Cost and Cancer Care

Dr. Bruce Hillner

NEWS

When Will the U.S. Flinch at Cancer Drug Prices?

High hopes in cancer research are waning as the cost of drugs that bring new treatments to the marketplace increases. Europe has seen increases of 20 times the average cost of producing drugs through chemical synthesis, while in the U.S. the costs have risen 30-fold. 

Attorneys General are adding to the pressure for lower prices. In 2014, two different attorneys general conducted an investigation into the high cost of cancer drugs. The attorneys general looked into the prices of a combination of drugs used to treat cancer patients with advanced colorectal cancer. The drugs used are expensive, and the combination is not covered by Medicare or Medicaid. The attorneys general found that the prices of these drugs were too high and recommended that the prices be lowered. 

Colon Cancer Leads the Way

Advanced colorectal cancer has experienced a dramatic increase in survival rates over the past decade. In 2004, two different chemotherapy drugs were approved for use in patients with advanced colorectal cancer. These drugs, FOLFIRI and FOLFOX, were found to increase survival rates by 70% over the standard therapy of 5-FU and leucovorin. 

Access to Care

Public hospitals are likely to see a steep rise in drug prices as the U.S. struggles to contain healthcare costs. The American Society of Clinical Oncology has called for a significant reduction in drug prices to make cancer care more affordable for patients. 

“Fast-tracking new drugs is the only way to bring down costs,” said Dr. Hillner. “We need to find better ways to fund cancer research and development.”
### Strong Niche

Spending on specialty pharmaceuticals, in billions:

<table>
<thead>
<tr>
<th>Year</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006*</td>
<td>$68.6</td>
</tr>
<tr>
<td>2004</td>
<td>$41.9</td>
</tr>
<tr>
<td>2003</td>
<td>$32.7</td>
</tr>
</tbody>
</table>

Spending on specialty pharmaceuticals as a percentage of the total pharmaceutical market:

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006*</td>
<td>24.6%</td>
</tr>
<tr>
<td>2004</td>
<td>17.8%</td>
</tr>
<tr>
<td>2003</td>
<td>15.1%</td>
</tr>
</tbody>
</table>

*Projections  
Note: 2005 figures are not available.  
Source: Health Strategies Group

### Background

- I've done $ industry supported retrospective CEAs
- I've done cancer CEAs using foundation $ support
- I've done cancer CEAs with no funding for academic advancement
- I extensively serve as a peer reviewer for CEAs
- I am currently *persona non grata* for doing negative assessments of approved cancer interventions
Nexavar
WSJ 12.20.05

• “The FDA approved the first new drug in more than a decade to treat advanced renal cell CA, the most common type of kidney cancer. The drug Nexavar, made by Bayer and Onyx is designed to block the growth of kidney tumors in a different way than other available treatments. The drug is taken orally. Dr. Pazdur, director of FDA's oncology product office, said the drug is a "major" advance over current treatments. He said the drug doubled a measure known as PFS or the amount of time that patients live without their tumors spreading or growing and that Nexavar was much less toxic than current drugs.”

Nexavar
WSJ 12.20.05

• Nexavar is approved for use as a first line treatment, meaning that patients don't have to try other therapies first.
• Nexavar had an average PFS of about 6 months compared to 3 months for patients not receiving the drug. Most patients in the study had previously been treated with drugs currently used for kidney cancer such as interleukin-2 or interferon-α.
• Studies are ongoing to determine if Nexavar improves overall survival in patients with advanced kidney cancer.”
Nexavar
Forbes 12.21.05

• A Morgan Stanley analyst reiterated an "over weight" rating on Onyx Pharm. after the company announced Tuesday that the U.S. FDA approved Nexavar, the company's kidney cancer drug with collaborator Bayer, and announced higher-than-anticipated pricing on the drug.
• Onyx announced that Nexavar will be priced at $4,333 a month, above the firm's estimate of $3,200 and a Street consensus of $3,000, the analyst said in a report issued Wednesday.

