Neoadjuvant systemic therapy: Practice, patient and research considerations

Dr Nicholas Zdenkowski
BMed, FRACP, ClinDipPallCare, GradDipClinEpi
Medical Oncologist/Clinical Research Fellow
Calvary Mater Newcastle/Hunter Cancer Centre
Faculty of Medicine and Public Health, University of Newcastle, Australia

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Disclosures

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“If systemic therapy is clearly indicated for early stage breast cancer, neoadjuvant scheduling is an option"\textsuperscript{1,2,3}"

Introduction

Neoadjuvant systemic therapy for breast cancer

Practice: What is the basis for current clinical practice?

Patients: What is important for them to consider?

Research: How will we move forward using neoadjuvant systemic therapy?
Clinical practice considerations

Background to neoadjuvant therapy for breast cancer

Early use:
- Locally advanced (T4 and/or N2/3) or inflammatory disease: to enable R0 resection
- Inflammatory - pCR
  - ER+/HER2- : 0% (6% breast only)
  - TNBC : 40%
  - HER2+ : 56%

- LABC – pCR rate independent of T or N stage
  - ER+/HER2- : 7%
  - TNBC : 23%
  - HER2+ : 48%

- Remains standard of care for this population

- Emerging data to support breast conservation in LABC responders

OS in inflammatory breast cancer

pCR is prognostic

MDACC retrospective cohort study (1989-2011)
1075 inflammatory breast cancer patients
527 treated with NAST and surgery

Masuda, Annals of Oncology 2014

OS remains poor
Neoadjuvant therapy in operable disease

Subsequently:
• Operable disease: NSABP B-18 and B-27, and others (including patients with LABC)
• Benefit from taxanes consistent with adjuvant trials
• Overall response rate 60-80%

However:
• No improvement in survival, recurrence, distant recurrence
• Increase in locoregional recurrence (25%) when surgery omitted in complete responders

This is in the pre-subtype era
More proliferative subtypes may experience greater benefits:
• TNBC
• HER2 positive

Time to chemotherapy matters
Reduced overall survival if >4 weeks
Especially TNBC or HER2+

Mauri, JNCI 2005; Bear, JCO 2003; Wolmark, JNCI 2001; Raphael, BrCaResTrt 2016
Clinicians’ reasons for offering NAST

**Australian/New Zealand survey**

- 78% offer NAST routinely to select patients with operable breast cancer, 93% were interested
- 45% would like to increase the proportion routinely given NAST, none were giving too much NAST
- TNBC, HER2 positive more likely to receive NAST
- Strong interest in NAST clinical trials
- Barriers: patient, clinician, system

Zdenkowski et al, IMJ, 2016
Prognostication

Cortazar, Lancet 2014
Impact of response

**Post-neoadjuvant therapy**

Create-X study:
- Post-neoadjuvant capecitabine

Neoadjuvant chemotherapy → Surgery → pCR/minimal residual → Usual care

**1º EP: DFS**
- 82.8 vs 73.9%

6 months adjuvant capecitabine (2/3 weeks, 2500mg/m²/d x 8)

At 3.6yrs
- OS 78.8 vs 70.8%
# Chemotherapy choice – HER2 negative

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trial</th>
<th>Population</th>
<th>Number</th>
<th>pCR</th>
<th>OS</th>
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<tbody>
<tr>
<td>AC – Surgery</td>
<td>NSABP B-27</td>
<td>cT1c-3, N0-1</td>
<td>2411</td>
<td>13%</td>
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<tr>
<td>AC – T – Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.97 (ns)</td>
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<tr>
<td>AC – Surgery - T</td>
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<td></td>
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<td>13%</td>
<td>HR 1.08 (ns)</td>
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<tr>
<td>FEC – Surgery</td>
<td>EORTC 10902</td>
<td>T1c-T4b, N0-1</td>
<td>698</td>
<td>3.7%</td>
<td>HR 1.09 (ns)</td>
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<tr>
<td>Surgery – FEC</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
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<tr>
<td>Dx4 – FECx4</td>
<td>Iwata</td>
<td>T1c-T3N0, T1-T3N1</td>
<td>137</td>
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<tr>
<td>TACx6</td>
<td>GeparTrio</td>
<td>T2N0-2, T4N0-3, responders</td>
<td>1390</td>
<td>21%</td>
<td>(ns)</td>
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<tr>
<td>TACx8</td>
<td></td>
<td></td>
<td></td>
<td>23.5%</td>
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<tr>
<td>TACx6</td>
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<td>T2N0-2, T4N0-3, non-responders</td>
<td>622</td>
<td>5.3%</td>
<td>(ns)</td>
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<tr>
<td>TACx2 – NXx4</td>
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<td></td>
<td>6%</td>
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Chemotherapy choice – HER2 positive

