The role of clinical trials in establishing and refining standards

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Let’s take a ‘simple’ question

• EBC: chemo or no chemo?
• We go back 10 years:
  • StGallen criteria
  • Nottingham prognostic index
  • Adjuvant Online -> at that time reported to be used by >70% of clinicians as an information tool
• Organizing a clinical trial (high level evidence) on such a question is very hard ...: CT vs no CT
• In these 10 years, 2 examples have been run, both in context of evaluating a genomic ‘competing’ tool: TAILORx in US for Oncotype DX (Genomic Health) and MINDACT in EU for Mammaprint (Agendia)
Why was AO the de facto standard?

• Some possible explanations:
  • Based on ‘most data’
  • Based on statistical approach, as compared to expert opinion
  • Available online, with a very easy calculator
  • Nice interactive tool
  • Free
EORTC-BIG MINDACT TRIAL DESIGN
The discordant cases

Evaluate Clinical-Pathological risk and 70-gene signature risk

Discordant cases 32% (as per protocol estimate)

Clin-Path HIGH and 70-gene LOW  
Clin-Path LOW and 70-gene HIGH

1st randomization  
treatment decision

Use Clin-Path risk to decide CT

Clin-Path HIGH and 70-gene LOW chemotherapy
Clin-Path LOW and 70-gene HIGH no chemotherapy

Use 70-gene risk to decide CT

Clin-Path HIGH and 70-gene LOW no chemotherapy
Clin-Path LOW and 70-gene HIGH chemotherapy

Potential CT sparing
The single hardest question in all of this design?

• What is the standard way of deciding CT? In other words, the control arm was the problem
• First idea was: let investigator decide -> too much variability
• Finally:
• Adjuvant Online 10 year Breast cancer specific estimate defines good prognosis as:
  • > 88% without trt for ER+
  • > 92% without trt for ER-
MINDACT TRIAL DESIGN

Registration & Screening Surgery

N = 6600

Clinical-Pathological (C) risk (Adjuvant! Online)

Genomic (G) risk (70-gene MammaPrint signature) and 44k complexe array from all

Discordant cases

C-HIGH / G-HIGH

C-HIGH / G-LOW or C-LOW / G-HIGH

C-LOW / G-LOW

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthraclycline –based vs. Capecitabine-Docetaxel

Endocrine therapy

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

No Chemotherapy

HR+

HR+
We recently returned to the ‘standard’ question

- Did a survey to revisit current practice, using MINDACT trial cases / profiles
- Will reassess when the data of MINDACT become available
Agreement in risk assessment among breast cancer specialists: a survey within the MINDACT cohort
Impakt 2015

- 82 breast cancer specialists assessed 37 cases from the MINDACT trial and gave a recommendation for adjuvant chemotherapy (aCT).

- The 37 cases have a discordant genomic (70 gene) vs. clinical (“Adjuvant Online!” - based cut-off (AOL)) risk assessment cases are either:
  - AOL high – 70-gene signature low (cHgL)
  - AOL low – 70-gene signature high (cLgH)

- Cases were presented in an online questionnaire in a random order.
- Most participants were:
  - medical oncologist (78%)
  - at least 10 years of experience (76%).
Mindact Survey on adjuvant CT administration

The overall agreement between the participants and the Adjuvant Online! based decision rule was low (64%), with a lot of variation across cases (range 5% to 100%).

cLgH = clinical (m-AOL) low risk / genomic (MammaPrint) high risk case
cHgL = clinical (m-AOL) high risk / genomic (MammaPrint) low risk case
Mindact Survey on adjuvant CT administration

There is in general a high agreement to administer aCT for patients:
• with high grade tumors
• and/or have at least 2 positive lymph nodes
• and/or who are of young age (<45).

$cLgH = \text{clinical (m-AOL) low risk} / \text{genomic (MammaPrint) high risk case}$

$cHgL = \text{clinical (m-AOL) high risk} / \text{genomic (MammaPrint) low risk case}$
Mindact Survey on adjuvant CT administration

• The overall agreement among breast cancer specialists regarding the administration of aCT was low to moderate (77%) and varied greatly from case to case (range 53% to 96%).
• Apart from the cases involving
  • young patients,
  • high grade tumors
  • ≥2 positive lymph nodes,
... no clear patterns in aCT recommendation in relationship to other tumor characteristics were observed. (!)
Some thoughts

• Treatment choices are an outcome of characteristics of
  • the patient (preferences)
  • the tumor/patient (prognostic and predictive)
  • the country’s health system
  • the hospital/medical team
• How to implement, maintain, evaluate a standard?
• In case of CT decision, in my opinion a lot also depends on patient preference: toxicity vs efficacy
• Fact: we have insufficient information about true long term toxicity/ QOL effects of CT decision
Thank you