in

disease-free survival and freedom from distant recurrence of 4.0% and 2.1% at 8 years, respectively.

Women with HER2-negative breast cancer experienced the most clinical benefit, especially those who also received adjuvant chemotherapy due to a higher risk of recurrence.

"We need better tools to identify the risk-benefit ratio of ovarian function suppression in women who do not need chemotherapy," Dr. Sharma said.

EXTENDED AROMATASE INHIBITOR THERAPY

"Data on efficacy of extended aromatase inhibitor therapy beyond 5 years in unselected patients are not convincing," Dr. Sharma stated, in reference to the Early Breast Cancer Trialists' Collaborative Group meta-analysis of over 22,000 women and 11 clinical trials.

Women who received aromatase inhibitor therapy after 5 years of tamoxifen had a 3.6% 5-year gain in any recurrence, and 1.5% gain in distant recurrence. Women who received extended aromatase inhibitor therapy after 5 to 10 years of tamoxifen and aromatase inhibitor therapy had a lower gain in any recurrence (2.1%) and only 1.0% gain in distant recurrence. For women who received extended aromatase inhibitor therapy after 5 years of initial aromatase inhibitor therapy, there was a very small gain in any recurrence with negligible gain in distant recurrence.

Dr. Sharma acknowledged that the benefit of extending endocrine therapy was much larger in patients with node-positive disease, with quite significant benefits in patients with 4+ positive nodes.

"Patient tolerance and long-term side effects, such as bone loss, should be kept in mind," she added.

NOVEL AGENTS IN TRIPLE-NEGATIVE BREAST CANCER

Finally, Dr. Sharma reviewed new approaches for treatment of triple-negative breast cancer.

She presented data on GeparNuevo, a randomized phase II trial evaluating the addition of durvalumab (an anti-PDL1 antibody) to an anthracycline- and taxane-based chemotherapy regimen in triple-negative breast cancer.

In this trial, patients who were assigned to durvalumab had a pathologic complete response rate of 53.4%, compared to 44.2% in the placebo arm, which was not statistically significant.

Dr. Sharma pointed out that the subgroup analysis suggested that patients with any level of tumor-infiltrating lymphocyte expression benefitted from durvalumab, and patients with the highest levels did the best.

The BrighTNess study, a randomized phase III trial, looked at the addition of veliparib (a PARP inhibitor) plus carboplatin vs. carboplatin alone to standard neoadjuvant chemotherapy in patients with triple-negative breast cancer.

Investigators found that the addition of the PARP inhibitor to carboplatin and paclitaxel in neoadjuvant therapy did not increase pathologic complete response. Pathologic complete response rate in patients who received carboplatin and paclitaxel was 58% vs 53% with carboplatin, paclitaxel, and veliparib. Pathologic complete response rate in the paclitaxel alone group was 31%.

"There are several ongoing trials of platinum agents and PARP inhibitors in triple-negative breast cancer, and results of these studies will further define the role of these agents in the clinic for us," she concluded.

YEAR IN REVIEW: METASTATIC BREAST CANCER

The final presenter at this year's Symposium was Dr. Roisin Connolly, from Johns Hopkins School of Medicine in Baltimore, MD. Dr. Connolly discussed several updates in metastatic breast cancer.

CDK INHIBITORS IN MONALEESA3 AND MONALEESA7

"We have numerous CDK inhibitors approved for use, and studies have been done in the first-line setting, the setting of progression on endocrine therapy, and later lines as well," Dr. Connolly said.

One CDK inhibitor study Dr. Connolly touched on was the MONALEESA3 trial. This trial enrolled patients with hormone receptor-positive, HER2-negative breast cancer who had received no prior therapy or one prior endocrine therapy. Patients were randomized to fulvestrant and ribociclib or fulvestrant and placebo. The study met its primary endpoint of progression-free survival, indicating a benefit of approximately 8 months for the combination.

"But until the presentation of the MONALEESA7 results, we didn't have any prospective analysis of premenopausal subgroups," Dr. Connolly said.

