Pharmacoeconomics of HCT

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Disclosures

- Received consulting fees from Jazz and Juno
- Received fees for Non-CPE services from Amgen
Learning Objectives

- Identify challenges associated with oral anticancer medications (OAM) in hematopoietic cell transplant (HCT) recipients
- Describe the potential role of biosimilars in HCT
- Elucidate possible cost-effective strategies pertaining to stem cell mobilization
- Review the pharmacoeconomics of antifungal use in HCT
Annual Number of HCT in the U.S.

Components of HCT costs

- Initial hospitalization for HCT
  - Autologous HCT: $36,000-$88,000
  - Allogeneic HCT: $96,000-$204,000

- Post-HCT complications

- Indirect costs

- Drugs

Rapid increase in new OAM

Rapid increase in the cost of new (and old) OAM

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2015

Year of FDA Approval

Median Monthly Price (per 5 year period)

Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center
Select high cost oral medications in HCT

- Maintenance therapy
  - AML – sorafenib
  - MM - lenalidomide, thalidomide
  - CML/Ph+ ALL – BCR-ABL TKIs

- Immunosuppressants
  - Tacrolimus, cyclosporine, mycophenolate mofetil, sirolimus, ruxolitinib

- Anti-infective prophylaxis
  - Azole antifungals, antivirals
Challenges associated with OAM

- **Cost**
  - Target populations
  - Cost of drug development
  - Complex delivery systems

- **Access**

- **Safety monitoring**

- **Adherence**

- **Patient counseling**

Spending and use of OAM in the U.S.

Data from IMS Health’s National Sales Perspectives
Consequences of financial toxicity

- Bankruptcy is an independent risk factor for mortality in cancer patients

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>No. at Risk</th>
<th>No. of Deaths</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>17,021</td>
<td>2,026</td>
<td>1.79</td>
<td>1.64 to 1.96</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Breast</td>
<td>3,788</td>
<td>280</td>
<td>1.48</td>
<td>1.15 to 1.91</td>
<td>.003</td>
</tr>
<tr>
<td>Lung</td>
<td>958</td>
<td>350</td>
<td>1.55</td>
<td>1.22 to 1.98</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1,197</td>
<td>51</td>
<td>1.50</td>
<td>0.83 to 2.72</td>
<td>.179</td>
</tr>
<tr>
<td>Thyroid</td>
<td>952</td>
<td>23</td>
<td>1.71</td>
<td>0.69 to 4.27</td>
<td>.249</td>
</tr>
<tr>
<td>Prostate</td>
<td>2,365</td>
<td>214</td>
<td>2.07</td>
<td>1.56 to 2.74</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
<td>1,792</td>
<td>254</td>
<td>1.22</td>
<td>0.93 to 1.61</td>
<td>.146</td>
</tr>
<tr>
<td>Uterine</td>
<td>739</td>
<td>42</td>
<td>1.09</td>
<td>0.55 to 2.16</td>
<td>.795</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1,430</td>
<td>217</td>
<td>2.47</td>
<td>1.85 to 3.31</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Other</td>
<td>3,800</td>
<td>595</td>
<td>1.49</td>
<td>1.25 to 1.78</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Table 3. Bankruptcy Impact on All-Cause Mortality in the Propensity Score Matched Sample

Abbreviation: HR, hazard ratio.

High cost sharing leads to reduced initiation of TKIs in CML patients

- Medicare Part D patients face high cost sharing

- 25-33% coinsurance (initial coverage phase) → 50% coinsurance (coverage gap phase) → 5% coinsurance

- Retrospective claims-based analysis using 100% Medicare claims between 2011-2013 in patients covered by Medicare Part D

Suggestions to reduce high cost sharing

- Reducing beneficiary cost-sharing responsibility for drugs that have demonstrated higher efficacy and value
- Establishing an out-of-pocket spending maximum similar to many private insurance plans
- Allowing beneficiaries to distribute total out-of-pocket costs more evenly throughout the year

Significant delays in starting OAM is common

- Retrospective study of 166 prostate and renal cell carcinoma patients prescribed on-label OAM at an academic medical center
  - Average days from time prescription written to initiation of therapy – 14 days
  - Prescriptions requiring 2 – 4 calls by staff to obtain drug – 49/149 (33%)
  - Prescriptions requiring 5 – 8 calls by staff to obtain drug – 15/149 (10%)
  - Prior authorization as main reason for calls – 36/149 (24%)

- The gatekeeper” - specialty pharmacies

- How can we extrapolate these data to the HCT setting?

