Assigning Causality to Anti-Cancer Agents: Decision Making in Early Phase Oncology Clinical Trials

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Outline of Presentation

Agenda

Introduction
Objectives
Rationale
Data Collection
Data Explication
Results
Conclusion
<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Maximally Tolerated Dose (MTD) is determined</td>
<td>10-80 participants</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Measure biologic activity &amp; adverse events</td>
<td>50-300 participants</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Evaluate effectiveness of an intervention</td>
<td>100s-1000s of participants</td>
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<tr>
<td>Phase 4</td>
<td>Long term surveillance</td>
<td>Unknown</td>
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Research Objectives

Threefold:

1. Come to a psychosocial understanding of causality assessment
2. Understand the role oncologist and physicians play in this decision making process
3. Understand the challenges faced by professionals when assigning causality
Rationale for this Research
Why is it needed?

- Definition of Harm
- Constraints of Error Reporting Systems
- Time Constraints
- Lack of a Standard Method
- Current Tools for Assessing Causality
- Under-Reporting of Adverse Events
Data Generation
How did we generate the data?

- Mukherjee and colleagues 2010 research paper entitled *A Qualitative Study Evaluating Causality Attribution for Serious Adverse Events During Early Phase Oncology Clinical Trials*
- 32 interviews; 25-50 minutes in length
- Semi-structured interview guide Piloted at the Juravinski Cancer Centre, Hamilton Ontario
# Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 32</th>
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<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Female</td>
<td>16 (50)</td>
</tr>
<tr>
<td>• Male</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Centre, n (%)</td>
<td></td>
</tr>
<tr>
<td>• BC Cancer Research Centre (Vancouver, BC)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>• Juravinski Cancer Centre (Hamilton, ON)</td>
<td>10 (31)</td>
</tr>
<tr>
<td>• London Regional Cancer Centre</td>
<td>5 (16)</td>
</tr>
<tr>
<td>• Ottawa Regional Cancer Centre</td>
<td>9 (28)</td>
</tr>
<tr>
<td>• Kingston Regional Cancer Centre</td>
<td>1 (3)</td>
</tr>
<tr>
<td>• NCIC (Kingston, ON)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Professional Group, n (%)</td>
<td></td>
</tr>
<tr>
<td>• Medical Oncologist/Hematologist</td>
<td>21 (66)</td>
</tr>
<tr>
<td>• Clinical Trial Coordinator (CTC)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Years as a clinical trial researcher (yrs), n (%)</td>
<td></td>
</tr>
<tr>
<td>• &lt; 5</td>
<td>5 (16)</td>
</tr>
<tr>
<td>• 5 – 10</td>
<td>13 (42)</td>
</tr>
<tr>
<td>• &gt; 10</td>
<td>13 (42)</td>
</tr>
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Data Explication
Secondary Data Analysis

1. Phenomenological Reduction
2. Gathering a Sense of the Whole
3. Delineating Meaning Units
4. Clustering Meaning Units and Forming Themes
5. Composite Summary
Themes

Uncertain because there is rarely objectivity

Subjective due to lack of resources

Lack of resources lead to apprehensive behaviour

Apprehensive due to competing goals

Coping with Uncertainty

Consider protocol drug
Consider other drugs
Cognitive approach: consider all variables
Comfort in grey area
Temporal association
Err on the side of caution
Rely on Experience

Subjective Judgments

Variations in experience level
Variations in work ethic
Patient Subjectivity
Lack of a standardized tool

Insufficient Resources

No causality tool
Lack of detail
Communication issues

Apprehensive Causality Attributions

Fear of under attributing causality
Fear of over attributing causality

Competing Goals

Patient safety vs. drug development
Accuracy vs. workload and timelines
Financial Pressures
Patient vs. physician

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Financial Pressures
Patient vs. physician
Insufficient Resources

• No training
  – “There’s no formal training really, you just kind of got thrown into the position.” - S32

• No tool
  – “None. [no] No, well I mean, I guess I shouldn’t say that, none in terms of standardized criteria that’s for sure. Resources, unless you mean basically going back to see maybe the investigator brochure and trying to understand some of the toxicities.” - S13

