Real World Cost-Effectiveness of Cancer Drugs

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CADTH
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Outline

Overview & Objectives

Rituximab Study
- Background
- Cohort Selection
- Survival
- Toxicity
- Costs
- Cost-effectiveness

Conclusion
Background

- Maximizing investment in healthcare involves making good choices about which drugs we choose to fund;

- Ontario’s HTA process for drugs involves careful scrutiny of cancer drugs before they are funded:
  - Pan Canadian Oncology Drug Review
  - Committee to Evaluate Drugs
  - Ministry of Health and Long Term Care (MOHLTC)
Why is this not enough?

- Data required to make confident decisions are typically not available;
- Clinical trials are often conducted in “ideal” scientific settings with subgroups;
- Pharmacoeconomic analyses use models based on assumptions; creating huge uncertainty
Why real-world analysis?

- Accurate information about true healthcare costs and patient outcomes only available after the drug is funded
- “phase-IV”; “post-market evaluation”

- Provide an accurate assessment of value for money and accountability for spending on cancer medicines in Ontario
Our study

- First study in Ontario that evaluates population-based post-market effectiveness and cost-effectiveness of cancer drugs (New Drug Funding Program)

- First study in Canada incorporating recently developed statistical methods for analyzing incomplete costs and cost-effectiveness of cancer treatments
Overall Objectives

- To determine whether it is feasible to conduct post-market evaluation of cancer drugs using Ontario’s administrative databases.

- To establish a robust template that links datasets across the province, applies rigorous methods for analyzing costs and cost-effectiveness and generates outcomes.

- To compare survival benefits and costs from the real-world to what is being reported in RCTs and economic models.
How is this done?

- Chose 5 cancer drugs (6 indications) based on policy-relevance and data availability
- Linked administrative data from Cancer Care Ontario and Institute for Clinical Evaluative Sciences (ICES)
- Worked closely with clinical and method experts to develop analytical framework

Population-based retrospective analysis of cancer drugs

Patterns of Care:
Who used these drugs and how?

Clinical Outcomes:
Did the drugs improve survival?
Were they safe?

Real World Outcomes

Direct Costs:
How much did Ontario spend?

Cost-effectiveness:
What was the real added value for each extra dollar spent?
Cancer drugs of interest

- Rituximab for diffuse-large-B-cell lymphoma
- Oxaliplatin for metastatic colorectal cancer
- Bortezomib for relapsed multiple myeloma
- Rituximab for follicular lymphoma
- Trastuzumab for breast cancer
- Docetaxel for hormone refractory prostate cancer
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Diffuse-large-B-cell lymphoma

- 3000 new cases of non-Hodgkin lymphoma in Ontario in 2010
- 1300 deaths attributed to the disease
- Diffuse-large-B-cell lymphoma is the most common form, represents approx. 25% of new cases
Evidence around Rituximab

- **Randomized trials**: addition of Rituximab (R) to CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) improved 3 to 5-year survival by 10-13%
  - Very elderly groups (80+) were under-represented or explicitly excluded

- **Published economic evaluations** used RCT results; showed RCHOP to be either a dominant strategy or cost-effective

- **Post-market reports** cited increased rates of complications
  - hepatitis reactivation, interstitial lung disease, bowel perforation or obstruction and progressive multifocal encephalopathy
In Ontario

- Approved for funding via the New Drug Funding Program in Ontario:
  - Jan 10\textsuperscript{th}, 2001 – 60-80 years old
  - April 2\textsuperscript{nd}, 2001 – ≥80 years old
  - July 1\textsuperscript{st}, 2004 – <60 years old

- Based on efficacy results from out-of-province trials and theoretical economic models
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Conclusion
Historical cohort selection