Nexavar (2)
Forbes 12.21.05

• With ~ 2,100 patients currently on the drug, "2006 sales of approximately $35 million are basically in the bag," he said. "We believe the drug should have limited exposure to price sensitivity, since Medicare Part D insulates Medicare patients from the cost of highly expensive drugs," said the research analyst.
• "Private insurers are likely to look favorably on this drug as well, especially when compared to potentially toxic competitors with high treatment-associated costs," he said.
Genentech Sales (1)
WSJ 10.11.05

• “Genentech Inc. rode expanding demand for several new-style cancer treatments to substantial increases in revenue and profit, leading it to boost its full-year per-share earnings forecast for the 2nd quarter in a row.
• 3rd quarter net of $359.4 million, a 56% jump from $230.9 million, in the year-earlier period.
• Revenue rose 46% to $1.75 billion from $1.2 billion.”

Genentech Sales (2)
WSJ 10.11.05

• “Much of the credit for that growth goes to Avastin, which starves tumors by cutting off the growth of new blood vessels. Although Avastin is approved for use only in colon ca, recent trials suggest it is effective against lung and breast tumors.
• Avastin U.S. sales jumped 78% in the quarter to $325.2 M from $183 M a year earlier. 15% of those sales reflect use of the drug outside colon cancer.
• U.S. sales of Herceptin, an older cancer treatment effective against 20-30% of breast
A Randomized Phase III Trial of Paclitaxel Plus Carboplatin with or without Bevacizumab in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer

An Eastern Cooperative Oncology Group Trial E4599

Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, and Johnson DH

Vanderbilt-Ingram Cancer Center, Dana-Farber Cancer Center, Johns Hopkins University, Case-Western Reserve University Hospitals, University of Wisconsin, University of Missouri-Ellis Fischel Cancer Center

Phase III Trial of Bevacizumab in Non-Squamous NSCLC: ECOG 4599

Eligibility:
- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

Stratification Variables:
- RT vs no RT
- Stage IIIB of IV vs recurrent
- Wt loss ≤5% vs ≥5%
- Measurable vs non-measurable

(Po) Paclitaxel 200 mg/m² Carboplatin AUC = 6 (q 3 weeks) x 6 cycles

(PCB) PC x 6 cycles + Bevacizumab (15mg/kg q 3 wks) to PD

No crossover to Bevacizumab permitted
• Bevacizumab improves survival when added to PC chemotherapy in patients with non-squamous NSCLC

• Bevacizumab also improves response rate and progression-free survival

• Bevacizumab is associated with a small increase in serious bleeding, including hemoptysis

### Back of the Envelope
Cost Effectiveness Projection

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 cycles of carboplatin and paclitaxel</td>
<td>$14,073</td>
</tr>
<tr>
<td>6 cycles of carboplatin, paclitaxel and bevacizumab</td>
<td>$88,343 (or $66,270)</td>
</tr>
<tr>
<td>Increase in median survival</td>
<td>2.3 mo.</td>
</tr>
<tr>
<td>Incremental Cost-</td>
<td>$345,000</td>
</tr>
</tbody>
</table>
Tarceva in Pancreatic CA
WSJ 11.2.05

- FDA approved Tarceva to treat patients with advanced pancreatic cancer when used in combination with Gemzar, a chemotherapy drug.
- In a phase III RCT of 569 pts showed that survival was improved by an average of 12.8 days among Tarceva and Gemzar compared with those who received Gemzar alone.
- At 1 yr, 24% of patients were alive in the Tarceva group compared w/ 19% in the Gemzar-only group.

The American Way

- In U.S. costs or CE issues are not formally considered in the regulatory environment.
  - Medicare in its decision making process to approve payment for a new clinical service,
  - the F.D.A. in its approval process, and
  - the N.C.I. in its physician data query of clinical practice guidelines all explicitly do not consider costs.
- No centralized independent assessment agency in the U.S.
Observations

• The majority of clinical economic analysis are sponsored by the pharmaceutical companies.
• Economic analyses types each have their biases
  – Cost-minimization
  – Cost-effectiveness
  – Cost utility
• Good business practice for industry to select studies likely to be advantageous to one’s product
• Desire to adhere to best scientific practice is highly variable

Conflict of Interest: Real or Imagined

• Friedberg et.al. (Northwestern) JAMA 1999
• Sacristan 1997
  – PharmacoEconomics 1988-1994
    • 92% of reports favorable to the drug understudy
    • 83% reports acknowledged drug company support
  – World wide general medical journals
    • 49% studies favorable to drug
    • 74% of these sponsored by government agencies
Should an RCT have an economic analysis?

