Optimal use of systemic therapy in the palliative setting

Trials and tribulations:
Lifetime experiences of a medical oncologist on chemotherapy intensification

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Barts Cancer Institute, St Bartholomew’s Hospital
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Chemotherapy Intensification in the Palliative Setting

Outline

• Why intensify chemotherapy?
• Is more better?
• Can we better define who might benefit from chemotherapy intensification?
• Is intensification of chemotherapy still the best way forward?
Why intensify chemotherapy?
Metastatic Breast Cancer
Can we achieve long-term remission?

- Response predictive of Outcome
- Some patients with CR achieve long-term PFS
  → Response matters
Metastatic Breast Cancer
Can we achieve long-term remission?

Very small group of MBC patients (<2%) achieve long-term remission with conventional chemotherapy.

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Greenberg et al., JCO 1996
Chemo-Intensification
Basic Considerations (I)

Optimal Dose

Linear Phase

Tumour Volume

Dose

Side Effects

Residual Cancer?
Chemo-Intensification
Basic Considerations (II)

Conventional Therapy

Dose Intensification

- High-Dose
- Dose-Dense
- Combination
- Total Dose
- No. of Cycles

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Chemo Intensification - Rationale
High-Dose Chemotherapy

Key assumptions
- Max. Cell Kill not reached
- Haem. Toxicity Dose-limiting
- Increased Cell Kill changes outcome

Heterogeneity and Selection of Resistant Clones?

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Key assumptions:
- Haem. Toxicity Dose-liming
- "Repopulation" of tumour cells between cycles
- Anti-angiogenic effects?

Most relevant for highly proliferating tumours?
Chemo Intensification - Rationale
Combination Chemotherapy

Key assumptions
- Toxicity only partially overlapping
- Incomplete cross-resistance

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Chemo-Intensification

Does disease setting matter?

Early Disease
- Microscopic Disease
- Sensitive Disease
- Heterogeneity?
- Vascularisation?

Advanced Disease
- Macroscopic Disease
- Resistance $\uparrow$
- Heterogeneity $\uparrow$
- Vasculature established
Is more better?
- Small benefit in PFS but not in OS
- Patients <50 years of age have modest OS benefit
- Biological subtype analysis limited
- Substantial acute toxicity
→ Potential benefit for subgroup but unclear who might benefit
Metastatic Breast Cancer
Dose-dense chemotherapy

Paclitaxel, 80 mg/m² weekly

Paclitaxel, 175 mg/m² q3 wks

Dose dense, but also dose intensity 1.37 x higher

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Seidman et al., JCO 2008
Metastatic Breast Cancer
Combination vs single agent therapy?

- Increased toxicity
- Limited data on QoL
- Limited data with modern agents
- Similar OS with sequential use of modern agents (e.g., Sledge 2003)
- Limited data on patient stratification

Meta-Analysis, 43 Trials, N=9742

- Response: Combination HR 0.78, 0.74 - 0.82, P<0.00001
- TTP: Combination HR 0.88, 0.83 - 0.93, P<0.00001
- OS: Combination HR 0.88, 0.83 - 0.93, P<0.00001
Breast Cancer: Aggressive vs non-aggressive therapy?

Patient Stratification

Slow Progression
Mild symptoms

Single agent Chemotherapy

PS ↓
Stabilisation

Rapid Progression
Marked symptoms

Poly-Chemotherapy

Rapid Progression
Symptoms ↑
Advanced NSCLC
Combination vs Single Agent Therapy?

- Doublet combination standard
- No benefit for triplet combinations


Response

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<tr>
<th>Combination</th>
<th>OR</th>
<th>P</th>
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<td>Single Agent</td>
<td>1.0</td>
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<td>2 Agents</td>
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Survival

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<th>Combination</th>
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<th>P</th>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>3 Agents</td>
<td>1.0</td>
<td>0.97</td>
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Delbaldo et al. JAMA 2004
Can we better define who might benefit from chemotherapy intensification?
Breast Cancer: Who benefits most from chemotherapy? Response to Chemo in Subtypes

Association between pCR and event-free survival, by breast cancer subtype

- **ER+ G1/2**: 0.49
- **ER+ G3**: 0.27
- **HER2+ ER+**: 0.58
- **HER2+ ER-**: 0.25
- **TNBC**: 0.24

TNBC & HER2+/ER- derive most benefit of chemotherapy

1 Cortazar, Lancet 2014
Triple-negative Breast Cancer
Heterogeneity requires different strategies

10-15% of all patients

Biological Clusters

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Lehmann et al, JCI 2011
Different Targets for Biological Clusters