Pre-era CHOP

- <60
- ≥80
- 60-80

Post-era RCHOP

- <60
- ≥80
- 60-80

Jan 1, 1997 to Dec 31, 2007

July 2004

Mar 31, 2009
### Characteristics

**Before matching**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-era CHOP</th>
<th>Post-era RCHOP</th>
<th>Std. diff</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hard-matched on age group</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Propensity score-matched on:</strong></td>
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</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>56.7± 16</td>
<td>65.5 ± 14</td>
<td>0.62</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>1%</td>
<td>&lt;1%</td>
<td>0.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20-59</td>
<td>56%</td>
<td>25%</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>19%</td>
<td>30%</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>20%</td>
<td>33%</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>5%</td>
<td>12%</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>47%</td>
<td>48%</td>
<td>0.01</td>
<td>0.74</td>
</tr>
<tr>
<td>ACG* Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1-3</td>
<td>7%</td>
<td>5%</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>24%</td>
<td>17%</td>
<td>0.18</td>
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<tr>
<td>7-9</td>
<td>28%</td>
<td>31%</td>
<td>0.05</td>
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<tr>
<td>10 +</td>
<td>40%</td>
<td>47%</td>
<td>0.16</td>
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<tr>
<td>Income Quintile</td>
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</tr>
<tr>
<td>1</td>
<td>16%</td>
<td>17%</td>
<td>0.02</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
<td>21%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>19%</td>
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<tr>
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<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0.02</td>
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</tr>
<tr>
<td>Treatment intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>32%</td>
<td>30%</td>
<td>0.04</td>
<td>0.04</td>
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<tr>
<td>High</td>
<td>54%</td>
<td>58%</td>
<td>0.08</td>
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<tr>
<td>Unclassifiable</td>
<td>15%</td>
<td>12%</td>
<td>0.07</td>
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<tr>
<td>Primary Histology Code</td>
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<td></td>
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<tr>
<td>9590</td>
<td>16%</td>
<td>20%</td>
<td>0.11</td>
<td>&lt;.001</td>
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<tr>
<td>9591</td>
<td>3%</td>
<td>3%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>9640</td>
<td>80%</td>
<td>69%</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>9680</td>
<td>2%</td>
<td>9%</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

*ACG – adjusted clinical group scores*
| Characteristics | Before matching | After matching |  |
|-----------------|----------------|----------------|
|                  | Pre-era CHOP | Post-era RCHOP | Std. diff | P value | Pre-era CHOP | Post-era RCHOP | Std. diff | P value |
|                  | N = 1196     | N = 2825       |           |         | N = 1131     | N = 1131       |           |         |
| **Age**         |              |                |           |         |              |                |           |         |
| Mean ± SD       | 56.7±16      | 65.5±14        | 0.62      | <.001   | 57.4±15      | 58.9±15        | 0.03      | 0.47    |
| 0-19            | 1%           | <1%            | 0.09      | <.001   | <1%          | <1%            | 0.00      | 1.00    |
| 20-59           | 56%          | 25%            | 0.67      |         | 54%          | 54%            | 0.00      |         |
| 60-69           | 19%          | 30%            | 0.25      |         | 19%          | 19%            | 0.00      |         |
| 70-79           | 20%          | 33%            | 0.30      |         | 21%          | 21%            | 0.00      |         |
| 80+             | 5%           | 12%            | 0.22      |         | 6%           | 6%             | 0.00      |         |
| **Female**      |              |                |           |         |              |                |           |         |
|                 | 47%          | 48%            | 0.01      | 0.74    | 47%          | 47%            | 0.00      | 0.93    |
| **ACG Group**   |              |                |           |         |              |                |           |         |
| 0               | <1%          | <1%            | 0.09      | <.001   | <1%          | <1%            | 0.02      | 0.56    |
| 1-3             | 7%           | 5%             | 0.10      |         | 7%           | 7%             | 0.01      |         |
| 4-6             | 24%          | 17%            | 0.18      |         | 23%          | 23%            | 0.00      |         |
| 7-9             | 28%          | 31%            | 0.05      |         | 29%          | 31%            | 0.06      |         |
| 10+             | 40%          | 47%            | 0.16      |         | 41%          | 38%            | 0.06      |         |
| **Income Quintile** |            |                |           |         |              |                |           |         |
| 1               | 16%          | 17%            | 0.02      | 0.18    | 16%          | 15%            | 0.03      | 0.91    |
| 2               | 20%          | 21%            | 0.02      |         | 20%          | 20%            | 0.02      |         |
| 3               | 20%          | 19%            | 0.02      |         | 20%          | 21%            | 0.01      |         |
| 4               | 24%          | 21%            | 0.08      |         | 23%          | 24%            | 0.02      |         |
| 5               | 20%          | 22%            | 0.06      |         | 20%          | 20%            | 0.01      |         |
| missing         | <1%          | <1%            | 0.02      |         | <1%          | <1%            | 0.03      |         |
| **Treatment intensity** |            |                |           |         |              |                |           |         |
| Low             | 32%          | 30%            | 0.04      | 0.04    | 31%          | 32%            | 0.03      | 0.16    |
| High            | 54%          | 58%            | 0.08      |         | 55%          | 56%            | 0.03      |         |
| Unclassifiable  | 15%          | 12%            | 0.07      |         | 15%          | 12%            | 0.08      |         |
| **Primary Histology Code** |           |                |           |         |              |                |           |         |
| 9590            | 16%          | 20%            | 0.11      | <.001   | 16%          | 17%            | 0.02      | 0.77    |
| 9591            | 3%           | 3%             | 0.02      |         | 3%           | 2%             | 0.04      |         |
| 9640            | 80%          | 69%            | 0.25      |         | 79%          | 79%            | 0.01      |         |
| 9680            | 2%           | 9%             | 0.29      |         | 2%           | 2%             | 0.00      |         |
Outline