- Is it a common disease?
- Is the therapy easily transferable to the marketplace and/or does it change current practice?
- Will the therapy supersede, not supplement, other interventions?

Potential Biases in Industry Cancer Economic Analyses

- Who runs the trial?
  - Industry sponsored and conducted
  - Industry sponsored and consortium controlled
    - Models in cardiovascular disease
  - NCI
- Who owns the data?
- Commitment to an economic companion made when?
Retrospective CEAs

• Mix of science and art
• Methodology standards exist, often are cited, and inconsistently followed
• What is the goal?
  – Retrospective analysis of registration trial
  – Retrospective analysis of a selected trial
• Independence in conduct and reporting?

3 Questions

• How can one determine if an industry sponsored CEA is correct since they all are favorable to a specific product?
• Who has any incentive to address a product or a clinical cancer strategy that suggests that it is not CE?
• Is their life for a clinical economist after publishing a negative CE in the U.S.?
Transparency Criteria

Objective
Perspective
Data Sources
Subgroup Data
Uncertainty
  Random events
  Sensitivity analysis
Incremental analysis

Data abstraction
Time Horizon
Costing
Primary outcome
Outcome Scales
Assumptions
Limitations
Potential Bias
Conclusions

Biases in Design

• Clarity of assumptions
• Compare relevant clinical strategies?
• Failure to address random events
• Using average vs. incremental costs
Biases in Reporting

- Confusing society and 3rd party perspective
- Failing to explore effect of uncertainty (95% CI) around efficacy and costs
- Impending assumptions thorough out the report
- Repeating the primary efficacy findings *ad nauseam*

Editors and publication bias

- Only a handful of journals have standards for reviewing CE reports
- Concern that weak work will get published somewhere
- Reports from public agencies often are never submitted for peer review
Dose-Dense therapy

- Give the same drugs
- At the same doses
- For the same number of cycles BUT
- Give them at a shorter-time interval

Two Selected Hillner et.al. Examples

- Adjuvant aromatase inhibitors vs. tamoxifen in early stage post menopausal breast Ca
- FOLFOX vs. IFL in first-line therapy of metastatic colorectal cancer
Aromatase Inhibitors in Early-Stage Disease: the ATAC Trial

**Patients** (N = 9366)
- Postmenopausal
- Completed primary surgery, chemotherapy, radiation therapy
- HR+/- or unknown
- No prior hormonal therapy

R A N D O M I Z E

- Anastrozole 1 mg/day (n = 3125)
- Tamoxifen 20 mg/day (n = 3116)
- Anastrozole 1 mg/day + Tamoxifen 20 mg/day (n = 3125)

Primary endpoint: Disease-free survival
Secondary endpoints: Time to relapse, contralateral breast cancer, time to distant relapse, overall survival, safety

ATAC: Time to Recurrence

- Disease-free survival was significantly improved with anastrozole vs tamoxifen (Hazard ratio, 0.86; \( P = 0.03 \))
- Time to recurrence was significantly improved with anastrozole vs tamoxifen (HR, 0.83; \( P = 0.007 \))
  - In population as a whole and HR+ patients
- Differences increased over time

### ATAC Trial Efficacy: First Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Anastrozole (n = 3125)</th>
<th>Tamoxifen (n = 3116)</th>
<th>Combination (n = 3125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All first events</td>
<td>413</td>
<td>472</td>
<td>488</td>
</tr>
<tr>
<td>Locoregional</td>
<td>84</td>
<td>101</td>
<td>107</td>
</tr>
<tr>
<td>Distant*</td>
<td>195</td>
<td>222</td>
<td>246</td>
</tr>
<tr>
<td>CLBC (invasive)</td>
<td>20</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>CLBC (DCIS)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Deaths w/o recurrence</td>
<td>109</td>
<td>109</td>
<td>100</td>
</tr>
</tbody>
</table>

CLBC = contralateral breast cancer; DCIS = ductal carcinoma in situ.

