New Options for the Treatment of Hormone Receptor Positive Breast Cancer

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Breast Cancer Worldwide

Some Facts about Breast Cancer

As of 2015, current estimates suggest 231,840 new cases of breast cancer in the USA annually.
About 70% of women diagnosed with breast cancer will have Hormone dependent breast cancer (Estrogen Receptor &/or Progesterone Receptor positive).
20-30% of individuals diagnosed with early stage breast cancer experience recurrence of breast cancer.
4-9% of newly diagnosed Breast Cancer will present with Metastatic breast cancer.
40,000 individuals are expected to die of breast cancer in the USA annually.

Overview of Talk

• Review early history regarding Rx of ER+ Breast Cancer
• Pathophysiology of Tumor Growth
• Previous Therapies for Early stages of ER + BC
• Resistance in ER + Breast Cancer
• What are Newer Approaches in ER+ BC
  • Role of Ovarian Function Suppression (OFS)
  • Duration of Therapy
  • Dosing Can Matter
• New Agents in the Management of Recurrent HR+ Disease
• New Role of Denosumab in Early Breast Cancer
• Novel Agents in Study for ER + Breast Cancer

History of Treatment of Hormone Sensitive Breast Cancer

• Use of strategies to reduce the concentration of circulating estrogen by interfering with estrogen signaling or reducing estrogen production has been and remains a key component of therapy in ER+ BC.
• George Thomas Beatson is most recognized/cited for the implementation of “castration” therapy for women with breast cancer due to his early reports in Lancet in 1896, reporting his experience with use of bilateral oophorectomy in 3 women with advanced breast cancer; many had observed the role of lack of estrogen (or some circulating substance) in the management of breast cancer.
History of Treatment of Hormone Sensitive Breast Cancer

- Very early on, Thomas William Nunn first noted a regression of a patient's breast cancer 6 months after her menstruation ceased.
- Other specialists including Dr. Stanley Boyd performed bilateral oophorectomy in many patients with advanced breast cancer in the 1880s & 1890s and published a report in 1900 that documented the observation of about 1/3 of patients so treated clearly benefited from this measure.
- Estrogen was first discovered by in 1923 by Dr. Edgar Allen at the University of Missouri.
- Due to successful research by Alexander Haddow in the 1940s, he discovered value of high dose Estrogen + BC - 30% Postmenopausal women responded to this therapy. DES - used regularly until the 1970s and lessened once Tamoxifen was approved.
- Estrogen Receptor was first discovered by Jansen in 1958 (University of Chicago).

The Estrogen Receptor

- Estrogen Receptors(and Progesterone Receptors) are a group of proteins found inside & on cells. They function as Transcription Factors when bound to the Ligand, 17Beta Estradiol.
- Two ER subtypes (isoforms) are recognized:
  - ER alpha which is encoded by the gene ESR1 (located on chromosome #6)
  - ER beta which is encoded by the gene ESR2 (located on chromosome #14)
- Hormone/Ligand activated Receptors form dimers:
  - Homodimerization results when either 2 alpha or 2 beta dimers bind together.
  - Heterodimerization results when 1 alpha dimer binds to 1 beta dimer.

The Estrogen Receptor

- Estrogen responsiveness or expression is controlled by co-activators and corepressors. Depending upon the ratio of coactivator to corepressor influences an agonistic or antagonistic response.
- Similarly, the ratio of alpha to beta subtype concentration may influence responses or estrogen receptor expression.
- Once ER activation occurs, this leads to alteration in transcription activity and expression of targeted genes including C-myc, cyclin D1, and the progesterone receptor.

The Estrogen Receptor

- There are 5 segments or domains to both isotypes labeled A-F in a N-C terminus distribution.
- The AB domain is able to transactivate gene transcription without ligand binding but this activation is weak and more selective than noted in other domains.
- The C domain is the DNA-binding domain where the dimer binds to estrogen response elements.
- The D domain is the hinge between C & E domains.
- The E Domain is the Ligand Binding domain.
- Role of the F Domain.

- Structural Organization of Nuclear Receptors
The Estrogen Receptor-Signal Transduction

- Typically the ER is in the cytosol of the cell but with binding of the ER by its Ligand (Estrogen), the ER migrates into the nucleus where dimerization of the ER occurs. The dimer binds to the hormone response elements and then this complex recruits other proteins that are responsible for transcription of DNA into mRNA downstream. Once new protein is formed, this changes the cell function of the cell.
- ER also form complexes with proteins, receptor tyrosine kinases (EGFR & IGF-1) & non-receptor tyrosine kinases (Src).

