WHAT’S NEW IN BREAST CANCER TREATMENT

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WHERE ARE WE GOING TODAY?

- Advances in screening imaging
- Chemotherapy:
  - Current guidelines for using neoadjuvant therapy
  - Can we redesign adjuvant chemo?
- Hormone therapy:
  - Should we give longer adjuvant hormone therapy?
- Insights into triple negative breast cancer and BRCA driven triple negative breast cancer
- New treatments for different types of breast cancer
- What about immunotherapy?
SCREENING ADVANCES

- The hot new tool: tomosynthesis
  - In effect a small CT scan of the breast
  - Slightly higher dose, but still in OK range
  - More cancers detected, without more DCIS
  - Fewer false positive images
  - Fewer patients recalled for further imaging
  - Thought to be MORE cost-effective

- Randomized trial in US in process.....
NEOADJUVANT CHEMOTHERAPY

- Chemo given before surgery has two roles:
  - Defining new treatment drugs—these are research studies
  - Reducing the size of initially bulky disease so that less surgery can be done

- Compared to postoperation chemo, does not improve survival, but predicts who will do well when treatment is completed
  - PCR: pathologic complete response means that no cancer found in breast specimen from surgery
  - Women with PCR do well—they are chemosensitive!
GUIDELINES FOR SURGERY/RADIATION AFTER NEOADJUVANT CHEMOTHERAPY

What to do with surgery?

- Extremely important to do good outline of what’s there before and after chemo
  - Cosmetic results better
  - Less likelihood of “positive margins”
- Node sampling to prove positive can be done by FNA before treatment (don’t do surgery then!)
- Node sampling at surgery with sentinel node techniques

- Mastectomy after neoadjuvant chemo may still be necessary; standard node dissection may be done at that procedure if warranted by stage.
Radiation Therapy after Neoadjuvant Chemotherapy

- Universally done for lumpectomy
  - Radiation typically includes entire breast
  - May include lower node areas also

- Should probably be done for mastectomy if the stage of the cancer means high risk of chest wall recurrence
  - Carefully integrated with reconstruction, if to be done
ADJUVANT HORMONE THERAPY

- Long term studies of multiple situations show:
  - Postmenopausal before treatment—use AI
  - Premenopausal before treatment or after chemo—
    - Younger women at highest risk: shut off period, use AI
    - Women close to menopause: Tamoxifen OK, or use AI with period shut off
  - Ten years of Tamoxifen was “better than” 5
    - HOWEVER: risk of uterine cancer continues, risk of blood clot events continues to rise
    - Difference was very small—2.5% at ten years
What about 10 years of AI?

- Research is new enough that only the risk of recurrence has been defined, not death
  - However:
    - 3 large studies done worldwide presented in December
    - DO NOT SHOW a benefit to longer use!
  - Most people think that we wouldn’t even discuss this with women who are started on an AI
  - Reminder: AI is aromatase inhibitor—anastrazole (Arimidex), letrozole (Femara), exemestane (Aromasin)
**STAYING ON HORMONE THERAPY**

- Adherence to treatment is defined by taking pills for five years: brief stops OK, months not OK
- Up to 40% of women started on hormone therapy do not complete 5 years; about 20% stop in the first year! This won’t help your outcome very much....
- Studies show that most common reason women stop is menopausal side effects (this is worse with Tamoxifene) and bone/joint pain (worse with AI)
- What to do about this? Doctors need to pay more attention to symptom management!!!
TRIPLE NEGATIVE BREAST CANCER

- What is it? Cancer cells do not have estrogen receptor, progesterone receptor, or overexpression of Her2/Neu.

- Clearly most aggressive form of breast cancer with poorest survival

- Most common in women who are BRCA positive, African American women, especially under age 50 (Latinas are number two here)
TRIPLE NEGATIVE BREAST CANCER

- Significance is clear: these cancer cells will not respond to hormone therapy or to Herceptin, since they are not equipped to do so
- Chemo is the only option!
  - Newest uses of chemo suggest that carboplatin can be added to the usual chemo with greater benefit
  - Length of chemo is otherwise the same—6 months or less, depending on schedule used
Is BRCA worse?

- Interesting data from December meeting shows that triple negative BRCA positive women do BETTER than triple negative BRCA negative women
  - 5 year disease-free survival 76% if BRCA, 66% if not. This was a smallish study, but it’s an interesting question

- Why might this be so? Actually having the BRCA defect lends these cancers a little higher sensitivity to chemo of certain kinds!
THE TARGET LANDSCAPE

Aromatase inhibitors
- Letrozole
- Anastrozole
- Exemestane

SERMs
- Tamoxifen
- Endoxifen
- Toremifene

SERD
- Fulvestrant

Trastuzumab
- Pertuzumab
- Lapatinib

Gefitinib
- Lapatinib

VEGF
- VEGFR
- IGF-1R

Aromatase T E2

MAPK inhibitors
- Selumetinib

HDAC inhibitors
- Panobinostat
- Vorinostat
- Entinostat

Repurposed approved drugs
- Metformin
  (Plasma and tumour insulin levels, pAMPK, p-Akt)
- Statins
  (Plasma cholesterol, tumour cholesterol pathway genes, HMGCA genotype)
- Antiresorptive therapy
  (Bone turnover markers)

