

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

State of the Science

Highlights and Summary

Julie Gralow, MD

Eric Winer, MD

We Should Speak the Same Language

- Medical therapy prior to surgery has been called:

- Neoadjuvant therapy
- Preoperative therapy
- Preoperative systemic therapy
- PST
- POT
- NAST
- NACT
- NCT



*All used during
this conference*

Goals for Breast Cancer Therapy

- No deaths from breast cancer
- No recurrences of the cancer
- No evidence of having had breast cancer or breast cancer treatment over long term
- No acute toxicity of the therapy

What We Know

- In locally advanced and inflammatory breast cancer, preoperative chemotherapy is standard of care
- In earlier stage breast cancer, preoperative chemotherapy is neither better nor worse (from standpoint of OS) compared to postoperative chemotherapy

Which Operable Patients are Candidates for Preop Therapy?

- Anyone who will require the therapy in question with certainty
 - If therapy is in question, surgery first is optimal
- On appropriate clinical trial, any patient with operable breast cancer

Advantages of Preop Therapy

- Increased ability to perform breast conserving therapy
 - Possible improvement in cosmesis ??
- Ability to observe in vivo response to therapy (but uncertain clinical implications)
 - Identification of tumors overtly resistant to systemic therapy
- In clinical trials, opportunity to assess surrogate endpoints (major advantage from translational research perspective)

Disadvantage of Preop Therapy

- Loss of complete pathologic staging
- Necessity for full multidisciplinary approach to achieve optimal results
 - Surg onc, med onc, rad onc, breast imaging, pathology
- Appropriate standards for local therapy less well established in setting of preop therapy
- Possible increase in local recurrence

Evaluation Prior to Preop Systemic Therapy

- Pathologic assessment with CORE BIOPSY (FNA not acceptable)
 - Fully assess tumor including grade, invasion
 - Adequate tissue for ER, PgR, and HER2 testing
 - Multiple cores, preferably under image-guidance

Evaluation Prior to Preop Systemic Therapy

- Adequate breast imaging to determine extent of disease
 - Mammography
 - U/S as appropriate
 - MRI may add, but remains controversial as standard procedure in all patients
- Clip placement except for rare cases (e.g. inflammatory breast cancer) for both surgical excision and pathologic examination
 - Clip placement: center vs bracketing and timing
- Staging for distant disease is standard of care for locally advanced disease
 - In operable patients, no firm rules but should be based on risk of distant disease and symptoms

Evaluation of the Axilla

- U/S with FNA of suspicious nodes in hands of experienced operators has high specificity and reasonable sensitivity
- If node is positive, additional information obtained with very low risk and no disadvantage

When to Perform the SNB?

- SNB not indicated if there is LABC or palpable adenopathy
- Substantial controversy exists regarding timing of SNB

Advantages of Post-Rx SNB

- Single surgical procedure
- Takes advantage of downstaging and ability to perform lesser procedure
- Nodal status after preop rx may be MORE PROGNOSTIC

Advantages of Pre-Rx SNB

- Allows for decision about radiation fields and systemic therapy based on initial stage
- Post-Rx SNB not validated (?? False neg rate and identification rate)

Preop Systemic Chemotherapy (1)

- Optimal chemotherapy regimen
 - No inherent reason to believe that a regimen that works post-op will not work pre-op
 - An acceptable adjuvant regimen is an acceptable preoperative regimen

Preop Systemic Chemotherapy (2)

- Achieving a pathologic complete response is prognostic and predicts for better outcome
 - BUT, not all patients with pCR remain free of recurrence
 - Path CR substantially more common in ER- than ER+ disease across multiple trials
 - Not all patients who do not achieve pCR do poorly
- Path CR as a single surrogate (or correlate) is not an adequate surrogate and we need to have better markers
 - Path CR after chemo probably most predictive for ER- /HER2-

Preoperative Systemic Therapy

- Endocrine
 - pCR virtually never seen
 - Clinical responses not uncommon, and breast conservation rates increase
 - Ki67 decline with preop therapy may be predictor of long term outcome
 - Optimal duration uncertain – longer probably better than shorter
- Outside of a trial, preop endocrine therapy reasonable for a postmenopausal patient who is not thought to be candidate (because of tumor biology or comorbidity) for chemotherapy

