Focusing on clinical results

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Disclosures 01/01/14-11/11/16: DJ Stewart

- Consulting/Advisory Boards:
  - Roche Canada 2014, 2016
  - Pfizer Canada 2014
  - Boehringer Ingelheim Canada 2015
  - Amgen/Amgen Canada 2014
  - Novartis Canada 2015
- Speaker:
  - Pfizer Canada 2015
- Scientific writing support (review on angiogenesis): Boehringer Ingelheim 2015
- Clinical trials support:
  - Boehringer Ingelheim
  - AstraZeneca
  - Novartis
  - Bristol-Myers Squibb
  - Celgene
Message # 1

Delays in regulatory approval of effective new therapies come at a very high cost
Improvement (years) in median survival vs control arm

Median survival improvement (years)

Median (range) improvement in median survival:
0.31 (0.12-1.31) years

Stewart et al. WCLC 2015
Life-years lost worldwide per year delay in drug approval

Total combined life-years lost / year: 2,541,274
1 for every 12 seconds delay

Stewart et al. WCLC 2015
Years from US patent application to US FDA approval

Median (range) time drug discovery to approval: 12 (6.1-23.3) years

Stewart et al. WCLC 2015
Life-years lost worldwide from patent application to approval

Total combined life-years lost: 31,537,958

Stewart et al. WCLC 2015
Time from drug discovery to approval:

- 1960s: 8 years
- 2000: 12.9 years (61% ↑)
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Caused largely by increasingly stringent regulation for “patient safety”
Message #2

Increasingly stringent clinical research regulation has had minimal impact on cancer patient safety
Toxic death rate on phase I trials: Minimal change despite ↑↑ regulation

<table>
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Increasingly stringent regulation is intended to improve safety

- Average 5,435 patients on all phase I-III studies for approval
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Toxic death rates on phase I trials:
- 1979-1990: 0.8% \downarrow 0.3%
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Stewart et al. WCLC 2015
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- Estimated life-years saved worldwide by enhanced study safety:
  - If median life expectancy = 2 years: 684 life-years saved
  - If median life expectancy = 1 year: 342 life-years saved
342-684 life-years saved by ↓ toxic deaths by ↑ regulation (but >30M lost from delays)

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\[ \text{If median life expectancy} = 2 \text{ years} \quad 684 \]
\[ \text{If median life expectancy} = 1 \text{ year} \quad 342 \]

\[ \text{Lost vs saved} = 50,000 : 1 \]

Stewart et al. WCLC 2015
Message #3

Excessive regulatory stringency markedly increases clinical research costs, and this directly slows progress.
Exploding clinical research costs can markedly slow progress

- Inflation-adjusted annual clinical research cost \( \uparrow \) much faster than inflation
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- Cost/patient on phase III trial ~tripled 2006 to 2013 ($26,000 to $74,800)
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- Massive costs of out-of-control excessive documentation requirements
- Costs (and delays) associated with study review, approval, activation, contract negotiations, etc
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- Progress is greatly slowed
- Translates into very high therapy costs

Average cost of 4 weeks of Rx in Canada

Anticancer agents = 31% of patented drug sales in Canada
Message #4

As a means of protecting patients, current regulatory stringency is not at all cost-effective
Toxic death rate on phase I trials: minimal change despite ↑↑ regulation

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**Costs of compliance with increasing regulatory stringency: $8,000,000 per life-year saved!**

Clinical trials regulations much more costly than most therapies & preventive measures

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<th>Procedure</th>
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<tr>
<td>Clinical trial regulations (2013)*</td>
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<tr>
<td>Hemodialysis</td>
<td>$104,000</td>
</tr>
<tr>
<td>Statins for heart disease</td>
<td>$25,000</td>
</tr>
<tr>
<td>Colonoscopy (colon Ca)</td>
<td>$14,000</td>
</tr>
<tr>
<td>Adjuvant trastuzumab, breast Ca</td>
<td>$20,000</td>
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<tr>
<td>Paclitaxel/cisplatin ovarian Ca</td>
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* Extrapolated from 2007 costs

Message #5: We must tackle the numerous speed bumps on the road to approval of effective new therapies!
There are solutions!