Strategies to overcome barriers associated with OAM

- Internal specialty pharmacy
- Oral parity
Potential benefits of a specialty pharmacy within a medical center

- Revenue
- Benefits investigation
- Prior authorization assistance
- Enrollment in patient assistance programs
- Face-to-face communication
- Adherence monitoring
- Patient counseling
- Drug interaction review
- Humanistic benefit

MyPennPharmacy – Penn Specialty Pharmacy Services

- Benefits Investigation
- Prior Authorization
- Copay Assistance
- Adherence Monitoring
- Medication Therapy Management
- Outcomes Reporting
One year of data summarizing specialty pharmacy activities (11/1/15 – 10/31/16)

- Prior authorizations submitted: 1,500
- PAs Approved: 84%
- PA Turnaround Time: 2.2 days
- Copay Assistance Dollars Obtained: $415,000
- Technician deliveries: 1,700
- Medication possession ratio* (%): 92%

*A ratio of missed doses divided by days of supply based upon fill dates
Oral parity

- Parenteral chemotherapy is billed under the medical plan whereas OAMs are billed under prescription benefit plan

- Implications
  - Out-of-pocket burden
  - Medication adherence and persistence

- Status of current legislation

- Limitation – only impacts patients with private insurance plans

Biosimilars – the complexity of reproducing biologics

- Approximate copies of branded biologic therapies

- Biologics are inherently variable complex molecules
  - Manufacturing process in living cells
  - Cannot be duplicated identically

Process of small molecule synthesis

Benzene $\xrightarrow{\text{H}_2\text{SO}_4}$ Benzene $\text{SO}_3\text{H}$ $\xrightarrow{\text{NaOH}}$ Sodium phenolate $\text{CO}_2, \text{H}_2\text{O}$ $\xrightarrow{\text{Kolbe-Schmidt reaction}}$ Salicylic acid $\xrightarrow{\text{Acetic anhydride}}$ Aspirin
Process of biologics manufacturing

FDA regulatory requirements for biosimilars

- **Definition**
  - Biological product is highly similar to the reference product not withstanding minor differences in clinically inactive components
  - There are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, potency

- **Approval is granted based on “totality of evidence”**
  - Structure, function, animal toxicity, human PK/PD, clinical immunogenicity, clinical safety, efficacy

Potential benefits and concerns of biosimilars

- **Benefits**
  - Cost savings
  - Increased access

- **Concerns**
  - Extrapolation of indications
    - Can extrapolation of biosimilar approval for all the clinical indications of the reference product be justified based on protein structure in the absence of clinical data?
  - Potential for immunogenicity
  - Lot-to-lot variations
  - Pharmacovigilance
The role of G-CSF in HCT

- Stem cell mobilization
- Neutropenic fever prophylaxis and neutrophil recovery post HCT
G-CSF biosimilar post allogeneic HCT

- Case-control study

- 43 consecutive adult allogeneic HCT recipients received either Tevagrastim (n=23) or Zarxio (n=20) starting day +7 after MRD/MUD or day +6 after haploidentical HCT

- No difference in hematologic recovery, infections, graft failure, 6-month relapse, death

- No difference in acute GVHD

- Total cost per patient €1164.94 vs. €778.55

Mobilization of HPCs from allogeneic donors using G-CSF biosimilar

- Retrospective cohort study
- 36 healthy related donors under PBSCT mobilization received either Neupogen (n=18) or Zarxio (n=18)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neupogen (N=18)</th>
<th>Zarxio (N=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of CD34+ cells collected/kg</td>
<td>8.4x10^6 (5.6-16.6)</td>
<td>6.7x10^6 (3.8-11.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Minimal target cell dose collected (≥2x10^6)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Optimal cell dose collected (≥5x10^6)</td>
<td>83.3%</td>
<td>100%</td>
<td>.23</td>
</tr>
</tbody>
</table>

- No difference in toxicities between the two G-CSF formulations
- No difference in outcomes for HCT recipients

Efficacy of G-CSF biosimilar in PBSCT mobilization in myeloma patients

- Single-center, prospective study

- 40 consecutive *de novo* MM who received cyclophosphamide 4 g/m² + Zarxio to mobilize stem cells compared to a control group of 37 patients who received cyclophosphamide + Neupogen

Results

- No difference in median number of CD34+ cells/kg (11.5 ± 5.8 vs. 12.3 ± 5.3; P=.51)
- No difference in mobilization failure rates (2.5% vs. 2.7%; P=NS)
- No differences in toxicity or post-HCT outcomes