In MONALEESA7, patients were randomized to ribociclib with endocrine therapy vs ribociclib with placebo in the treatment-naive setting. The combination offered a progression-free survival advantage of over 10 months.

"This confirms that we can use CDK inhibitors in premenopausal patients," Dr. Connolly said.

PI3K INHIBITOR TRIALS

The Sandpiper trial divided patients with prior progression on aromatase inhibitors according to whether they had PIK3CA-mutant tumors. Patients were then randomized to taselisib (a PI3K inhibitor) plus fulvestrant vs placebo plus fulvestrant.

The primary endpoint of the study was progression-free survival in the PIK3CA-mutant group. The study indicated a statistically significant 2-month advantage in progression-free survival in the mutant cohort. "But eventually, this was felt to not be clinically meaningful, and due to the toxicity of the agent, it was decided not to move forward," Dr. Connolly said.

However, results from the SOLAR1 trial, which looked at a similar patient population, were statistically significant. In this study, patients with prior progression on aromatase inhibitor therapy treated in the first- or second-line setting were randomized to alpelisib plus fulvestrant vs placebo plus fulvestrant.

The primary endpoint was locally assessed progression-free survival in the PIK3CA-mutant cohort. There was a statistically significant difference of 5.3 months between the arms.

"There are multiple other studies ongoing, including those testing this combination after CDK inhibition and in combination with CDK inhibition," Dr. Connolly said.

NOVEL HER2 AGENTS

This year there were updates in regards to tucatinib (a selective and reversible HER2 tyrosine kinase inhibitor) in combination with T-DM1 in the phase Ib setting, and also in combination with capecitabine or trastuzumab. According to Dr. Connolly, the studies suggest that the combinations are felt to be well tolerated, "and we now have an ongoing phase III study investigating a tucatinib, capecitabine, and trastuzumab combination."

Dr. Connolly briefly highlighted agents that may be helpful to patients with central nervous system disease, which she called an area of unmet need. Agents such as neratinib in combination with T-DM1 are being investigated in the TBCRC022 trial.

A secondary prevention trial looking at patients with newly diagnosed low-volume HER2+ breast cancer treated with local therapy is trying to determine whether T-DM1 alone or T-DM1 plus temozolomide has a role in preventing development of brain metastases in HER2+ breast cancer.

IMPASSION130: ADVANCES IN TRIPLE-NEGATIVE BREAST CANCER

"It appears that immune checkpoint agents in combination with chemotherapy have the most promise in PDL1+ triple-negative breast cancer, which accounts for approximately 40% of the population studied in IMPASSION130," Dr. Connolly said.

The IMPASSION130 trial enrolled patients with metastatic or advanced triple-negative breast cancer who had treatment-free interval of ≥12 months and an excellent score on the ECOG Scale of Performance Status. Patients were randomized to atezolizumab with Nab-paclitaxel vs placebo with Nab-paclitaxel.

Among patients in the PDL1+ cohort, the median progression-free survival advantage for the combination was 2.5 months, which was statistically significant. The median overall survival advantage in an interim analysis was >10 months (not yet statistically significant at the time of analysis).

"I feel that these results will be clinically meaningful if they are confirmed with longer follow-up and statistical significance," Dr. Connolly said.

CAN TUMOR PROFILING GUIDE USE OF TARGETED THERAPY?

"It appears that the mutations that we find in metastatic breast cancer can evolve over time, and can be subtype-specific. The question is, can we target them?"

One trial Dr. Connolly highlighted was the SAFIR-01 trial, which found targetable mutations in 46% of breast cancer patients. Ultimately, 13% of those patients matched to a clinical trial. And the response rate to targeted therapy within that group was 9%.

In the SHIVA trial, patients with solid tumors (not limited to breast cancer) carrying targetable molecular alterations were randomized to the indicated targeted therapy vs chemotherapy. Disappointingly, the median progression-free survival was around 2 months, and not significantly different between the arms. "There was actually less toxicity in the chemotherapy arm," Dr. Connolly pointed out.

"We still have many ongoing trials to answer these questions, including the NCI MATCH and TAPUR trials," concluded Dr. Connolly.