*First events only.*


### ATAC Trial Results: Safety

- ANA has a favorable safety profile to TAM
  - Less endometrial malignancy
  - Less vaginal bleeding/discharge
  - Less thromboembolic events
  - ? Fewer strokes
  - Less hot flashes
  - BUT more fractures and bone loss
- Fewer women overall stopped therapy due to medication effects

### Results: Breast Cancer Free Survival

**Anastrozole vs. tamoxifen**

<table>
<thead>
<tr>
<th>Yrs since start Rx</th>
<th>Increase in DFS, %</th>
<th>Benefit DFS, days</th>
<th>ICE per DFS ($ / yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.8</td>
<td>14</td>
<td>167,500</td>
</tr>
<tr>
<td>8</td>
<td>3.4</td>
<td>48</td>
<td>60,700</td>
</tr>
<tr>
<td>12</td>
<td>4.1</td>
<td>88</td>
<td>32,800</td>
</tr>
<tr>
<td>20</td>
<td>3.4</td>
<td>161</td>
<td>18,300</td>
</tr>
</tbody>
</table>

Hillner San Antonio Breast Symposium 2003

### Results: Project Survival Benefit

**Anastrozole vs. tamoxifen**

<table>
<thead>
<tr>
<th>Yrs since start Rx</th>
<th>Increase in OS %</th>
<th>Benefit OS, days</th>
<th>ICE per OS ($ / yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.4</td>
<td>2</td>
<td>1.1 million</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>11</td>
<td>235,400</td>
</tr>
<tr>
<td>12</td>
<td>1.6</td>
<td>26</td>
<td>96,000</td>
</tr>
<tr>
<td>20</td>
<td>1.8</td>
<td>60</td>
<td>40,600</td>
</tr>
</tbody>
</table>

Hillner San Antonio Breast Symposium 2003
INTRODUCTION

– In 2000, the bolus regimen of irinotecan plus FU/LV (IFL) was approved as 1st-line therapy for advanced colorectal CA. At that time, the Oncologic Drug Advisory Committee recommended to the FDA that this combination be considered a regulatory standard.

– Intergroup N9741 demonstrated that pts treated with FOLFOX (oxaliplatin and infusional FU/LV) had improved response rates, longer time to disease progression and better overall survival compared to the control regimen of IFL.
INTRODUCTION

– While FOLFOX has rapidly been embraced as a standard of care, the financial implications of its use are substantial.
– A strong case for a CEA can be made based on the price difference between oxaliplatin and irinotecan and the need to change from bolus to infusional FU/LV.

DESIGN

• Markov model simulation of the observations and consequences of care
• Metastatic Colorectal Ca patients eligible for 1st-line chemotherapy with FOLFOX or IFL.
• The probabilities derived from N9741
  – Actual dosages and toxicity rates
  – Observed and protected rates of 2nd-line chemotherapy
  – Updated 3-year overall and progression free survival
## Probability of Clinical Events - IFL

<table>
<thead>
<tr>
<th>Event</th>
<th>FOLFOX</th>
<th>IFL</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Well to Progression</td>
<td>3.1 x 10^{-3}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Progression to Death</td>
<td>4.1 x 10^{-3}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Toxic Death in First 60 days</td>
<td>8.5 x 10^{-4}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Relative Risk Reduction

<table>
<thead>
<tr>
<th>Event</th>
<th>Initial Therapy to Progression</th>
<th>Progression to Death</th>
<th>Toxic Deaths in first 60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.74</td>
<td>1.00</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.83</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.61-0.89</td>
<td>0.83-1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.55-1.0</td>
</tr>
</tbody>
</table>

## Delays or deferral in 1st-line treatment if progression free

<table>
<thead>
<tr>
<th>Duration</th>
<th>FOLFOX</th>
<th>IFL</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 2 to 6 months</td>
<td>77%</td>
<td>85%</td>
<td>77-100%</td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>50%</td>
<td>50%</td>
<td>50-100%</td>
</tr>
<tr>
<td>12.0 to 17.9 months</td>
<td>15%</td>
<td>25%</td>
<td>0-100%</td>
</tr>
<tr>
<td>&gt; 18 months</td>
<td>1%</td>
<td>1%</td>
<td>0-100%</td>
</tr>
</tbody>
</table>

