Under-reporting of harm in clinical trials

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Disclosures

I do not have any conflict of interest to declare
Outline

- Under-reporting of harm
- Impact of under-reporting of harm
- Possible solutions to mitigate the under-reporting of harm
Under-reporting of harm

- **In clinical trials**
  - perception of harm in patients vs. physicians
  - reporting of detected harm by physicians
  - updated vs. first report of a clinical trial

- **In postmarketing experience or everyday clinical practice**
  - patients treated outside of clinical trials have more co-morbidity and are more likely to have toxicity
  - outside clinical trials health care resources may be less abundant
How good are physicians in reporting of harm in clinical trials?

- Physician‘s reporting of symptomatic AEs lacks reliability
  - agreement between different physicians is moderate at best,
- Clinicians under-report the incidence and severity of symptoms compared to reports of patients
- Patient reports better than clinician reflecting the underlying health status

Basch et al, JNCI, 2009
Reporting of 6 subjective toxicities was compared for 1090 patients in 3 phase III clinical trials with reports of their physicians.

<table>
<thead>
<tr>
<th>Under-reporting of</th>
<th>Any toxicity</th>
<th>&quot;Very much&quot; toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>74%</td>
<td>50%</td>
</tr>
<tr>
<td>Nausea</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation</td>
<td>69%</td>
<td>44%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50%</td>
<td>24%</td>
</tr>
<tr>
<td>Hair loss</td>
<td>65%</td>
<td>43%</td>
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A growing body of evidence shows that physicians under-detect harm in clinical trials.
Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer

F. E. Vera-Badillo, R. Shapiro, A. Ocana, E. Amir & I. F. Tannock*

Division of Medical Oncology & Hematology, Princess Margaret Hospital and University of Toronto, Toronto, Canada

Ann Oncol, 2013

- Quality of reporting of the primary endpoint (PE) and of toxicity in RCTs of breast cancer assessed
- Of 164 included trials, 33% showed bias in reporting of the PE and 67% in the reporting of toxicity
  - only 32% of articles indicated the frequency of grade 3 and 4 toxicities in the abstract
  - a positive PE was associated with under-reporting of toxicity (OR= 2.0; p=0.044)

Physicians/investigators not only under-detect but also under-report detected harm in clinical trials
Comparison of results between the first and updated reports of RCTs

- 311 initial reports of RCTs, published between 1990-2010 (prostate, breast and lung cancer)
- Of these, 64 (21%) had updated reports
- Independent predictors for an update:
  - prostate cancer site
  - conduct of an interim analysis
  - larger sample size
  - smaller HR (a larger magnitude of effect)

Elimova et al, ASCO 2014
Comparison of results between the first and updated reports of RCTs

<table>
<thead>
<tr>
<th></th>
<th>First publication</th>
<th>Updated publication</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR - primary endpoint</td>
<td>0.71</td>
<td>0.78</td>
<td>0.003</td>
</tr>
<tr>
<td>HR - secondary endpoint</td>
<td>0.76</td>
<td>0.82</td>
<td>0.35</td>
</tr>
<tr>
<td>Patients with G 1/2 AEs (%) (IQR)</td>
<td>21 (6-42)</td>
<td>23 (8-43)</td>
<td>0.012</td>
</tr>
<tr>
<td>Patients with G 3/4 AEs (%) (IQR)</td>
<td>5 (2-9)</td>
<td>6 (2-12)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Benefit-risk ratio of new anticancer agents may be less favourable according to the updated reports.
From clinical trials to post-marketing experience
(an example: lapatinib)

Randomized clinical trial

Original publication
2006

Initial drug label
2007
From clinical trials to post-marketing experience (an example: lapatinib)

Randomized clinical trial
- Original publication: 2006

Post-marketing surveillance
- Active labeling revision: #2 2007
- Passive labeling revision: #12 2015

Added: Black box warning on hepatotoxicity, interstitial lung disease, severe cutaneous reactions
Updated drug labels for 12 targeted agents

All Serious ADRs
N=76

Potentially fatal ADRs
N=38

ADR: Adverse Drug Reaction
Updated drug labels for 12 targeted agents

<table>
<thead>
<tr>
<th>All Serious ADRs</th>
<th>NOT reported in initial drug labels</th>
<th>NOT reported in pivotal RCTs</th>
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</thead>
<tbody>
<tr>
<td>N=76</td>
<td>49%</td>
<td>39%</td>
</tr>
<tr>
<td>Potentially fatal ADRs</td>
<td>58%</td>
<td>39%</td>
</tr>
</tbody>
</table>

ADR: Adverse Drug Reaction; RCT; Randomized Clinical Clinical Trial

Published reports of pivotal RCTs and initial drug labels contain limited information about serious ADRs
Do participants of clinical trials reflect the real-world population of patients?

Anti-Tumour Treatment

Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies


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CrossMark

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COPENHAGEN ESMO 2016
Patients treated with 3-weekly docetaxel (2001-2011) | Routine practice N=314 | Clinical trials N=43 | TAX 327 N=335 | p
---|---|---|---|---
Median # of cycles | 6 | 8 | 9.5 | < 0.001
Median OS (mo) | 13.6 | 20.4 | 19.3 | < 0.001
Febrile neutropenia | 9.6% | 0% | 3% | < 0.001
Death during therapy | 4% | 0% | 3% | ns

A substantial proportion of patients are ineligible for clinical trials and their outcomes are inferior.
Impact of under-reporting of harm in clinical trials

- Patients do not know what symptoms to expect based on prior experience
- Drug developers may have a false impression as to how a drug is tolerated
- Regulators may not have confidence in the fidelity of information about balancing risks and benefits
- Payers cannot accurately predict the utilization of health-care services

Basch et al, JNCI, 2011
What can we do to improve the situation?

• At the level of clinical trials
  - A patient-centered approach to AE reporting in clinical trials: development of the National Cancer Institute‘s Patient Reported version of the CTCAEs (PRO-CTCAE)
  - Presentation of updated reports of clinical trials
  - Conduct of specific trials addressing the unmet needs of protocol ineligible patients

• Post-marketing setting/every-day clinical practice
  - Observational population-based outcomes studies

Basch et al, JNCI, 2014
EFFORT

IT'S USUALLY NOT HARD TO TELL IF IT'S BEEN USED.
Conclusions

- In contemporary clinical trials harm is under-detected and under-reported by investigators
- With a current trend to very restrictive eligibility criteria the application of results of clinical trials to everyday practice is seriously compromised
- Oncologists (and journal editors and societies like ESMO and ASCO) need to introduce measures to ensure complete reporting of toxicity to serve our patients better
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