Previous forms of Endocrine Therapy for ER+Breast Cancer

- Tamoxifen (SERM) binds to the ER which results in production of a nuclear complex that reduces DNA formation.
- Tamoxifen induced altered ER conformation prevents binding by coactivators and prevents transcription.
- Tamoxifen use leads to inhibition of estrogen effects.
- Preferred Endocrine therapy in Males with ER+ BC avoids feedback loop that is potentially a problem for Testosterone production when AI therapy is used.
- When Tamoxifen is used, it creates a static effect on tumor growth with an arrest of cell division in the G0 & G1 phase.

What is the Role of Ovarian Function Suppression with Tamoxifen and with Aromatase inhibitor in Premenopausal Females?
Role of Ovarian Suppression (OFS) and Survival: TEXT & SOFT trials

- Joint analysis (4690 subjects)-reported @ ASCO 2014 after Median Follow-up of 5-7 years.
- 91% of the women treated with Exemestane + OFS improved DFS versus 87% in the Tamoxifen + OFS group.
- Group benefitted the most: women <40 years of age, Node Positive and at higher risk of relapse.
- More toxicity: 50% depression, Menopause symptoms (hot flashes, sweats), more Osteoporosis and Sexual Dysfunction.

Duration of Endocrine Blockade in ER+ BC

- NSABP B-14 Established that Breast Recurrence Rates & Mortality were less good with Extension of Tamoxifen for >5 years.
- ATLAS & aTTOM-studies looking at events after longer follow-up: ATLAS enrolled 6846 women in this Randomized Tamoxifen use of 5 versus 10 years. Clear improvements reported that were statistically significant that longer use even b/w 5-9 years but more clearly difference seen >10 years of follow-up in RR & BC Mortality (Analysis presented @ SABCS 12/2012).
- At ASCO 2013, data from aTTOM demonstrated similar findings
- Currently, Tamoxifen use 10 years NOT 5 years in appropriate setting.

Duration of Therapy-Tamoxifen

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Resistance to Estrogen Blockade

- De novo or Acquired Resistance to Endocrine therapy can limit the effectiveness of competitive inhibition by drugs like Tamoxifen or the effects of Hormone Deprivation from drugs like Aromatase Inhibitors.
- Commonly, point mutations in ESR1 are being discovered that appear to be one mechanism for resistance. These mutations lead to conformational changes within the ER alpha which appears to allow for agonist activity of the this isoform without the need of Ligand binding. This leads to estrogen independent activity which leads to promotion of cell proliferation and tumor progression without the need for hormone stimulation.

Estrogen Independence

- Cross-talk where signaling for cell growth and production occurs that allows for tumor growth signaling that is independent of the ER
- Numerous alternate pathways are recognized including PI3 Kinase and MAPKinase
- Activation of signaling has also been identified via Insulin-like Growth Factors
- Downstream activation of signaling has also been mediated by Cyclin D1 overexpression (seen in high % of patients with recurrent BC treated with antiestrogen therapy including Aromatase inhibitors)

Mechanisms of Resistance to Endocrine Blockade in Breast Cancer

- Variation of Expression of the ER
- Modifications of the ER
- Increased activity of ER coactivators
- ER-independent growth
- Upregulation of Growth Factor Signaling Pathways
- Stabilization of ER in spite of Endocrine blockade.
- Patient non-compliance to Endocrine Therapy.
Cross-talk Between Signal Transduction and Endocrine Pathways

Newer Strategies for Recurrent/Resistant ER+ Breast Cancer

Fulvestrant—an Example that Dose Can Matter

- Fulvestrant is a Selective Estrogen Receptor DownRegulator—it works as an ER antagonist that downregulates the ER and has no agonist effects.
- Mechanism of Action:
  - Impairs ER Dimerization
  - Affects the energy-dependent Nuclear-Cytoplasmic Shuttling
  - Blocks Localization of ER in the Nucleus
  - Fulvestrant-ER complex is inactive (AF1&AF2 of the domain is disabled)
  - Fulvestrant binds, blocks and accelerates degradation of the ER protein leading to complete inhibition of the Estrogen signaling through the ER.

