Triple-Negative Breast Cancer Webinar Series – Part One: A Medical Update

Rita Nanda, M.D.
Assistant Professor of Medicine
Co-Director, Breast Medical Oncology Program
University of Chicago Medicine

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Overview

- Definition of Triple-Negative Breast Cancer
- Current Treatment Options
- Recent Advances
- Ongoing Research
- The Role of Clinical Trials
Definition of TNBC
Breast Cancer Subtypes

Basal-like  HER-2  “Normal”  Luminal B  Luminal A

"Intrinsic" gene set on 78 single tumor samples

476 cDNA clones

85 Arrays

Sorlie et al, PNAS 2001
Triple-Negative Breast Cancer

- TNBC refers to a form of breast cancer which lacks expression of ER, PR and HER2/neu
- Approximately 15-20% of breast cancers
- No targeted therapies for TNBC
  - anti-estrogen therapy
  - anti-HER2 therapy
Risk Factors for TNBC

- More common in young women and women of African ancestry
- More common in women with a $BRCA1$ mutation
  - 75% with TNBC
- 15-20% of women with a $BRCA2$ mutation develop TNBC
- Patients with TNBC should consider genetic testing if they have family history of breast/ovarian cancer or are diagnosed at a young age
Current Treatment Options for TNBC
Systemic Treatment for Breast Cancer

Tumor Size
Lymph node Status
Distant Metastases

Evaluation for systemic treatment

HR Positive
Hormone Therapy

HER-2+
Biologic Therapy

HR+ and HER2+
Biologic Therapy + Hormone Therapy

Triple-negative
Chemotherapy
Treatment Settings

- **Neoadjuvant**
  - Therapy prior to surgery
  - Treatment aimed at curing the cancer and preventing a recurrence

- **Adjuvant**
  - Therapy after surgery
  - Treatment aimed at curing the cancer and preventing a recurrence

- **Metastatic**
  - Treatment for advanced breast cancer
  - Treatment aimed at helping patients live longer and better
Standard Treatments for Early-Stage TNBC

- Neoadjuvant/Adjuvant treatment
- Goal of therapy is curative
- Anthracycline and taxane-based chemotherapy
  - Typically administered for 8 cycles (4 of each)
  - Order doesn’t matter (T-AC vs AC-T)
  - Anthracycline doesn’t matter (A vs E)
- Surgery
  - Mastectomy vs Lumpectomy
- Radiation Therapy
  - To breast and/or lymph nodes
Recurrence Patterns of TNBC

- Most women with metastatic TNBC are first diagnosed with early stage breast cancer.
- Recurrences are most common about 3 years after initial diagnosis.
- Metastases are more common in Lungs, Liver, Brain.
- Metastases are less common in Bone.
Treatment for Metastatic TNBC

- **Single-Agent Chemotherapy**
  - Taxanes
  - Capecitabine
  - Eribulin
  - Liposomal doxorubicin
  - Other microtubule inhibitors (ixabepilone, vinorelbine)

- **Combination Chemotherapy Regimens**
  - Carboplatin+Gemcitabine
  - Ixabepilone+Capecitabine

- **Clinical Trials**
Research Advances
What we do know about TNBC

- Research about TNBC is relatively new
- TNBC is defined by characteristics it does not have
- TNBCs are genetically unstable
  - Chromosomes are actively rearranging
  - Gene alterations are ongoing
  - Treatments to target this instability
- There are different types of TNBC
## Triple Negative Subtype GE Patterns are Reproducible

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Training Set</th>
<th>Validation Set</th>
<th>GO Terms/Canonical Pathways</th>
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<tr>
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<td>Luminal/AR</td>
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- **Cell cycle/DNA replication**
- **p63/cell communication**
- **Immune Signaling**
- **Androgen Signaling**
What does this mean for women with TNBC?

- Being able to subdivide triple-negative breast cancers into subcategories will help us identify new targets for therapy.
- Clinical research is ongoing to target pathways that are implicated in TNBC and newer trials are being developed based on this work.
Targeted Therapies Currently Under Investigation for TNBC

- **PARP inhibitors**
  - Mutation carriers (monotherapy)
  - TNBC (in combination with chemo)
- **Androgen receptor**
- **Death receptor 5 (Tigituzumab)**
- **Glucocorticoid receptor**
- **AKT/PI3K/mTOR inhibitors**
- **Jak2 inhibitors**
- **Macrophages (the tumor microenvironment)**
- **Immune therapy (PD-1/PD-L1 inhibitors)**
Recent Clinical Trial Results

- Two randomized, phase II neoadjuvant trials presented in 2013 demonstrated promising efficacy for new treatments for early-stage TNBC

- CALGB 40603
  - T-AC
  - +/- bevacizumab
  - +/- carboplatin

- I-SPY2
  - T-AC
  - +/- carboplatin plus veliparib (ABT-888)
Summary of Results

- **CALGB 40603**
  - Addition of bevacizumab lead to increased in breast pCR rates but not in breast+axilla
  - Addition of bev lead to an increase in serious toxicities
  - Addition of carbo lead to significant increases in pCR rates in breast and axilla, with increased but manageable toxicities

- **I-SPY2**
  - T→AC +/- (ABT-888+carboplatin)
  - Estimated pCR rate for ABT-888+carbo predict a high likelihood of success over control arm
  - ABT-888/carbo arm associated with higher rates of hematologic toxicity
Conclusions

- Both CALBG 40603 and I-SPY2 suggest a role for carbo in the management of a subset of TNBCs.
- While carbo did increase risk of hematologic toxicities, these toxicities were manageable (delays, dose mods).
- Addition of bev only seemed to increase in breast pCR rates, but at the risk of life-threatening toxicities.
- Contribution of ABT-888 is unclear.
- A phase III studies investigating the contribution of carbo and carbo/ABT-888 has been planned and will be open within the next few months.
Clinical Trials
The Role of Clinical Trials

- Phases of Clinical Trials
  - Phase I, II, III

- Clinical trials are designed to build on the current standard of care

- Without clinical trials we cannot develop better treatment for the future
Clinical Trial Phases

- **Phases I**
  - Safety, dose finding
  - New drugs
  - New combinations of old drugs

- **Phase II**
  - Efficacy, specific for tumor type

- **Phase III**
  - Testing again standard treatment
  - +/- placebo
Pros and Cons of Clinical Trials

- **Pros**
  - Access to newer promising therapies before they are approved
  - No guarantee that you will be assigned to study treatment
  - Help to move the field forward

- **Cons**
  - No guarantee trial treatment is better
  - Treatment has to be at sponsoring institution
  - Not everyone is eligible for a trial
  - Additional time/visits/biopsies
How can I find out about clinical trials in my area?

- Treating oncologist
- ClinicalTrials.gov
- Triple-Negative Breast Cancer Foundation
Why has it been so hard to find a treatment?

- TNBC is not one disease
  - PARP inhibitors and other targeted therapies likely benefit a subset of patients with TNBC
  - It is important to understand which type of TNBC will respond to which type of therapy

- Tumors are genetically unstable and are constantly undergoing changes

- Newer technologies and clinical trials hold great promise
Summary

- Much research is ongoing in the field of breast cancer
  - Understand mechanisms of resistance
  - Develop more personalized therapy
- New therapies are being developed and tested in clinical trials specifically for TNBC
- Hope for the future
  - More effective therapies
  - Fewer side effects
Thank you!