• Lack of resources
  – “It’s more on a, just based on the experience of taking part in the study and the hunch factor. I don’t actually have a tool that I use, so I think something like this would be very handy.” - S10
Communication Issues

• Between Physicians and Trial Sponsors
  – “Well usually there’s teleconferences and other meetings to discuss what’s happening with other patients. But a lot of times communication isn’t as good as it could be.” - S07

• Coping Strategy: Searching for additional resources online, and by consulting with other physicians.
• Between Physicians and Patients
  - “A lot of the times I find it’s hard and I don’t think it’s an on purpose thing from patients, but I don’t necessarily think that we do get every single bit of information all the time.” - S11

• Coping Strategy: Getting to know their patients. By coming to a better understanding of the patient’s personality and outlook on the trial, both of which are viewed to be very subjective, the physician is better equipped to make more informed decisions when assigning causality. This can also help eliminate the inaccurate representations of adverse events from patients.
Over Attributing Causality

• Fear of making the wrong attribution
  – “If it’s done incorrectly, it’s a pain in the ass for all the trial nurses and all the investigators, all the trial doctors all over the world because it takes time to sort out.” - S03

• Over/Under Reporting Adverse Events
  – I think there’s two big concerns. One is if you assign causality and say it’s related improperly then it might tarnish a good drug and stop dose escalation in a way that wouldn’t be appropriate. Alternatively if you ignore it, it might cause further toxicities in others and be potentially dangerous to other patients. I think it’s a very dangerous thing. I also think that sometimes as oncologists we tend to minimize rather than maximize because we’re used to toxicity with drugs and that can be dangerous. - S16
• Consequences of Over Attributing Causality
  – “...I think one concern is over assigning causality. Because patients are, they can get sick, morbidities, multiple medications, actually a lot of reasons and it sometimes it’s easier to blame it on the drug. But I think my fear is that if you do that liberally you’d be, not discrediting the drug but...it could lead to dose reductions, could eventually work their way into an ineffective treatment schedule for that population...”- S04

• Coping Strategy: Try to better understand the protocol drug and its sister agents in order to better equip themselves to make these important decisions.
Internal Pressures

- Physicians Feeling Pressured by Patients
  - “…But the patients of course feel that they’re on the treatment to help their cancer so there’s a little bit of a disconnect there. So they’re more interested in what the drug is doing for their cancer and they kind of are hunkered down with the idea, many of them are very stoical right they say I’m going to put up with whatever side effects I have to put up with um, to get through this treatment because it’s going to help my cancer…”- S19
  - “….sometimes I will have a patient who is having a serious toxicity and I want to stop the drug and the patient is pressuring me to keep on the drug…. if you are going to keep them on the drug then maybe you have to under report the toxicity.”- S21

- Coping Strategy: Clinicians cope with patient pressures by reassuring themselves that patient safety is their top priority.
Conclusion
Pattern of Main Themes

Identified Grey Area
Potential Consequences
Coping Strategy
The Process of Assigning Causality
Conclusion

Main Findings

- It is very difficult to keep consistency between professionals when there is no universally accepted tool to assign causality.
- Subsequent research could include using the information gathered from this study to design and evaluate a standardized tool that can be used for causality assessment in early phase oncology clinical trials.
- With a deep understanding of the decision making process, the goal of designing a standardized tool is closer to reality.
- Such a tool will aid clinicians in dealing with time constraints without sacrificing the quality of their decision-making.
Conclusion

Future Research

Develop a Training Program

1. Further research direction may include developing a training program for causality assessment in early phase oncology clinical trials.
   - It is hypothesized that the reason for the high utilization of clinical judgment stems from the lack of formal training.
   - Clinical judgment is criticized on aspects of validity primarily because of its low reproducibility rates.
   - If formalized training were introduced, it is hypothesized that this would promote greater consistency when using clinical judgment, and therefore raise reproducibility rates.

Develop Standardized Tool

2. However, if a standardized tool were developed, this could become a standard practice for training.
   - This educational process could also be extended to trial sponsors and be used to help inform patients about how decisions are made.
   - This type of future research could help eliminate error, improve patient safety, narrow communication gaps, promote more confident attributions, and promote consistency amongst professionals.
Acknowledgements

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THANK YOU!

QUESTIONS?

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