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<thead>
<tr>
<th>Regimen</th>
<th>Trial</th>
<th>Population</th>
<th>Number</th>
<th>pCR</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>DH – Surg - FEC</td>
<td>NeoSphere</td>
<td>cT2-4, N0-3, M0</td>
<td>417</td>
<td>29%</td>
<td>NS</td>
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<td>DHPtz – Surg - FEC</td>
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<td></td>
<td>46%</td>
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<td>HPtz – Surg - FEC</td>
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<td>17%</td>
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<tr>
<td>DPTz – Surg – FEC</td>
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<td></td>
<td>24%</td>
<td></td>
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<tr>
<td>EC – DH - Surg</td>
<td>GeparQuinto</td>
<td>cT3-4N0, T1-4N+</td>
<td>630</td>
<td>30%</td>
<td>NR</td>
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<tr>
<td>EC – LH – Surg</td>
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<td></td>
<td></td>
<td>23%</td>
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<td>PLH – Surg – FEC</td>
<td>NeoALTTO</td>
<td>cT2-4N0-3</td>
<td>450</td>
<td>51%</td>
<td>NS</td>
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<td>PT – Surg – FEC</td>
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<td>29.5%</td>
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<tr>
<td>PL – Surg - FEC</td>
<td></td>
<td></td>
<td></td>
<td>24.7%</td>
<td></td>
</tr>
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</table>

Gianni, Lan Onc 2016; Untch, Lan Onc 2012; de Azambuja, Lan Onc 2014
Chemotherapy choice – Triple negative

Platinum agents

pCR Rates (ypTis/ypN0) in TNBC With Platinum

No disease-free or overall survival benefit

Meta-analysis: pCR 53.3% vs 37.8%

Chemotherapy dose density

Dose dense sequential epirubicin/paclitaxel vs q3w concurrent

668 patients:
Inflammatory: 101
Tumour >3cm: 567

Toxicity:
Greater haematological toxicity
Similar infection rates

Subgroups:
Better outcomes in grade 3 and/or ER negative

Similar outcomes in other studies:
Meta-analysis, significantly higher pCR with dose dense

Untch et al, JCO 2009; Petrelli et al, Anti-Cancer Drugs 2016
Chemotherapy scheduling: Neo-Tango

**Taxane -> Anthracycline is superior to conventional sequence**

831 patients, 25% with inflammatory or locally advanced disease
pCR rate:
- Paclitaxel -> EC: 20%
- EC -> paclitaxel: 15% (p=0.03)

Larger difference in HER2 positive, triple negative and/or grade 3
This complicates administration of HER2-directed therapy, unless concurrent trastuzumab and anthracyclines are given, with the increase in cardiac risk.

Earl, Lancet Oncology 2014
Neoadjuvant endocrine therapy

Similar response rates to chemotherapy, less toxicity

Postmenopausal women for whom chemotherapy is not appropriate
- Comorbidities
- Ability to administer chemotherapy due to location/resources

Results:
- pCR rates < 10%
- Response rate higher with AI than tamoxifen
- No difference in response rate between endocrine therapy and chemotherapy

Premenopausal:
- Neoadjuvant endocrine monotherapy not routinely recommended (insufficient evidence)

Spring et al, JAMA Oncol 2016
Neoadjuvant endocrine therapy

Recurrence outcomes

Locally advanced, ER+/HER2- disease
48 months median follow up
No difference in recurrences:
• Chemotherapy (26.8%)
• Endocrine therapy (21.0%)
  • P=0.979

Combination vs monotherapy

Recurrence rate:
• Neoadjuvant endocrine therapy then salvage chemotherapy in poor responders (23.5%)
• Endocrine therapy (33.4%)
  • P=0.143

Wright, Am J Clin Oncol 2017
Neoadjuvant endocrine therapy

How long? - Duration matters

Response time is slow on endocrine therapy – at least 3 months

pCR rate doubled:
• 12% at 6 months vs 6% at 3 months
• BCS increased 70.6% vs 61.8%