Fulvestrant

- Studies showed comparable benefit when compared to Anastrazole.
- Initial dosing of 250 mg was felt to be effective.
  - First-Line Study Comparing Endocrine Treatments (FIRST-Randomized Phase II Study).
    - Showed a Clinical Benefit Rate of 73% versus 67%
    - Significant time to Treatment Progression (Median 23 months versus 13 months HR 0.64)
    - Longer Overall Survival (Median 54 months versus 48 months HR 0.71)

Newer Approaches for ER+, Recurrent/Metastatic Breast Cancer: Palbociclib

- This drug is a potent & selective inhibitor of Cyclin Dependent Kinases (CDK) 4 & 6.
- Cyclin Dependent Kinases are a part of the cell cycle regulatory process which appears to have an important role in tumorigenesis.
- Disruption of this part of the regulatory process is reported to be common in breast cancer and appears to be a mechanism for resistance leading this cycle to be of interest for targeted forms of therapy.

CONFIRM: Fulvestrant 250 mg vs 500 mg After Prior Endocrine Therapy
Cell cycle in Breast Cancer

- During Breast Cancer Development, cell cycle deregulation is known to promote atypical hyperplasia & tumor cell growth.
- Abnormal gene function and oncogenic activity as well as loss of tumor suppressor function occur (p53 loss and loss of RB).
- Aberrant expression of cell cycle mediators occur including Cyclin D1 and Cyclin Dependent Kinases.
- Cyclin D1 binds to inhibitors of cell cycling promoting cell division and growth. This inhibition influences RB inactivation as well.
- Overexpression of Cyclin D1 is found in many cancer types including at least 35-40% of breast cancers. Blockade of Cyclin D1 has proven important in treatment of recurrent breast cancer.

Cell cycle in Breast Cancer

- Early research had shown that use of Palbociclib + the Aromatase Inhibitor, Letrozole provide a dual inhibition in breast cancer.
- Letrozole works outside of the cancer cell by reducing estrogen production.
- Palbociclib works within the nucleus of the cell by direct inhibition of CDK 4 & 6.

Palbociclib + Letrozole - Use in 1st Line MBC

- In 2/2015, the use of Palbociclib + Letrozole was given an accelerated Approval for use in Women with MBC who experienced their 1st relapse of BC or who presented with de novo Stage IV disease.
- Approval was based on a Phase II trial, the Paloma study that enrolled 165 women with advanced ER+ breast cancer: Randomization between Letrozole @ 2.5 mg po daily alone or in combination with Palbociclib @125 mg daily from D1-21/28 day cycle.
- Significant PFS seen with 20 months versus 10 months – HR 0.49
- Improvement of OS reported of 37 versus 33 months though p=0.81
Palbociclib + Letrozole - Use in 1st Line MBC

- Side Effects include Leukopenia - may need to dose modify
- Common symptoms related to AI effects with hot flashes and osteoporosis risk
- Rare risk of pulmonary embolism.

PALOMA-3: A Double-blind, Phase III Trial of Fulvestrant with or without Palbociclib in Pre & Post-Menopausal Women with HR+HER2 Neu – Metastatic Breast Cancer That Progressed on Prior Endocrine Therapy.

- **Palbociclib:** Ongoing trials in the Management Of Breast CA – PALOMA-3 study include Palbociclib with combination of Fulvestrant - this experience of 521 patients with ER+HER2 Neu negative was presented @ ASCO in June 2015.
- PFS for the combination of P+F was 9.2 months compared with 3.8 months for F alone (placebo based study).
- All patients had undergone prior endocrine therapy and had either relapsed or progressed while on Endocrine therapy.
- Palbociclib in combination with Fulvestrant may reverse resistance to endocrine Blockade.

Everolimus + Exemestane

- Everolimus (Afinitor) is known as an mTOR (Mammalian target of Rapamycin) Inhibitor.
- The value of this combination of Everolimus + Steroidal AI was demonstrated in the Breast Cancer Trials of Oral Everolimus (BOLERO-2). Patients in this study had to have progression on the non-steroidal AI, Anastrazole and then were randomly assigned to Exemestane 25 mg po daily versus the combination of Exemestane + Everolimus @ 10 mg daily.
  - Improvement in PFS (Median of 7 versus 3 months - HR for mortality 0.43).
  - Improved ORR (9.5 versus 0.4%)
  - No difference in OS (median of 31 versus 26.6 months HR 0.89)
Everolimus + Exemestane

- Common side effects of Everolimus include Stomatitis/Mucositis, Non-infectious Pneumonitis (if cough/SOB develop – think of this and trial of steroids) and increase in LFTs.
- Potential of immune deficiency
- Common side effects of antiestrogen therapy also.
- TAMRAD study and other reports show safety and benefit with Everolimus + Tamoxifen in Premenopausal women with improvement in TTP