Publications outlining required steps, eg:

- J Clin Oncol 27:328, 2009
- J Clin Oncol 28:2925, 2010
Start by resetting the focus:

_Progress-Centered Regulation for clinical research in lethal diseases!!_
Start by resetting the focus:

Progress-Centered Regulation for clinical research in lethal diseases!!

- Priority: Get effective new drugs to patients:
  - as rapidly as possible
  - as inexpensively as possible
Areas that need to be addressed / opportunities

- Regulatory systems, processes, regulations and regulators for lethal diseases different and separate from those for nonlethal diseases
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• Allow PI latitude for rational protocol overrides without IRB approval
  • Replace tight control of PI decisions with pragmatic accreditation

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- Simplify requirements for use of biomarkers to select trial patients
- Accelerated approval of drugs based on high phase I/II response rates without need for phase III

Accelerated approval / breakthrough drug designation: the goal posts have been moved closer (phase III not required)…..

But the mud between us and the goal posts keeps getting deeper!
Message #6: Aim high, not low: Riveroxaban vs placebo in patients with a recent acute coronary syndrome

Mega, NEJM 366:9, 2012
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Mega, NEJM 366:9, 2012

n = 15,526
Message #6: Aim high, not low: Rivaroxaban vs placebo in patients with a recent acute coronary syndrome

Mega, NEJM 366:9, 2012
Message #6: Aim high, not low

- Large trials:
  - $\rightarrow \uparrow$ statistical power:
    - $\rightarrow$ Permits / encourages detection of small gains
    - $\rightarrow$ Lowers the efficacy bar & slows progress
Why have we gained so little?

“Every system is perfectly designed to get exactly the results it gets!”

-P Batalden, F Davidoff, 2007

We have only gained little since RCTs are often specifically designed to detect small gains
Message #6: Aim high, not low

- Large trials:
  - → ↑ statistical power:
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  - Impede progress:
    - ↑ no. patients needed:
      - → ↑ time required to complete a trial
      - → ↓ patients available to test other new ideas
**Message #6: Aim high, not low**

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  - Impede progress:
    - ↑ no. patients needed:
      - → ↑ time required to complete a trial
      - → ↓ patients available to test other new ideas
    - ↑ Costs:
      - → ↓ resources to test other new ideas
Large trials are primarily about getting marginal drugs approved, **not** about helping patients!
Message #7

- Identify the drug target
- Select patients based on the target
Common cancers are common since they can be caused by many different mutations.

One may need different treatments for each group of patients with cancers caused by different mutations.

- Braiteh & Kurzrock, 2007
Targeted agents work in small subpopulations driven by specific mutations.
Tumor regression in > 90% of patients with target

Vemurafenib in BRAF mutant melanoma

Erlotinib/gefitinib in EGFR mutant NSCLC

Crizotinib in EML4/ALK fusion NSCLC

Crizotinib in ROS1 fusion NSCLC
Gefitinib: much better than chemo in NSCLC patients with an EGFR mutation

T Mok et al, NEJM 2009
Gefitinib:
- much better than chemo in NSCLC patients with an EGFR mutation

-not as good as chemo if there is no mutation

T Mok et al, NEJM 2009
Simulations

- Actual survival in 334 patients as the “control”
- Simulated experimental group:
  - Target present in 10%
  - New agent:
    - Quintuples survival in those with target
    - No effect in those without target
Therapy would be inappropriately abandoned if it hit a target present in only every 10th patient and quintupled their survival.

668 patients “accrued”

HR = 0.85, P = 0.16
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Study costs $50,000,000

Wrong answer: “drug is ineffective”
Tripling patient numbers to 2000 → magic!

↑ statistical power → p < 0.03

- New standard of care
- ASCO plenary / NEJM / promotion / speakers circuit
- Study costs $150,000,000
- We have wrong answer!
- “Drug is effective.”
But if 1\textsuperscript{st} identify target and select patients with target, only need 16 patients
But if 1\textsuperscript{st} identify target and select patients with target, only need 16 patients

- no. patients required $\downarrow$ 99%
- costs $\downarrow$ 98%
Every 12 minutes another person in the Netherlands dies of cancer: ~5 over the past hour (and >700 worldwide)

This is unacceptable!
This is an international problem. We must all work together to fix this!

“It’s not enough that we do our best; sometimes we have to do what’s required.”

- Winston Churchill

Life Saving Therapies Network

www.lifesavingtherapies.com
dstewart@toh.ca