BL1: DNA Damage Repair
BL2: MET
IM: Immunomodulatory

Mesenchymal: Alk, Src, PI3Ki

Luminal Androgen Receptor: Anti-androgen

Subtyping also reveals heterogeneity in probabilities of pCR to neoadjuvant CT

<table>
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<tr>
<th>Clusters</th>
<th>pCR</th>
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<tr>
<td>Basal-like 1</td>
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<tr>
<td>Basal-like 2</td>
<td>-</td>
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<tr>
<td>Immunomodulatory</td>
<td>(++)</td>
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<tr>
<td>Mesenchymal-like</td>
<td>(++)</td>
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<tr>
<td>Mesenchymal stem-like</td>
<td>±</td>
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<tr>
<td>Luminal androgen receptor</td>
<td>±</td>
</tr>
<tr>
<td>Unclassified</td>
<td>(++)</td>
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Masuda et al, ASCO 2013

Lehmann et al, JCI 2011
Is intensification of chemotherapy still the best way forward?

New Therapeutic Strategies
Combination chemotherapy versus Biologicals

EGFR-Inhibition in EGFR-M+ NSCLC

Gefitinib
Carbo/Paclitaxel

HR=0.30,
95% CI 0.22 - 0.41, p<0.001
Median PFS : 10.8 vs 5.4 months

Response

74%
31%
Patients with HER2-positive MBC centrally confirmed (N = 808)

- Trastuzumab: n=406
- Docetaxel: n=402
- Pertuzumab + trastuzumab + Docetaxel

Baselga, SABCS 2011

- Pertuzumab/Placebo:
  - 840 mg loading dose, 420 mg maintenance
- Trastuzumab:
  - 8 mg/kg loading dose, 6 mg/kg maintenance
- Docetaxel:
  - 75 mg/m², escalating to 100 mg/m² if tolerated

Combination of chemotherapy and Biologicals

Dual vs Single Target Inhibition

Cleopatra Study (n=808)

- Ptz + T + D: median 18.5 months
- Pla + T + D: median 12.4 months

Δ = 6.1 months

n = 433 PFS events

HR = 0.62
95% CI 0.51–0.75
p<0.0001
Increased Local Intensity: Antibody-Drug-Conjugates

**Trastuzumab-DM1**

- **Targeted Intra-cellular Delivery of DM1**
- **Mitotic arrest & apoptosis**
- **Low systemic exposure due to HER2 targeting**

DM1: Potent cytotoxic agent
Retains biologic activity of Trastuzumab

**EMILIA Trial**

- **Patients with HER2-positive MBC and PD or relapse after Trastuzumab (n = 980)**
- **Capecitabine + Lapatinib**
  - **6.4 months**
  - HR = 0.65 (95% CI 0.55-0.77, P < 0.0001)
- **T-DM1**
  - **9.6 months**

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Konecny, Cancer Res 2006; Scaltriti, Oncogene 2009
Targeting Immune-Checkpoints

Tumour-Cell

TCR

PD-L1

T-Cell

Activated

Activated

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Anti-PD-L1 (MPDL3280A)

<table>
<thead>
<tr>
<th>PD-L1 Status* <em>(N = 53)</em></th>
<th>ORR,† %</th>
<th>Pts With PD, %</th>
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</thead>
<tbody>
<tr>
<td>IHC 3 (n = 6)</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>IHC 2 &amp; 3 (n = 13)</td>
<td>46%</td>
<td>23%</td>
</tr>
<tr>
<td>IHC 1/2/3 (n = 26)</td>
<td>31%</td>
<td>38 %</td>
</tr>
<tr>
<td>All patients (N = 53)</td>
<td>23%</td>
<td>40 %</td>
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*PD-L1 status determined using proprietary Genentech Roche IHC.
†ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.
Patients first dosed at 1-20 mg/kg by October 1, 2012. Data cutoff April 30, 2013.
Chemotherapy Intensification in the palliative setting

Summary and Conclusions

• Intensification of chemotherapy includes high-dose, dose-dense and combination strategies

• Benefits of intensified strategies might differ between early and advanced disease

• There is an optimal dose and dose intensity for most treatments and for most patients in the palliative setting intensification does NOT have added benefit

• Small subsets might benefit from more intensive approaches; strategies to date have not considered enough the tumour biology

• New developments such as targeted treatments, ADCs or immune therapy are reducing the need for conventional intensification
Optimal use of systemic therapy in the palliative setting

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