Ethical tension in placebo-controlled randomized trials for cancer: a review of recently published trials

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Disclaimer

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Introduction: Cancer and Placebo

- Until recently placebo not used in cancer trials
  - No placebo effect / chemotherapy ➔ not necessary?
  - Prognosis ➔ unethical?
  - Challenge with molecularly targeted agents
    • Efficacy: Stable disease
    • Long term, costs

- Placebo outcomes
  - Symptom control
    • 0-27% per trial
  - Tumor response (ORR, WHO)
    • 0-7% per trial, 11 patients (2.4%)
  - Stable disease
    • 52% of trials

37 placebo RCT
1977-1997
(Chvetzoff and Tannock JNCI 2003)

40 placebo RCT - Molecularly targeted agents
1977-2012
(LeTourneau, Paoletti at al. JCO 2013)
Introduction

- Placebo-controlled randomized trials (P-RCT)
  - Necessary / desirable for cancer
  - “Placebo-only” 1:1 trial
    - Might not be feasible
      - Scientific, practical, ethical reasons
    - Some alternative strategies are proposed
      (ICH E10, 2000; Daugherty CK, et al. JCO, 2008)

Objective

Describe the frequency of “alternative” strategies for randomized placebo-controlled trials for cancer

Review of published P-RCT
Methods

- Sample of cancer P-RCT, 2014
  - Pubmed/Medline (October 2014)
    - Cancer [Tiab] and Placebo [Tiab]
    - Randomized Controlled Trial [Ptype]

  - Inclusion criteria
    - P-RCT, evaluating clinical endpoints

  - Exclusion criteria
    - Protocol without results
    - Secondary analysis
Alternative strategies using placebo (1)

- “Add-on” placebo controlled trial
  - If proved active standard treatment (A)
  - A + E (experimental) vs. A + Placebo of E

- As opposed to placebo “only” trials
  - E vs. Placebo of E
  - Salvage therapy
    - After failure to standard therapy
Alternative strategies using placebo (2)

- Additional control groups
  - Dose-finding
  - Factorial design

- Early escape / rescue treatment
  - Access E upon progression
  - “one-way crossover”

- Randomized maintenance

- Unbalanced randomization (ratio 2:1…)

- Stopping rules

Doussau A. SCT Conference 2015
Alternative strategies using placebo (2)

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Decrease exposure to placebo
Results: 53 eligible trials

91 abstracts

38 excluded

Efficacy of anticancer intervention 29

Prevention of adverse effects 24

29 “Treatment” P-RCT

- 20 Phase III (69%), 9 phase II
- Molecularly targeted agents 16
- Cancer
  - Lung 7
  - Prostate 5
  - Breast 3
  - Other: pancreas, ovary, urothelial, liver, uterus, gastric, oesophagus, brain, neuroendocrine, thyroid

24 “Symptom” P-RCT

- Symptom
  - Urogenital 5
  - Neuropathy 4
  - Gastrointestinal 3
  - Bone 3
  - Other: fatigue, pain, metabolic, surgical complication

Not cancer / healthy volunteers 13
Subgroup analysis/Reanalysis 16
No clinical endpoint or results 4
No design information 2
Doubloon 1
Animal 1
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Results (2) Design in 29 “Treatment” P-RCT

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<td>Stopping rule</td>
<td>15</td>
<td>51.7</td>
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<td>Unbalanced randomization</td>
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<td>17.2</td>
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<tr>
<td>&quot;Cross-over&quot;</td>
<td>5</td>
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<tr>
<td>Maintenance</td>
<td>2</td>
<td>6.8</td>
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<td>Factorial</td>
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<td>3.4</td>
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9 “placebo only”
Placebo “only” RCT, no alternative design

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<tr>
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<th>Clinical Setting</th>
<th>Treatment</th>
<th>Primary Endpoint</th>
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<tbody>
<tr>
<td>Cervix</td>
<td>Low grade intraepithelial neoplasia (CIN1) HPV+</td>
<td>Green tea*</td>
<td>CIN1 and HPV clearance</td>
</tr>
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<td>Esophagus</td>
<td>Advanced Failure to chemotherapy</td>
<td>Gefitinib</td>
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*phase II. OS overall survival.
**Placebo “only” RCT, alternative strategies**

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*phase II. SD stable disease, OR objective response, OS overall survival, PFS progression free survival.*
**Placebo “only” RCT, alternative strategies**

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## Placebo “only” RCT, alternative strategies

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Discussion

- First study to describe alternative strategies in P-RCT

- Preliminary results
  - Delay in PubMed
    - Randomized Controlled Trial [Ptype]
  - ~ 250 abstracts, 2014 year
Discussion

- Majority of cancer “Treatment” trials use alternatives strategies to classical 1:1 P-RCT
  - “Placebo only” rare
  - Advanced disease/salvage therapy (8/9)
- Most frequent “alternative” strategies
  - Add-on (70%)
  - Stopping rules (52%)
  - Unbalanced randomization (17%)
  - “Cross-over” (17%)
    - Patients access E after progression
    - Long-term outcomes (mortality) difficult to assess
    - Controversy: “Misguided” ethics? (Prasad V, Grady C, CCT 2014)
Discussion

Study aims

Factorial Dose-finding
Maintenance
Add-on
Unbalanced randomization
Adaptive/stopping rule

Patient benefit

"Cross-over"

Add-on
Unbalanced randomization
Adaptive/stopping rule
Conclusion

- Alternatives to 1:1 placebo “only” RCT are very frequent
  - Address specific scientific questions
  - Try to address ethical tension of placebo in cancer patients

- Some more analysis needed
  - Evolution?
  - Ethical/scientific balance for “cross-over” trials
Aknowledgement

- C Grady, L Colloca (Dept of Bioethics, NIH, Bethesda, USA)
- T Fojo (National Cancer Institute, NIH, Bethesda, USA)
- I Tannock (Princess Margaret Cancer Centre, Toronto, Canada)

Reference

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