## Semi-permanent venous access prior to treatment

<table>
<thead>
<tr>
<th>Access</th>
<th>FOLFOX</th>
<th>IFL</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>30%</td>
<td>0-100%</td>
</tr>
</tbody>
</table>

## Costs per uncomplicated 6-wk interval

<table>
<thead>
<tr>
<th>Costs per uncomplicated 6-week interval*</th>
<th>FOLFOX</th>
<th>IFL</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation and laboratory</td>
<td>$389</td>
<td>$350</td>
<td>11%</td>
</tr>
<tr>
<td>Oxaliplatin or Irinotecan</td>
<td>$7,605</td>
<td>$4,687</td>
<td>62%</td>
</tr>
<tr>
<td>5-FU, leucovorin, and anti-emetics</td>
<td>$588</td>
<td>$548</td>
<td>7%</td>
</tr>
<tr>
<td>Chemotherapy delivery</td>
<td>$3,855</td>
<td>$1,680</td>
<td>229%</td>
</tr>
<tr>
<td>Office based administration</td>
<td>($2,178)</td>
<td>($1,680)</td>
<td></td>
</tr>
<tr>
<td>Infusion pump rental and management</td>
<td>($1,677)</td>
<td>($0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$12,437</td>
<td>$7,265</td>
<td>71%</td>
</tr>
</tbody>
</table>
# ICE per Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Benefit</th>
<th>Incremental Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>0.37 yrs (4.4 mo.)</td>
<td>$80,400 per LY</td>
</tr>
<tr>
<td>QALYS</td>
<td>0.26 yrs (3.1 mo.)</td>
<td>$111,890 per QALY</td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td>0.27 yrs (3.2 mo.)</td>
<td>$89,080 per PFS year</td>
</tr>
</tbody>
</table>

# Sensitivity Analyses

<table>
<thead>
<tr>
<th>Alternative Assumption</th>
<th>Benefit, LY</th>
<th>ICE ($/LY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk FOLFOX 0.61</td>
<td>0.54</td>
<td>59,250</td>
</tr>
<tr>
<td>Relative risk FOLFOX 0.89</td>
<td>0.22</td>
<td>121,220</td>
</tr>
<tr>
<td>100% Treatment delivered if PFS for first 12 mo.</td>
<td>0.37</td>
<td>118,000</td>
</tr>
<tr>
<td>100% Treated if PFS indefinitely</td>
<td>0.37</td>
<td>222,200</td>
</tr>
</tbody>
</table>
Ladder of Treatment and Incremental CEs

- Ideally, benefits and costs of new therapies should be sequentially compared as a menu or ladder of interventions ranging
  - Best supportive care
  - Single agent FU/LV or capecitabine
  - Doublets or triplets of cytotoxic regimens like FOLFOX and IFL
  - Add monoclonal antibodies such as bevacizumab and cetuximab.

Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs and Schedule of Administration</th>
<th>Drug Costs $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil and oxaliplatin</td>
<td>Weekly bolus of fluorouracil plus oxaliplatin</td>
<td>9,497</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>Weekly bolus of fluorouracil plus irinotecan</td>
<td>9,539</td>
</tr>
<tr>
<td>FOLFOX + bevacizumab</td>
<td>FOLFOX with biweekly bevacizumab</td>
<td>21,399</td>
</tr>
<tr>
<td>FOLFOX + cetuximab</td>
<td>FOLFOX with biweekly cetuximab</td>
<td>22,833</td>
</tr>
<tr>
<td>Irinotecan + bevacizumab</td>
<td>Irinotecan plus bevacizumab</td>
<td>21,399</td>
</tr>
<tr>
<td>Irinotecan + cetuximab</td>
<td>Irinotecan plus cetuximab</td>
<td>28,798</td>
</tr>
<tr>
<td>FOLFOX + oxaliplatin</td>
<td>FOLFOX with oxaliplatin</td>
<td>11,819</td>
</tr>
</tbody>
</table>

*Costs represent 95 percent of the average wholesale price in May 2004.*

Conclusion

• The pricing of new oncology therapies in the U.S. has been minimally influenced by societal needs for making rational allocation of limited resources (cost-effectiveness concerns).
• If or when, the public will ever begin to push back against the costs of innovative therapy is one of the great challenges in oncology