PI3K inhibitors
- Buparlisib
- Taselisib
- Alpelisib
- Pictilisib

Rapamycin (mTOR) inhibitors
- Everolimus
- Temsirolimus

CDK4/6 inhibitors
- Palbociclib
- Ribociclib
- Abemaciclib
NEW TREATMENTS FOR BRCA POSITIVE

- BRCA gene defects affect DNA repair, which must occur every time a cell divides.
- Several new drugs have been shown to interfere with a specific DNA repair enzyme, called PARP.
- These oral drugs are approved for BRCA related ovarian cancer; work better for women with BRCA breast cancer.
- Drugs are fairly well tolerated, too. Not yet clear how to mix them with other chemo except for carboplatin and docetaxel.
NEW TREATMENTS FOR ER POSITIVE

- Oral drugs that inhibit CDK4 and CDK6, molecules that are part of the cell growth pathways
- Generally well tolerated, with low blood counts being major side effect
- Approved as second line treatment with fulvestrant
- Now approved as first line treatment with letrozole! Nearly doubles the time to progression
NEW TREATMENTS FOR ER POSITIVE

- PI3 Kinase (PI3K) is a protein involved in growth pathways and is commonly mutated or overexpressed in ER + breast cancer
- Several new oral drugs to inhibit this protein have been developed; major side effect is low blood counts
- Preliminary results suggest that these drugs have effect on their own, and work even better with an anti-estrogen therapy
- Likely to get approval fairly soon
NEW CONCEPTS FOR ADJUVANT THERAPY

- **Observation**: diabetic women who took oral pill metformin had longer survival from breast cancer than diabetic women who did not take the pill
- Randomized trial done; results pending
- **Observation**: women taking aspirin for prevention of heart disease/stroke also appeared to do better after breast cancer
- Randomized trial just getting underway
- **Observation**: women taking statins also appear to have better prognosis
- Randomized trials in the works
Bone Agents and Breast Cancer

- Adjuvant therapy is associated with enhanced bone loss when either early menopause occurs or AI’s are used after menopause.
- Treatments for osteoporosis include both oral and iv agents that halt the degradation of bone:
  - Observational studies suggested that use of the iv drugs might be associated with better outcomes.
  - Overview of multiple trials, multiple doses, suggests survival benefit for postmenopausal ER+ cancer.
  - Multiple new trials of the oral agents are ongoing.
Immune System Challenges

**Acute Inflammation**
- Th1
- B cell
- IL-2
- INFγ
- Anti-tumor Ig
- M1 Macrophage polarity
- Innate anti-Tumor Cell Cytotoxicity
- CTL Mediated Killing

**Chronic Inflammation**
- Treg
- Th2
- B cell
- IL-10
- TGFβ
- IL-4
- IL-10
- IL-13
- IL-6
- Stromal Ig/IC
- M2 Macrophage polarity
- Antigen presentation
- CTL Mediated Killing

Tumor Rejection

Tumor Promotion
HARNESSING THE IMMUNE SYSTEM?

- Basic method(s) in current use involve shutting OFF the ways that normal cells protect themselves from activating immune cells.
  - Many/most cancer cells protect themselves by actively expressing the molecules in this system
  - By shutting off or interfering with these protective mechanisms, the immune cells can now react to the cancer cells
  - However, shutting off the protection system affects normal cells as well, causing autoimmune side effects
IMMUNOTHERAPY IN BREAST CANCER

- Target the most aggressive, mutated cancers—triple negative breast cancer
- Use the newest therapy, perhaps in combination
- Treat women with advanced cancer
- Aggressively treat autoimmune side effects
- Consider vaccines: either made to order or generic, targeting specific pathways
But....

- Early reports of single agent PD-1 targeted antibodies are unimpressive in triple negative breast cancer, with less than 20% responses

- Trials are going on like crazy:
  - PD-1 antibodies with another immune agent
  - PD-1 antibodies with chemo(s)
  - Vaccines—individualized or generic
  - Gene engineering with various manipulations (viruses, CAR-T cells)
PERSONALIZED MEDICINE IN BREAST CANCER? GENE SEQUENCING CANCER

Drawbacks:

- Breast cancer, relative to other types of cancer, has fewer mutations that produce specific targets.
- And the majority of significant abnormalities are very few in number—ER, Her2, PI3K, p53, CDK4/6, myc, (BRCA)
  - We have drugs for all but p53 and myc.
- Other known “targetable” mutations are found in fewer than 5% of breast cancers, and often not similar to other mutations in other cancers.

Given these issues, routine gene sequencing of breast cancers is not recommended.
In conclusion....

- Breast cancer continues to be intensively studied and spawns new drug development.
- Controversies can usually be settled through clinical trials—but breast cancer patients do so well that these take a long time!
- Hottest new technologies for cancers like lung, bladder, colon, are not yet performing for breast cancer.