Automated Synthesis and Visualization of a Chemotherapy Treatment Regimen Network

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Background and Motivation

- Most cancer contexts have multiple treatment options.
  - E.g. 20+ NCCN® recommended regimens for adjuvant treatment of breast cancer
- Few direct comparisons.
- Thus, guidelines are usually derived by expert opinion.
- Guidelines outdate rapidly.

NCCN: National Comprehensive Cancer Network
Network Meta-Analysis

- A variety of methods to quantitatively compare multiple treatment options
- Methodology is still evolving in this area
- We proposed to investigate:
  - Visualization of chemotherapy regimens (vertices) including summary efficacy
  - Visualization of relationships between regimens (edges), including quality of comparisons
  - Automated network layout for readability

http://www.bmj.com/content/342/bmj.d1199
Leveraging Network Attributes

- Layout
- Vertex size, color
- Edge color, width, duplication
- Transparency

versus
Vertex Attributes

• Size: proportionate to N enrolled
• Color: gradated tri-color schema
  - Inferior treatment regimen
  - Regimen of equivocal value
  - Superior treatment regimen
• Transparency: dynamic “aging” effect
  - Assigned initial alpha of 1.0 and decayed by 0.1/year to a minimum of 0.2
  - Refreshed to 1.0 if/when new RCT uses regimen
Vertex Coloration

– Calculated by a “contest” between regimens:
  
  • Win \((E = 1)\): superiority, as defined by an improved outcome with p-value \(\leq 0.05\)
  
  • Lose \((E = -1)\): inferiority, as defined by an inferior outcome with p-value \(\leq 0.05\)
  
  • Tie \((E = 0)\): either an outcome with a non-significant p-value or an equivalent outcome as defined by formal non-inferiority, with p-value \(\leq 0.05\)

\[
\hat{v}_n = \sum_{y=1}^{m} \frac{RV_y \times E_y}{m} \times \log(N_G[v_n])
\]
Edge Attributes

• Width: proportionate to # patients compared
• Duplication
• Color
  - Weak surrogate measure (e.g. RR; \( RV = 1 \))
  - Strong surrogate measure (e.g. PFS; \( RV = 1.25 \))
  - Overall survival (\( RV = 1.5 \))
• Transparency: same as for vertices

**PFS:** Progression-free survival  
**RR:** Response rate  
**RV:** Relative value

- Busulfan (BU, N=216) median survival: 45.4 months
- Hydroxyurea (HU, N=225) median survival: 58.2 months

<table>
<thead>
<tr>
<th>Vertex 1</th>
<th>Vertex 2</th>
<th>$E_v$</th>
<th>RV</th>
<th>log($N_G[v_n]$)</th>
<th>$v_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Hydrea</td>
<td>-1 (p=0.008)</td>
<td>1.5</td>
<td>2.64</td>
<td>-3.96</td>
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Node Layout

- Determined by the Kamada-Kawai force-based algorithm.
- Some manual modification to improve readability.
- Layout fixed by final state; historical graphs can be viewed as subsets.

Proof-of-concept

- First-line treatment of chronic myelogenous leukemia (CML)
- Relatively few treatment options, but they have been rigorously tested.
Search Results

- **197** publications identified through PubMed
  - MeSH: Leukemia, Myelogenous, Chronic, BCR-ABL Positive
  - Publication Type: Randomized Controlled Trial
- **24** RCTs were identified between 1968-2012
- **17** unique regimens

**MeSH:** Medical subject headings

**RCT:** Randomized controlled trial
Temporal Growth of Patients Enrolled, Vertices and Edges

Cumulative enrolled patients: 9700
Cumulative vertices: 17
Cumulative edges: 40
Conclusions

• Network meta-analysis demonstrates the dynamic evolution of treatment regimen evidence for untreated CML.
• Over time, the quality of RCT evidence degrades as surrogate outcomes are substituted.
• Older regimens, e.g. IFNA-LoDAC, may retain usefulness.
• These findings are in close parallel to the NCCN Guidelines ®.
Limitations and Future Directions

• Some manual curation remains necessary
• Non-randomized information is omitted
  – Phase I, I/II, and II studies
  – Single arm and CER analyses
• Toxicity and cost information missing
  – **Toxicity:** can sometimes trump efficacy with chemotherapy regimens
  – **Monetary Cost:** newer regimens often costs a great deal more for various reasons.
  – **Non-monetary cost:** e.g. infusion room time

**CER:** Comparative effectiveness research
Example: Toxicity vs. Efficacy

ACVBP-R

ACVBP-R: Adriamycin, Cyclophosphamide, Vindesine, Bleomycin, Prednisone, Rituximab

Synonyms: R-ACVBP

Structured Concept: none

Level of Evidence: Phase III, Improved OS, Increased toxicity

Induction Regimen

3-year OS 92% (ACVBP-R) vs. 84% (R-CHOP)

- Cyclophosphamide (Cytoxan) 1200 mg/m2 IV on day 1
- Doxorubicin (Adriamycin) 75 mg/m2 IV on day 1
- Vindesine (Eldisine) 2 mg/m2 IV on days 1 & 5
- Bleomycin (Blenoxane) 10 units IV on days 1 & 5
- Prednisone (Sterapred) 60 mg/m2 PO on days 1-5
- Rituximab (Rituxan) 375 mg/m2 IV on day 1
- Methotrexate (MTX) 15 mg intrathecal on day 1 for CNS prophylaxis

14-day cycles x 4 cycles

Supportive medications:
- Filgrastim (Neupogen) 300 mcg (for patients <75 kg) or 480 mcg (for patients at least 75 kg) SC daily on days 6-13

“Grade 3–4 haematological toxic effects were more common in the R-ACVBP group, with a higher proportion of patients experiencing a febrile neutropenic episode (38% [75 of 196] vs 9% [16 of 183])”

Value Equation

\[
Value = \frac{Benefits \ (Efficacy)}{Harms \ (Costs, Toxicities)}
\]

• **Challenge:** Incorporate these multiple dimensions into a coherent visualization
QUESTIONS?