Risk of Incremental Toxicities and Associated Cost of New Anticancer Drugs: A Meta-Analysis

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Disclosure

I have no actual or potential conflict of interest

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Introduction

- New cancer therapies have improved outcomes of people with cancer but they also add toxicities and cost

- Improvements in relevant efficacy outcomes with ‘acceptable’ toxicities observed in registration trials are mostly sufficient for drug approvals

- Rare but serious toxicities may not be captured in pivotal clinical trials

- Drug regulation process does not consider cost
Cost of Cancer Care

Direct Cost
- Drug Investigation
- Physician
- Hospitalization
- Rehabilitation

Indirect Cost
- Reduced productivity
- Job Loss
- Caregiver time

Intangible Cost
- Pain and suffering
- Bereavement
- Family health
- Psycho-social
Aims

• For new anticancer drugs approved by the United States Food and Drug Administration (FDA):
  I. To quantify the difference in occurrence of Grade III and IV Adverse Events (AEs) in experimental versus control arms of the pivotal clinical trials
  II. To estimate incremental price of new anticancer drugs
  III. To estimate the cost of managing incremental toxicities
Hypotheses

1. There would be a substantial increment in the price of new anticancer drugs compared to previous standard of care

2. New anticancer drugs would be more toxic and therefore would incur higher cost for management of toxicity

3. Toxicity and associated costs would differ among the types of new anticancer drugs
Methods

- FDA website was assessed to identify newly approved anticancer drugs from 2000 to 2011
- Phase III RCTs leading to drug registration for treatment of advanced cancers were identified
- Data extraction:
  - Frequency of 12 most common grade III or IV AEs were collected from each arms of the RCTs
  - Relative Risk (RR) and Absolute Excess Risk (AER) were calculated for the 12 AEs between the arms
- RR and AER for each of the 12 AEs were pooled in a meta-analysis using RevMan 5.2
Sub-groups of new anticancer drugs

I. Specific targeted agents
   - Agents were selected based on a molecular target on cancer cells

II. Less-specific targeted agents
   - No biomarker was available to guide drug selection, includes angiogenesis inhibitors

III. Chemotherapy
Sub-groups of included studies

1. Studies with active anticancer drugs in the control arm

2. Studies with either placebo or best supportive care in the control arm
Methods: Data on Cost

• Price of anticancer drugs:
  – Pharmacy RED BOOK 2011
    www.micromedex.com

• Cost of toxicity:
  – Published data from Medline and Embase
  – In case of more than one report on same toxicity, most recent cost used
  – Non-US currencies were converted to US$

• All costs adjusted for inflation to reflect 2013 US$ value
Total unique drug approvals by FDA Jan 2000 to Dec 2011 (n=1,265)

Pivotal trials leading to cancer drug approvals (n=69)

Studies included, n=41
Unique new drugs, n=19 (27,000 patients)

Excluded:
Studies on supportive care (n=18)
Studies with unavailable or unusable data on grade III-IV toxicities (n=4)
Duplicate studies (n=3)
Studies of non-cancer indication (n=3)
## 12 Most Frequent Toxicities

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>% of Studies</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>88%</td>
<td>Neuropathy</td>
<td>30%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>85%</td>
<td>Erythrodysesthesia</td>
<td>27%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>82%</td>
<td>Hypertension</td>
<td>27%</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>51%</td>
<td>Thromboembolism</td>
<td>20%</td>
</tr>
<tr>
<td>Rash</td>
<td>49%</td>
<td>Hemorrhage</td>
<td>20%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>40%</td>
<td>GI perforation</td>
<td>8%</td>
</tr>
</tbody>
</table>
# Relative risk of Gr III-IV AEs

<table>
<thead>
<tr>
<th>Sub-groups (based on drugs)</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific targeted agents:</td>
<td>0.7</td>
<td>0.4 to 1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Less specific targeted agents:</td>
<td>3.4</td>
<td>2.2 to 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy:</td>
<td>1.7</td>
<td>1.2 to 2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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<table>
<thead>
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<th>Sub-groups (based on controls)</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group contained active anticancer treatment:</td>
<td>2.1</td>
<td>1.5 to 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control group with placebo/BSC:</td>
<td>3.0</td>
<td>1.6 to 5.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Absolute risk of Gr III-IV AEs

<table>
<thead>
<tr>
<th>Sub-groups (based on drugs)</th>
<th>AER (%)</th>
<th>95% CI (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific targeted agents</td>
<td>-1.0</td>
<td>-2.2 to 0.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Less specific targeted agents</td>
<td>3.0</td>
<td>1.2 to 4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3.0</td>
<td>1.0 to 5.1</td>
<td>&lt;0.01</td>
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<td>2.4</td>
<td>1.6 to 3.3</td>
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</tr>
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</table>
# Incremental Drug Price

<table>
<thead>
<tr>
<th></th>
<th>Median (US$) /patient/month</th>
<th>Range (US$) /patient/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td>6000</td>
<td>*-600 to 33,000</td>
</tr>
<tr>
<td>Specific agents:</td>
<td>4,600</td>
<td>-600 to 9,100</td>
</tr>
<tr>
<td>Chemotherapy:</td>
<td>5,700</td>
<td>2,800 to 7,800</td>
</tr>
<tr>
<td>Less specific agents:</td>
<td>6,700</td>
<td>2,900 to 33,000</td>
</tr>
</tbody>
</table>

*Negative sign denotes experimental agents were cheaper.*
Incremental Cost of Toxicities

- Incremental cost of managing AEs was relatively low compared to drug price
- Total cost of toxicity was divided among ALL patients in respective arms of the RCTs to get a median per patient ‘share’ regardless of whether they experienced any AE

<table>
<thead>
<tr>
<th>Sub-groups (based on drugs)</th>
<th>Median/patient (US$)</th>
<th>Range/Patient (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific targeted agents:</td>
<td>-50</td>
<td>-50 to 35</td>
</tr>
<tr>
<td>Less specific targeted agents:</td>
<td>140</td>
<td>15 to 500</td>
</tr>
<tr>
<td>Chemotherapy:</td>
<td>275</td>
<td>85 to 740</td>
</tr>
</tbody>
</table>

*Negative sign denotes lower cost in experimental arms esmo.org
Cost of Toxicities (Range)

• Specific targeted agents: (Values in US$)
  – Minimum: Hemorrhage: -125 (-165 to 150) per patient
  – Maximum: Diarrhea: 12 (5 to 85) per patient

• Less specific agents:
  – Minimum: Stomatitis: 5 (1 to 20) per patient
  – Maximum: Neuropathy: 560 (220 to 1355) per patient

• Chemotherapy
  – Minimum: Hypertension -75 (-100 to 95) per patient
  – Maximum: Neuropathy 745 (320 to 1690) per patient
Limitations

• We only used published data - toxicities are underreported in published clinical trials
• Information on recurring AEs are usually not clear in clinical trial reports
• We did not consider low grade AEs
• Sources of cost of toxicity were heterogeneous - such cost is sensitive to local healthcare market
• Therefore, our data on toxicity are likely to be underestimates of the true cost
Conclusions

• Health related and financial consequences of new anticancer drugs are substantial
• Specific targeted agents have lower toxicities than control treatments unlike less specific agents and chemotherapy
• Less selected patients in the community may suffer from more AEs and cost
• Competing social priorities necessitate estimation of economic consequences of new anticancer drugs because resources are finite
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