# Biosimilars on the oncology horizon

<table>
<thead>
<tr>
<th>Biosimilar name</th>
<th>Company</th>
<th>Indication</th>
<th>Primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab</strong></td>
<td>Biocad</td>
<td>Indolent NHL</td>
<td>December 2015</td>
</tr>
<tr>
<td></td>
<td>Pfizer</td>
<td>Follicular lymphoma</td>
<td>November 2016</td>
</tr>
<tr>
<td></td>
<td>Amgen</td>
<td>NHL</td>
<td>March 2018</td>
</tr>
<tr>
<td></td>
<td>Sandoz</td>
<td>Follicular lymphoma</td>
<td>December 2017</td>
</tr>
<tr>
<td></td>
<td>Celltrion</td>
<td>Follicular lymphoma</td>
<td>February 2017</td>
</tr>
<tr>
<td></td>
<td>mAbxience</td>
<td>Diffuse large B-cell lymphoma</td>
<td>May 2016</td>
</tr>
<tr>
<td><strong>Trastuzumab</strong></td>
<td>Biocad</td>
<td>HER2+ breast cancer</td>
<td>March 2015</td>
</tr>
<tr>
<td></td>
<td>Pfizer</td>
<td>HER2+ breast cancer</td>
<td>October 2017</td>
</tr>
<tr>
<td></td>
<td>Amgen</td>
<td>HER2+ breast cancer</td>
<td>December 2016</td>
</tr>
<tr>
<td></td>
<td>Celltrion</td>
<td>HER2+ breast cancer</td>
<td>December 2017</td>
</tr>
<tr>
<td></td>
<td>Samsung</td>
<td>HER2+ breast cancer</td>
<td>January 2016</td>
</tr>
<tr>
<td></td>
<td>Bioepis</td>
<td>HER2+ breast cancer</td>
<td>January 2016</td>
</tr>
<tr>
<td></td>
<td>Mylan GmbH</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bevacizumab</strong></td>
<td>Biocad</td>
<td>Non-small cell lung cancer</td>
<td>November 2015</td>
</tr>
<tr>
<td></td>
<td>Pfizer</td>
<td>Non-small cell lung cancer</td>
<td>July 2017</td>
</tr>
<tr>
<td></td>
<td>Amgen</td>
<td>Non-small cell lung cancer</td>
<td>July 2015</td>
</tr>
</tbody>
</table>

Economics of mobilization in autologous HCT

- Costs associated with PBSC mobilization are highly variable
  - $6,000 - $52,000 per patient

- Many components of mobilization cost – drugs, apheresis, storage, hospitalization, complications, readmissions, transportation, lodging, office visit copays, home nursing, catheter care

## PBSC mobilization strategies for autologous HCT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>- Outpatient administration</td>
<td>- Lower CD34+ cell yields vs. combination regimens</td>
</tr>
<tr>
<td></td>
<td>- Low toxicity</td>
<td>- More apheresis sessions</td>
</tr>
<tr>
<td></td>
<td>- Predictable time to peak CD34+ cells</td>
<td>- Lower probability of stem cell products with high CD34+ cell content</td>
</tr>
<tr>
<td></td>
<td>- Predictable timing of apheresis</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>- Higher number of CD34+ cells compared to G-CSF</td>
<td>- Need for inpatient hospitalization</td>
</tr>
<tr>
<td></td>
<td>- Fewer apheresis sessions</td>
<td>- Unpredictable time to peak CD34+ cells</td>
</tr>
<tr>
<td></td>
<td>- Possible antitumor activity</td>
<td>- Unpredictable timing of apheresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Toxicity from chemotherapy</td>
</tr>
<tr>
<td>Plerixafor</td>
<td>- Higher number of CD34+ cells compared to G-CSF alone</td>
<td>- Cost</td>
</tr>
<tr>
<td></td>
<td>- Fewer apheresis sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Predictable time to peak CD34+ cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Stem cell grafts with higher CD34+ cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Higher likelihood of successful mobilization and collection rates</td>
<td></td>
</tr>
</tbody>
</table>

Strategies that may reduce costs associated with mobilization

- **Biosimilars**
  - 2014 ASBMT Guidelines – “larger controlled studies with longer term follow-up are necessary before recommending the use of these agents for mobilization”

- **Chemomobilization**
  - Mobilize after planned cycle of chemotherapy rather than as a stand-alone regimen

- **Plerixafor**
  - ~$8,600 per 24 mg vial (AWP)
  - Up-front vs. “Just-in-time”
  - Dosing in obese patients

### FDA-approved plerixafor dosing schema

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF (10 mcg/kg)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plerixafor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apheresis</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>If required

- Administer G-CSF each morning x 4 days prior to first evening dose of plerixafor and each morning of apheresis
- Administer plerixafor 11 hours prior to each apheresis
  - Dose 0.24 mg/kg
  - May administer for up to 4 consecutive days
  - Recent data suggests administering plerixafor 17 hours prior yields adequate collection

Common scenarios for plerixafor use

- Up-front with G-CSF in patients with high risk for poor mobilization

- “Just-in-time” approach – Pre-emptive rescue of a failing mobilization after a conventional regimen

