Objective Response Rates of Placebo in Randomized Controlled Trials of Anticancer Medicines: 2015 – 2019

Background
- Patients want to know the probability of response without treatment.
- This can be inferred from placebo ORR from clinical trials.
- This may also have regulatory significance regarding drug approval based on ORR alone.

Methods: Systematic Review and Meta-Analysis

Published Search: randomized controlled trials for anticancer drugs conducted between January 1, 2015 to December 31, 2019.

Inclusion Criteria:
- Adult solid tumours
- Randomized controlled trials
- Placebo groups
- Outcome measures: objective response rate (ORR)

Exclusion Criteria:
- No pediatric cancer
- No hematological cancers
- No adjuvant therapies
- No single agent studies
- No local therapies, e.g., radiation or surgery
- No phase 1/II/III clinical trials
- No subgroup analysis

Data Collection: number of patients randomized into each trial arm, endpoints (e.g. objective response, complete response, partial response), tumour type, and maintenance therapy.

Meta-Analysis:
- Freeman-Tukey double arc sine transformation to account for studies that reported zero for some endpoints.
- Clopper-Pearson method to calculate confidence intervals for each study.
- Random effects model using the DerSimonian and Laird method.

Preliminary Results

Published Information: Full Text Review: n = 480
Randomized Controlled Trials: n = 310
RCTs Analyzed: n = 30

<table>
<thead>
<tr>
<th>Study</th>
<th>n Responders</th>
<th>Weighted Proportion</th>
<th>Weighted ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin® 2016</td>
<td>237</td>
<td>1</td>
<td>3.7%</td>
</tr>
<tr>
<td>Bevacizumab 2016</td>
<td>194</td>
<td>8</td>
<td>3.7%</td>
</tr>
<tr>
<td>Pantoprazole 2016</td>
<td>171</td>
<td>5</td>
<td>3.6%</td>
</tr>
<tr>
<td>Gaurdian 2018</td>
<td>357</td>
<td>7</td>
<td>2.6%</td>
</tr>
<tr>
<td>Kang 2016</td>
<td>89</td>
<td>2</td>
<td>3.1%</td>
</tr>
<tr>
<td>Kang 2017</td>
<td>171</td>
<td>0</td>
<td>3.0%</td>
</tr>
<tr>
<td>Noxop 2016</td>
<td>108</td>
<td>2</td>
<td>3.0%</td>
</tr>
<tr>
<td>Level 2017</td>
<td>199</td>
<td>2</td>
<td>3.0%</td>
</tr>
<tr>
<td>Nexa 2017</td>
<td>22</td>
<td>1</td>
<td>2.9%</td>
</tr>
<tr>
<td>Preda 2017</td>
<td>116</td>
<td>9</td>
<td>3.4%</td>
</tr>
<tr>
<td>Stomaker 2015</td>
<td>151</td>
<td>2</td>
<td>3.5%</td>
</tr>
<tr>
<td>Shara 2018</td>
<td>149</td>
<td>3</td>
<td>3.6%</td>
</tr>
<tr>
<td>Nox 2016</td>
<td>59</td>
<td>0</td>
<td>3.0%</td>
</tr>
<tr>
<td>Yaz 2016</td>
<td>97</td>
<td>1</td>
<td>3.5%</td>
</tr>
<tr>
<td>Zhou 2015</td>
<td>282</td>
<td>2</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity \(I^2\% = 79%\)

Avastin 2017 | 213 | 34 | 3.7% | 0.16 (0.01; 0.37) |
Chesn 2018 | 32 | 12 | 3.6% | 0.04 (0.02; 0.09) |
Han 2018 | 143 | 1 | 3.6% | 0.01 (0.00; 0.04) |
Han 2018a | 27 | 0 | 3.0% | 0.00 (0.00; 0.46) |
Liu 2018 | 30 | 0 | 2.4% | 0.00 (0.00; 0.12) |
Random effects model

Heterogeneity \(I^2\% = 82%\)

Grolay 2018 | 42 | 1 | 2.7% | 0.02 (0.01; 0.13) |
Hinch 2017 | 182 | 0 | 3.4% | 0.00 (0.00; 0.04) |
Li 2017 | 48 | 0 | 3.1% | 0.00 (0.00; 0.12) |
Li 2016 | 126 | 0 | 3.3% | 0.00 (0.00; 0.19) |
Van Cobben 2011 | 34 | 0 | 2.9% | 0.00 (0.00; 0.07) |
Xu 2017 | 78 | 0 | 19.9% | 0.00 (0.00; 0.06) |
Random effects model

Heterogeneity \(I^2\% = 3%\)

Fazl 2016 | 146 | 6 | 3.6% | 0.03 (0.01; 0.07) |
Saal 2015 | 235 | 37 | 3.7% | 0.19 (0.11; 0.29) |
Ban 2016 | 46 | 1 | 2.2% | 0.04 (0.02; 0.09) |
Random effects model

Heterogeneity \(I^2\% = 0%\)

Random effects model

Heterogeneity \(I^2\% = 87%\)

Conclusions
- Two percent of patients with advanced solid tumours can expect to achieve some response even in the absence of treatment.
- Higher placebo responses in maintenance therapy trials and prostate cancer trials.
- Complete regression without treatment is rare.

Limitations
- Systematic review can include more recent trials.
- Systematic review can include pediatric and hematological cancers.

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