Inter-observer Variability in Radiographic Assessment of Response in Chemotherapy Trials for Pancreatic Cancer

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Background Information

- In the era of evidence-based medicine, the quality of the evidence is critical
- Previous studies examining inter-observer variability in the radiographic assessment of drug response revealed significant discrepancies
- Response rates reported by investigators (NIH) were significantly higher than rates reported by an independent review committee (IRC)
- No studies have examined differences between investigators and independent central review panels for the imaging response of drug response in unresectable pancreatic cancer

Summary Table – Previous Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Cancer</th>
<th>Total # Patients</th>
<th>Lesions evaluated by NIH</th>
<th>Objective Response Rate (INV or IRC)</th>
<th>Summarized in Response to IRC</th>
<th>Change in Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geyler</td>
<td>Ovarian</td>
<td>211</td>
<td>20.6% (DIV) 12.3% (IRC)</td>
<td>21%</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
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<tr>
<td>Thun</td>
<td>Breast</td>
<td>480</td>
<td>66%</td>
<td>123</td>
<td>87</td>
<td>32%</td>
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<tr>
<td>Miller</td>
<td>Breast</td>
<td>444</td>
<td>N/A</td>
<td>19.3-20.9% (DIV) 91-109% (IRC)</td>
<td>45%</td>
<td>N/A</td>
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<tr>
<td>Stebbing</td>
<td>Colorectal</td>
<td>402</td>
<td>73%</td>
<td>452</td>
<td>N/A</td>
<td>39%</td>
</tr>
</tbody>
</table>

Results

- In 50/133 cases, there was sufficient discrepancies between investigators and reviewers to result in a change in overall response
- In 10 of these cases, investigators reported responses inconsistent with protocol standards for the investigator’s reported tumor measurements
- In 40 cases, reviewers disagreed with the radiological findings reported by investigators

Best Response Corrected to Conform to Protocol Criteria

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>FD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>50</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>67</td>
<td>45</td>
<td>15</td>
</tr>
</tbody>
</table>

Discrepancies between investigators and reviewers could be classified into the following categories:

- Improperly measured target lesions
- Incorrect selection of target lesions
- Failure to identify new lesions
- Missing data
- Incorrect response form paradigm (disease identified at baseline not subsequently followed, yet response was reported)
- Failure to apply the protocol standards correctly

- In 47 of the 50 cases of discrepancy between investigators and reviewers, the files were available for a second review by the adjudicator
- The adjudicator confirmed the reviewers’ assessment of response in 39/47 (83%) of cases
- Discrepancies in response were not randomly distributed between investigators and reviewers
- Investigators reported significantly more objective responses (CR + PR) than reviewers even after investigators’ response coding errors were corrected
- Investigators reported favorable responses in 27/133 (20%) cases of compared with 61/133 (5%) responses noted by reviewers, a significant discrepancy (p<0.01)

Discussion & Conclusions

Discussion

- 7% decrease in response rate in this study was even more pronounced than previously reported 23 – 52% decreases in response rates in studies of other primary malignancies
- Possible explanations for the significant discrepancy between investigators and independent reviewers:
  - Investigator bias: Limited alternative treatment options for unresectable pancreas cancer may bias investigators to assess a more favorable response that would ensure patient continued participation in the trial
  - Challenge of accurately measuring pancreatic cancer lesions with existing CT-based imaging technology

Conclusions

- This study supports the use of independent review of trial endpoints, e.g. response rate, is based on imaging data.