Clinical response rate:
• 83.5% at ≥4 months vs 69.8% at 3 months

pCR may not be the best metric:
• Less likely with ER positive disease
• CPS-EG or RCB may be preferable
• Reduction in Ki-67 is favourable

Charehbili, Ca Trt Rev 2014; Carpenter, Br Ca Res Trt 2014
Surgery

Management of the breast

30% of mastectomy candidates downstaged to lumpectomy by NAST
However, 1/3 of those will still opt for mastectomy
Bilateral mastectomy rates in the USA are higher in those who have had NAST (26.4 vs 14.7%)

Breast conserving surgery is oncologically safe in stage 3 patients after NAST

Mastectomy preferred:
• Inflammatory disease
• Multicentric disease
• If radiotherapy is not available

NAST can facilitate immediate breast reconstruction

OS and RFS worse if surgery delayed longer than 21 days from last chemotherapy (HR 3.1)

Management of the axilla

1. Clinically node negative at baseline:
   – sentinel node biopsy after neoadjuvant chemotherapy reduces axillary clearance by 2/3

2. Clinically node positive at baseline and post-NAST:
   – axillary clearance

3. Clinically node positive (N1) baseline -> clinically node negative post-NAST (controversial):
   – SLNB, dual mapping and 3 nodes removed, FNR<10% (ACOZOG 1071)
   – Overall FNR 13%, identification rate 91%
   – Clip positive node(s) and remove those as well
   – If SLNB positive -> axillary clearance
   – Axillary clearance if premenopausal or TNBC
   – Consider breast response and pattern

4. Clinically node positive (N2-3) baseline:
   – Axillary clearance irrespective of response

Progression during neoadjuvant therapy

Likelihood (MDACC experience)

Response: 91% (1762)
Stable disease: 6% (107)
Progression: 3% (59)

Predictors

African American race
Higher stage
Higher grade/Ki67
TNBC

Impact

Progressive disease (59)
   Surgery: 68% (40) mastectomy; 20% (12) lumpectomy
   No surgery: 12% (7 patients: 3 metastatic disease, 3 inoperable, 1 patient refusal)

Progression during NAST is associated with adverse prognosis
Patients who became inoperable were unlikely to have ever benefited from an operation

Caudle, JCO 2010; Caudle, Ann Surg Onc 2011
Radiotherapy

Timing and indication

Traditionally, radiotherapy has been based on pre-NAST staging. Response-guided treatment has limited evidence.

Breast conserving surgery: Radiotherapy is indicated.

Post-mastectomy chest wall radiation: In patients who remain node positive.
- pCR breast and nodes, radiotherapy may be over-treatment (awaiting NSABP B-51).

Nodal irradiation: Baseline node positive -> post-NAST node negative, SLNB negative.
- Controversial: omission of regional nodal radiotherapy in HER2+ or ER+, with complete response in breast and nodes.
- Observational data suggests OS benefit to PMRT even in cN1-> ypN0.

Pre-operative radiotherapy may be offered:
- Insufficient response in locally advanced disease.
- Planning for immediate reconstruction.

Rusthoven, Annals of Oncology 2016
The patient perspective
Patient views on NAST

Results of interviews

The dominant themes identified in interviews were:
- High level of trust in the treating clinician
- A lack of awareness of NACT prior to it being raised as an option
- A lack of information specifically addressing NACT
- Confidence in the effectiveness of chemotherapy
- A high degree of satisfaction with the treatment decision that was made
- Marginalisation – feeling that their case must be unusual

Barriers

- Desire for immediate surgery
- Lack of interest in downstaging
- Fear or progression during NAST
- Lack of awareness

These barriers can be addressed with information

A decision and information tool is now available to inform patients about NAST

www.breastcancertrials.org.au > About > Brochures

Zdenkowski, Breast, 2016
Patient reported outcomes

During and after neoadjuvant therapy

Inflammatory/locally advanced: 84 patients in India – HADS score during neoadjuvant CAF chemotherapy
- Depression reduced in those who had a clinical response to chemotherapy

Operable breast cancer: 59 Australian patients – multiple scales including distress, anxiety, fear of progression, fear of recurrence, satisfaction with decision, decisional regret

Chintamani, JR Soc Med Sh Rep 2011; Zdenkowski, unpublished
Moving forward in clinical practice and research
Correlation between difference in pCR and difference in DFS or OS

**FDA Meta-analysis to define role in drug approval**

Poor correlation for both overall survival and event-free survival

FDA: Surrogate approval may be given based on pCR, but it requires confirmation in a fully powered study.