Denosumab (Prolia): ?Role in Breast Cancer

- Denosumab is a fully humanized monoclonal antibody that is a RANKLigand Inhibitor.
- MOA: Precursors to osteoclasts (pre-osteoclasts) express RANK. RANK is activated by RANK Ligand which promotes maturation of pre-osteoclasts into osteoclasts (increase bone destruction). Denosumab inhibits this by binding to & inhibiting RANKLigand. This action prevents degradation of bone leads to a reversal of osteoporosis.
- Denasumab is also approved for reducing risk of Skeletal Related Risk in metastatic cancer.
- ? Role in prevention of cancer relapse.

Denosumab (Prolia): ?Role in Breast Cancer

- Preclinical studies have shown that Denosumab (Nuclear Factor B Ligand) inhibited both skeletal bone destruction and tumor burden of bone.
- In early breast cancer, microscopic deposits of cancer may travel to bone (~2/3 of breast cancer recurrences are in bone).
- The aim of ongoing studies is to determine the role of this agent, Denosumab, in reduction of tumor metastases, primarily within bone.

Figure 1: Proposed mechanism of denosumab action
Endocrine Therapy + PI3K Pathway Inhibitors

- The PI3K/AKT signaling pathway is known to play a critical role in cell growth, survival and angiogenesis.
- Mutations in the PI3K pathway are commonly detected in 40% of BC.
- Several ongoing studies to evaluate the value of PI3K inhibition have taken place.
- Pan –PI3 Kinase inhibitors BKM120 (Buparlisib) & GDC-0941 (Pictilisib) have been studied and preliminary information shows promise with use of these agents in combination with endocrine therapy in HR resistant BC patients. Common side effects include Stomatitis, Rash and Hyperglycemia.

Cyclin Dependent Kinase Inhibitors

Use of Agents that Target Mutations in the Estrogen Receptor-ESR1

- Numerous reports from studies of patients who progressed on prior endocrine therapy have shown that an acquired resistance may occur after use of these agents including patients treated with AI therapy. This resistance appears to be related to development of mutations of the Estrogen Receptor1 gene.
- These mutations appear to cluster around the Ligand binding domain of the ER.
- These changes lead to conformational changes of the receptor leading to agonistic activity independent of Ligand that allows so called ER+ systems to be resistant to estrogen deprivation strategies.

ESR1 mutations-clear targets for Resistant ER+ Breast Cancer
Novel Agents in ER+ BC: Aurora Kinase Inhibitors

- Expression of the Aurora Kinase has been shown in many tumors including breast cancer. When overexpression is present, it may have oncogenic properties.
- Alisertib is an oral agent that is an ATP-competitive & reversible Aurora Kinase Inhibitor.
- Early phases of study have shown modest response rates in heavily treated patients with recurrent breast cancer. Duration of responses for >1 year have launched this drug into a Phase II program to determine the value of this alone and in combination with other drugs in the treatment of resistant breast cancer.

A New SERD

- RAD 1901
- New agent being studied
- May reduce menopausal symptoms
- Oral formulation
- ? Penetrate the Blood Brain Barrier

Another Oral SERD

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- Novel Agents in Study for ER+Breast Cancer
THANKS for the Honor to Speak to you today!

Newer Approaches for Estrogen Receptor Positive Metastatic Breast Cancer-HER2 Neu Negative

- If a patient appears to be hormone refractory or aggressive pattern of disease develops with fast growth of cancer, involvement with visceral organs like liver, lung & brain, cytotoxic chemotherapy is still considered and can be often very effective.
- Various strategies exist with use of cytotoxic therapy with initial use of this therapy alone and if disease control is achieved, using maintenance with cytotoxic therapy at least
The Estrogen Receptor-Signal Transduction

• Once bound to receptor Tyrosine Kinases, signals are sent to the nucleus through the Mitogen-Activated Protein Kinase (MAPK/ERK) pathway & the Phosphoinoside 3 Kinase (PI3K/AKT) pathway.
• Glycogen Synthase Kinase-3 (GSK) is known to normally inhibit transcription by nuclear ER by inhibition of phosphorylation of a serine 118 on nuclear ER alpha. However, if phosphorylation occurs through the PI3K/AKT or MAPK/ERK pathways, this inhibition of transcription is removed and new cell production can occur.