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- Toxicity
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- Cost-effectiveness

Conclusion
Kaplan-Meier Survival Curves

(a) Survival Curves before matching

- Pre-era CHOP
- Post-era RCHOP

3-year: 4%↑
5-year: 3%↑

(b) Survival Curves after matching

- Pre-era CHOP
- Post-era RCHOP

3-year: 10%↑
5-year: 8%↑

p<0.001
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Conclusion
## Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Pre-era CHOP</th>
<th>Post-era RCHOP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1131</td>
<td>N = 1131</td>
<td></td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>23%</td>
<td>25%</td>
<td>0.15</td>
</tr>
<tr>
<td>Hepatitis Reactivation</td>
<td>&lt;0.5%</td>
<td>0.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatitis B Reactivation</td>
<td>&lt;0.5%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Hepatitis C Reactivation</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>HIV</td>
<td>0.9%</td>
<td>&lt;0.5%</td>
<td>0.18</td>
</tr>
<tr>
<td>Other Infections</td>
<td>3%</td>
<td>4%</td>
<td>0.36</td>
</tr>
<tr>
<td>CHF</td>
<td>1%</td>
<td>0.9%</td>
<td>1.00</td>
</tr>
<tr>
<td>Angina</td>
<td>&lt;0.5%</td>
<td>1%</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1%</td>
<td>0.9%</td>
<td>0.68</td>
</tr>
<tr>
<td>Dementia</td>
<td>&lt;0.5%</td>
<td>&lt;0.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>Progressive Multifocal Encephalopathy</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>&lt;0.5%</td>
<td>0.8%</td>
<td>0.15</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3%</td>
<td>3%</td>
<td>0.72</td>
</tr>
<tr>
<td>Intestinal Problems</td>
<td>2%</td>
<td>2%</td>
<td>0.87</td>
</tr>
<tr>
<td>Mucocutaneous Reactions</td>
<td>&lt;0.5%</td>
<td>&lt;0.5%</td>
<td>0.69</td>
</tr>
<tr>
<td>Hospitalization within one year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at least one hospitalization</td>
<td>68%</td>
<td>61%</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean SD</td>
<td>3.7</td>
<td>3.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>
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Rituximab Study
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Conclusion
Cost analysis

- Cost components
- Adjusting for censoring
- Fixed time-frames: 3-year and 5-year
- Effect of discounting
Costing Components

- Hospitalization
- Outpatient laboratory/Imaging Services
- Physician Services
- Emergency Room Visits/Same Day Surgery
- Prescription Drugs (≥65 or low income group)
- Chemotherapy (Physician & drug costs)
- Radiation Treatment
- Home Care Services
- Complex Continuing Care
Estimating mean cost by adjusting for censoring

- Complete cost data not available
  - Not enough observation time – “censoring”

- Severely biased estimates can arise without appropriately adjusting for censoring