Neoadjuvant pertuzumab is a case in point.

Again, this is not subtype-specific. Response definitions may be important.
Correlation between pCR and DFS/OS

Lessons from NeoALTTO/ALTTO and NeoSphere/APHINITY

NeoALTTO: Significant 17% pCR difference with Trastuzumab and Lapatinib c/w Trastuzumab alone
Adjuvant ALTTO: no difference
   Lapatinib arm closed early due to futility

NeoSphere: Significant 22% pCR difference with Trastuzumab and Pertuzumab c/w Trastuzumab alone
Adjuvant APHINITY: Small DFS difference 0.9% (statistically, but perhaps not clinically significant)

De Michele, Clin Ca Res 2015
Accelerating drug development

I-SPY studies

A series of linked studies using biomarker-directed treatment with a standard backbone
Successes: Carboplatin/veliparib in TNBC
Pembrolizumab in TNBC (pCR 60 vs 20%); and HR+ (pCR 34 vs 13%)
TDM-1/Pertuzumab vs paclitaxel/trastuzumab in HER2+ (pCR 52% vs 22%)

These drug combinations 'graduate' to phase 3 confirmatory trials

The future will also include de-escalation, eg targeted therapy alone pre-operatively.
Post-neoadjuvant therapy to select those most in need of additional endocrine therapy

CDK 4/6 inhibitor - Palbociclib

**PENEOLOPE B Study Design**

- Neoadjuvant Chemotherapy
- Surgery +/- Radiotherapy
- R
- Palbociclib
  - 125 mg once daily p.o.
  - d1-21, q28d for 13 cycles
- Placebo
  - d1-21, q28d for 13 cycles

All patients will receive concomitantly endocrine therapy according to local standards
Combination chemo- and endocrine therapy

One study published: chemotherapy and AI vs chemotherapy
- 50 patients, locally advanced ER positive breast cancer
- pCR 25% with combination vs 10% with chemotherapy alone

Breast Cancer Trials ELIMINATE study (ANZ1401)

Patient Population | Stratification |
--- | --- |
Intact clinical Stage 2 or 3, Grade 2 or 3 invasive breast cancer for future resection | Menopausal status |
ER positive, HER2 negative | Clinical Stage 2 vs Stage 3 |
cT2-4 (> 20 mm) |

Randomisation
1. Chemotherapy
2. Chemotherapy + Letrozole (+ Goserelin*)

Surgery
Routine care adjuvant endocrine therapy and radiotherapy

Chemotherapy: \( \geq 18 \) weeks anthracycline + taxane
Letrozole: 2.5mg per day following randomisation until surgery for postmenopausal women
\( 2.5 \)mg per day starting 4 weeks after goserelin for pre- and peri-menopausal women
*Goserelin: for pre- and peri-menopausal women only. Inject following randomisation and repeat every 4 weeks until surgery
Immunotherapy

**PD-1, PD-L1 and CTLA4 inhibitors with or without chemotherapy**

Mutational load correlates with efficacy of immunotherapy
Highest mutational load: TNBC, HER2+
May be more effective when primary tumour is present – neoantigen presentation, less immune evasion, greater lymphocyte infiltration
pCR may not be the best marker of immunotherapy efficacy

Alexandrov, Nature 2013
Rationalising curative intent treatment

**Overtreatment vs undertreatment**

For those who are at greatest risk of relapse: More

For those who do not need intensive therapy: Less
Unanswered questions

Studies needed, or as yet unreported

Ultimate goal: no surgery in exceptional responders
• Studies investigating biopies only in MRI complete response

Axillary downstaging – not yet routine

Omission of radiotherapy in exceptional responders

Avoidance of cytotoxics
• TDM-1 and pertuzumab in HER2+
• Immunotherapy in TNBC
• Endocrine therapy +/- targeted agents eg CDK4/6
Summary

Neoadjuvant systemic therapy for breast cancer

• Indications:
  • Locally advanced or inflammatory (pCR rates similar to EBC)
  • Operable breast cancer, in those who are expected to receive chemotherapy (especially TNBC and HER2+)

• Disease recurrence benefits
  • Faster access to chemotherapy
  • Possibility of post-neoadjuvant therapy

• Facilitates surgical planning
• Prognostication
• Patients may also experience psychological benefits

• Will remain an important approach
  • Routine clinical care
  • Research
Thank you

nick.zdenkowski@newcastle.edu.au