Selective Estrogen Receptor Modulators (SERMs)

Class of Drugs that act on the Estrogen Receptor
These Agents work differently on different tissues leading to either an inhibition or stimulation of estrogen-like action in different tissues. They may act as an Estrogenic or Antiestrogenic influence.
Tamoxifen & Raloxifene are examples of SERMS.
Tamoxifen acts as an antagonist in Breast Cancer cells and an Agonist in Uterine and Blood Vessel Systems.

Cell cycle control & Breast Cancer

• There are 4 phases of Cell Division: S Phase-DNA synthesis, M-Mitosis; 2 gap Phases: G1 & G2.
• 4 proliferation Phases of Cyclin Dependent Kinases; of these, it appears that CDK 4 & 6 are critical drivers of oncogenesis and regulate transition from G1 to S Phase.
• Another factor in cell cycle regulation is the Retinoblastoma Tumor suppressor Gene 2. RB expression is a negative regulator of Cell Cycle growth and transition from G1-S Phase.
• Tumor systems that have intact RB & ER+ are responsive to Antagonists.1


Role of Ovarian Suppression (OFS) and Preservation of Fertility

• Recent Metaanalysis from Annals of Oncology:
• 1231 Premenopausal Women @ Time of Breast Cancer diagnosis were evaluated in a total of 12 studies.
• All women received Chemotherapy and were assigned to CT alone or CT + concurrent OFS with use of Luteinizing Hormone-Releasing Hormone Agonists.
• Findings: 45-64% resumed Menstrual cycle during chemotherapy. In 5/12 studies reported, pregnancy rates were higher in the OFS group: 33 pregnancies in those with CT+OFS compared to 19 pregnancies in the CT group alone.
**Endocrine Therapy for Breast Cancer**

- Tamoxifen is effective in pre & postmenopausal women and is the preferred treatment in men with BC.
- Estradiol levels are significantly higher in older men compared with PMP women: 20% of estrogen is produced by the testes while the rest is produced by peripheral conversion of Androgens to Estrogens. Feedback loop leads to Increase FSH & LH lead to Increase in Testosterone.
- Aromatase Inhibitors (AIs) are used primarily in Postmenopausal Women with BC.
- AIs suppress estrogen levels by inhibiting the enzyme Aromatase.
- Aromatase is the enzyme known to convert androgens into estrogens.

**Fulvestrant in Breast Cancer**

- Fulvestrant is a pure antagonist
- Fulvestrant Degrades the Estrogen Receptors.
- It is a 7-Alkylamide derivative of E2
- It has Estrogen Antagonistic Activity
- Does not Possess Estrogen Agonist Activity.

**Previous Therapies for Early stages of ER + Breast Cancer**

- Selective Estrogen Receptor Modulators (SERMs) are known to behave as ER antagonists in breast cancer but agonists in other tissues like the Uterus & Bone—Nolvadex &Raloxifene.
- Aromatase Inhibitors which block conversion of androgens to estrogen by inhibition of the Aromatase enzyme-Anastrazole, Letrozole and Exemestane.
- Gonadotropin Releasing Hormone Agents- Zoladex & Lupron limit estrogen production by the ovary by switching off the release of Luteinizing hormone from the pituitary gland in the Premenopausal Female.

**Role of Ovarian Suppression (OFS) and Survival: TEXT & SOFT trials**

- TEXT trial: 2672 Premenopausal Females <ER> BC Randomized between Tamoxifen +OF5 versus Exemestane +OF5 X 5 years- No chemotherapy was given.
- SOFT [Suppression of Ovarian Function Trial]: 3066 premenopausal women Randomized to same treatment. Some received Chemotherapy after surgery. 2 cohorts: Premenopausal preservation within 12 weeks of surgery & those who remained premenopausal after 8 months from chemotherapy. Tam alone versus Tamoxifen +OF5 versus Exem +OF5.
- In chemotherapy group, 22% RR with Addition of OFS to T versus T alone.
- 35% RR in Exemestane +OF5 compared with Tamoxifen alone.
- Best Benefit seen in High Risk, ‘Younger’ Premenopausal BC with addition of OF5

**Cell cycle in Breast Cancer**

- Cellular growth and proliferation are promoted by Cyclin Dependent Kinases (CDKs).
- CDKs bind to (complex with) cyclin and this process promotes cell cycle progression in the presence of estrogen.
- In the presence of CDK4 & CDK6, cell cycle control is lost and new tumor cell growth occurs.
PI3 Kinase Inhibition