Preoperative Systemic Therapy

- HER2-targeted therapy
 - HER2 targeted therapy preop increases pCR rate
 - Data consistent with adjuvant trials
- Angiogenesis as a target
 - Under investigation
 - Small trials to date, many planned
 - Caution warranted about wound healing
 - pCR may not be augmented even if better in long term outcome (which may be an issue with other biologic therapies)

Preoperative Systemic Therapy

- Basal-like disease
 - Path CR rate relatively high after chemo
 - Failure to obtain path CR predicts poor outcome
 - Small trials completed
 - Novel ideas under investigation

Evaluating Response to Preop Therapy

- Breast imaging to monitor response
 - Moderate correlation between imaging and pathologic residual disease
 - MRI for assessment of response under investigation (a promising “surrogate of a surrogate”)

Evaluating Response to Preop Therapy

- Pathologic assessment
 - PATHOLOGIC CR needs a uniform definition!!
 - Residual DCIS alone has same prognosis as pCR without DCIS
 - Any nodal disease after preop therapy is of concern
- Accurate assessment of tumor bed and appropriate processing of tissue are essential
- Pathologist needs to know that preop therapy was administered
- In AJCC 6, “y” indicates stage after preop therapy

Definitions of Pathological Complete Remission (pCR)

- Malignant cells undetectable in breast and lymph nodes
- Invasive tumor undetectable in breast and lymph nodes (DCIS allowed)
- Invasive disease absent in breast
- Total or near total therapeutic effect in the primary tumor and evidence of therapeutic effect in lymph nodes, no metastasis

Finer Assessments of Residual Disease

- Invasion vs in-situ
- Miller-Payne (cellularity assessment)
- Stage
 - Size of residual tumor
 - Nodal involvement
- Residual Cancer Burden (RCB)

Endpoints in Trials

- DFS and OS remain gold standard
- Surrogates (correlates) have tremendous value IF fewer patients needed for trials and results are available sooner
- Path CR is best available surrogate/correlate in chemotherapy trials, but dependent on both
 - Sensitivity to therapy
 - Volume of initial disease
- Clinical response of some value, but less robust
- Are there are other surrogates in preop trials?
 - Biologic endpoints
 - Imaging endpoints
- Will likely depend on treatment

Can Response to Chemotherapy be Used to Guide Subsequent Therapy?

- Early clinical response
 - Trials have not shown consistent improvement in outcome with mid-course switch based on response
 - Early responders have better outcome
 - Non-responders (or those with progression) are potential candidates for alternate therapies
- Residual disease at surgery
 - High burden marker of high risk of recurrence
 - Standard therapy, such as hormonal rx and trastuzumab, should be administered and can alter outcome
 - No trial has shown that additional chemotherapy after “modern” chemotherapy improves outcome
 - Untapped opportunity for clinical trials

Locally Advanced Breast Cancer

- Due to increased risk of distant disease, appropriate staging is critical
- If axillary metastatic disease identified, ALND is standard of care
- Mastectomy may not be mandatory in non-inflammatory T4 disease
- Treatment of regional nodal disease with XRT greater consideration
- Use optimal and appropriate systemic therapy

Inflammatory Breast Cancer

- Presentation and definition
 - Frequently acute and rapid onset
 - Involves one third or more of the breast
 - Distinct mass often not evident
 - Skin changes, including *peau d'orange* and erythema
 - Pathologic identification of dermal lymphatic involvement not required
- Distant metastases present at dx in substantial minority
- High proportion of IBC is HER2+
- Is IBC a unique entity?
 - MAYBE (increase in angiogenic/lymphangiogenic markers)

LABC and IBC

- With optimal systemic therapy, long term freedom from distant disease not uncommon
- Systemic therapy likely to improve in future
- Local regional therapy and control has greater importance – TRIALS NEEDED