- A number of methods have been proposed
Estimating mean cost by adjusting for censoring

- Lin’s Kaplan-Meier sample average (KMSA) estimator (1997)

\[
\hat{\mu}_{KMSA} = \sum_{j=1}^{K+1} \hat{S}_j \hat{E}_j
\]

- Bang and Tsiatis’ estimator (2000)

\[
\hat{\mu}_{Bang} = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{K} \frac{\Delta_i^j M_{ij}}{\hat{R}_j}
\]

- Basu’s two-part estimator (2010)

\[
\hat{\mu}_{Basu} = \sum_{j=1}^{K} \hat{S}_j \left[ \hat{h}_j \hat{E}_j^{dead} + (1 - \hat{h}_j) \hat{E}_j^{alive} \right]
\]
Adjusted 5-year costs

Total healthcare cost (CAD$)

Treatment

CHOP

RCHOP

Unadjusted
Bang
Lin
Basu

5-year costs

$90,000
$85,000
$80,000
$75,000
$70,000
$65,000
$60,000
$55,000
$50,000

$71,639
$71,640
$71,640

$79,668
$88,536
$88,536

$71,640
$71,640
$71,640

$79,668
$88,536
$88,536

$88,536
$88,536
$88,536
Cost drivers
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Conclusion
# Incremental Cost-effectiveness Ratios

<table>
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<tr>
<th></th>
<th>no discounting</th>
<th>3% discounted</th>
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<tbody>
<tr>
<td></td>
<td>Censor</td>
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<tr>
<td></td>
<td>adjusted</td>
<td>adjusted</td>
</tr>
<tr>
<td></td>
<td>incremental</td>
<td>incremental</td>
</tr>
<tr>
<td></td>
<td>cost (CAD$)</td>
<td>survival (Years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3 year</td>
<td>14,923</td>
<td>0.16</td>
</tr>
<tr>
<td>5 year</td>
<td>16,896</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Scatter Plot from Bootstrapping

ICER $96,764/LYG
(95%CI: 36,667; 139,273)

ICER $51,687/LYG
(95%CI: 19,769; 59,738)
Cost-effectiveness acceptability curve

Bootstrap ICERs vs WTP

Percentage

Willingness-to-pay ($/LYG)

0 50000 100000 150000 200000 250000

23% 92% 99.7% 91%

3 Year 5 Year

Pharmacoeconomics Research Unit
RESEARCH. DECISION SUPPORT. KNOWLEDGE TRANSLATION. CAPACITY BUILDING

Canadian Centre for Applied Research in Cancer Control
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  • Cost-effectiveness

Conclusion
How do we compare?

2-year Absolute Survival Benefit

- Our study: 8
- Europe GELA Trial: 13
- BC observational study: 26
How do we compare?

5-yr Incremental Cost

- **Our study**: $16,785
- **US model**: $12,740
- **BC microsimulation**: $7,900-9,700

Cost ($)
Overall Conclusions

- It is feasible to perform real-world cost-effectiveness analysis with Ontario’s administrative data.
- Cost-effectiveness results in a real-world analysis differ from those from clinical trials and economic models.
- Decision-makers should be cautious about conclusions from results of trials/models.
Key findings

- Using appropriate methods to adjust for confounding variables is important

- Adjusting for incomplete cost data is essential

- Selection of timeframe has a big effect of cost-effectiveness results
  - “coverage with evidence”
  - “only in research”
Future steps & recommendations

- Compare results to Canadian economic models submitted to the Ministry of Health by the drug company
  - Help evaluate assumptions made in original model and improve methods used

- Post-market analyses be incorporated in the standard evaluation of funded cancer drugs
  - As a decision tool to help calibrate policies (re-evaluate/ calibrate decisions)
  - As a foundation for accountability and sustainability
Thank you

Contact us:

Sara Khor
Email: sara.khor@cancercare.on.ca

Websites:
http://healtheconomics.utoronto.ca
http://www.cc-arcc.ca
Limitations

- Data availability – relying on existing administrative databases (completeness, data variables)

- Historical cohort design – temporal changes over time might not be adjusted for

- Missing quality of life information