Local Regional Therapy After Preop Therapy

- After preoperative therapy, residual disease is associated with greater risk of local regional recurrence than same amount of disease at dx
- MD Anderson data demonstrate that increased risk of local regional recurrence associated with
 - Stage III disease at presentation
 - 4 or more lymph nodes at time of surgery
 - No tamoxifen
- XRT indications
 - Need to consider both pre-therapy clinical stage and post-therapy pathologic stage
 - Few trials done of XRT post preoperative chemo and surgery - No need to repeat trials of XRT to show benefit of treatment given robust nature of XRT benefit

Local Regional Therapy After Preop Therapy

- Surgery
 - Preop treatment increases breast conservation rates
 - Surgeon needs to see patient before starting therapy
 - Timing of surgery, in absence of progression, should occur after predetermined course of therapy has been completed
 - What to resect?
 - Shrinkage of tumor may not be concentric
 - Adequacy of margin not determined fully
 - Questions about long term local recurrence rates remain
- Reconstruction
 - Incorporate plastic surgeon in team
 - Need for better understanding of deformity related morbidity

Key Unresolved Clinical Issues

1. Role of MRI in initial assessment and in monitoring response
2. Need for axillary evaluation prior to therapy and timing of SNB
3. Adequacy of margins following systemic therapy
4. XRT – for whom and using which fields
5. Definition of pathologic complete response

Key Unresolved Clinical Issues

6. Optimal therapy for patients who develop disease progression during preoperative therapy
7. Can lack of response (clinical/radiographic) can be used to change therapy?
8. Timing of surgery with regard to systemic therapy
9. Should we be giving preop chemotherapy to improve rate of BCS in patients with ER+ breast cancer, particularly those with invasive lobular carcinoma?
10. Appropriate therapy for patients with significant residual risk after preoperative therapy

Research Issues

- The preoperative setting provides a unique opportunity to study the impact of systemic therapies on breast biology.
- This approach has the potential to facilitate drug development and lead to more rapid improvements in the care of women with breast cancer.
 - Answers available in less time
 - Greater potential to understand predictive markers

Research Issues

- Although the excitement about preoperative therapy stems from the ability to conduct translational research and develop new systemic treatments, many of the unresolved clinical issues relate to local regional disease.
- If we are to pursue an aggressive agenda in the preoperative arena, we need to address these unresolved local regional questions if we are to provide optimal care to women with breast cancer both on and off trial.

Research Considerations

- Tissue Collection
 - Uniform procedure(s) needed
 - Value of frozen tissue (or in RNA later) in addition to fixed
- Imaging
 - Promising as possible prognostic and predictive factor
 - May help guide local and systemic therapy
 - Standardization of tools needed

Research Considerations

- Biomarkers of interest
 - Genomic profiling/microarray
 - Markers of proliferation and apoptosis
 - Many others
 - Need for standardization of markers, particularly those used in “standard” clinical practice
 - Novel trial design
 - Window of opportunity studies
 - Adaptive designs
 - Statistical considerations
- More nimble clinical trials process**
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Advocacy

- Balance between care and research
- Participant burden with these studies, as with all trials
- What is possible at major center vs community hospital?
- Women with breast cancer are full partners in this process
 - And they are not patient!
 - Nor are the researchers!

Conclusions (1)

- Continued emphasis on preoperative setting for clinical trials
 - Great promise
 - That said, surrogate/correlative endpoints not sufficient to change clinical practice in 2007
- Outside of trial setting
 - Preop therapy is standard of care for women with LABC or those not deemed to be candidates for BCS yet still want it
 - Caution needed when considering preop therapy in other settings – multidisciplinary treatment team
CRITICAL
 - Not a license to practice “creative oncology”

Conclusions (2)

- Evidence-based treatment guidelines should be established
- Local therapy panel should be convened to discuss unresolved local therapy questions with goal of developing feasible trials
- Need to move beyond underpowered single institution phase II trials – need larger data sets
 - Risk of false discovery in microarray is high when sample size is small
- Trials of systemic therapy should respect known biologic subtypes whenever possible

Funding Issues

- A major priority
- Need partnerships between academia, government, foundations, and pharma
- This research is expensive!