- Remobilization in patients who have failed prior mobilization attempts

Up-front mobilization with plerixafor + G-CSF

- Retrospective study in 34 MM and lymphoma patients who received plerixafor and G-CSF for initial mobilization
- Compared vs. matched historical control mobilized with Cy/G-CSF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Plerixafor+G-CSF</th>
<th>Cy+G-CSF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD34+ cell collected</td>
<td>10.7x10^6</td>
<td>11.6x10^6</td>
<td>.5</td>
</tr>
<tr>
<td>Minimal target cell dose collected (≥2x10^6)</td>
<td>100%</td>
<td>100%</td>
<td>1</td>
</tr>
<tr>
<td>Optimal target cell dose collected (≥5x10^6)</td>
<td>94%</td>
<td>76%</td>
<td>.04</td>
</tr>
<tr>
<td>Median number of apheresis days</td>
<td>1 (1-4)</td>
<td>1 (1-4)</td>
<td>.45</td>
</tr>
<tr>
<td>Weekend apheresis</td>
<td>0%</td>
<td>48%</td>
<td>≤.0001</td>
</tr>
<tr>
<td>Neutrophil engraftment</td>
<td>12 (9-23)</td>
<td>11 (10-13)</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet engraftment</td>
<td>17 (10-61)</td>
<td>14 (10-67)</td>
<td>NS</td>
</tr>
<tr>
<td>Median total cost of mobilization</td>
<td>$14,224</td>
<td>$18,824</td>
<td>.45</td>
</tr>
</tbody>
</table>

## “Just-in-time” addition of plerixafor

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Criteria for adding plerixafor</th>
<th># of pts requiring plerixafor</th>
<th>Mobilization success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abhyankar, et al.</td>
<td>MM, NHL, HD,</td>
<td>1. Peripheral CD34+ count on day 5 of G-CSF:</td>
<td>55/159 (34.5%)</td>
<td>47/55 (85.5%)</td>
</tr>
<tr>
<td>(N=159)</td>
<td>GCT, ES</td>
<td>• &lt;10 x10^6 cells/L and need ≥ 2.5 x10^6/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;10 x10^6 cells/L but &lt;20 x10^6 cells/L and need ≥5 x10^6/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Day 1 collection product CD34+ count/kg less than half of desired dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vishnu, et al.</td>
<td>MM, NHL</td>
<td>Peripheral CD34+ count &lt;10 x10^6 cells/L after 4 days of G-CSF</td>
<td>24/42 (57.1%)</td>
<td>22/24 (91.7%)</td>
</tr>
<tr>
<td>(N=42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li, et al. (N=188)</td>
<td>MM, NHL, HD</td>
<td>1. Peripheral CD34+ count &lt;15 x10^6/L and WBC &gt;10 x10^9/L after ≥ 5 days of G-CSF</td>
<td>64/188 (36%)</td>
<td>60/64 (93.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Prior failure or predicted failure due to prior therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Just-in-time” plerixafor is more cost efficient

- Retrospective study of 136 MM and lymphoma pts receiving up-front plerixafor + G-CSF vs. G-CSF + just-in-time plerixafor

- 60% of pts in the just-in-time arm required plerixafor

- Mean number of plerixafor doses: 2.2 vs. 1.3; P=.0001

- Mobilization failures: 5.3% vs. 3.3%; P=.06

- Mean total mobilization cost: $27,513.29 vs. $23,596.74; P=.01

Dosing of plerixafor in obese patients

- Dose rounding to vial size?
- Dose capping?
Dose capping as cost-saving measure in stem cell mobilization for autologous HCT?

- Informal survey of 15 BMT centers

- Does your center dose cap for G-CSF?
  - Yes 4/15 (27%)
    - All cap at 1200 mg
    - No 11/15 (73%)

- Does your center dose cap for plerixafor?
  - Yes 10/15 (67%)
    - 6/10 cap at 24 mg
    - 4/10 cap at 40 mg
    - No 5/15 (33%)
Antifungal use in HCT

- Invasive fungal infections (IFIs) are a significant contributor to morbidity and mortality in HCT recipients

- Invasive aspergillosis is the most common followed by candidiasis and mucormycosis

- Mortality rates of invasive aspergillosis up to 60% despite adequate treatment

- Incidence of IFIs steadily increasing

Relative size of target population for antifungal therapy

Prophylaxis

Empiric

Pre-emptive

Targeted

Pharmacoeconomic concerns of IFIs

- Antifungal costs
- Prolonged hospital length of stay
- Long-term treatment
Antifungal strategies that may alleviate cost burden

- Use of fluconazole as primary prophylaxis for related/unrelated donors (BMT CTN 0101)\(^1\)

- Intermittent high-dose micafungin\(^2\)
  - Single center 5-year study of 83 pts with acute leukemia and allogeneic HCT receiving micafungin prophylaxis
  - Dose: micafungin 300 mg three time a week
  - 5/83 (6%) developed breakthrough IFI

- Coupon cards, manufacturer prescription assistance programs

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Overall survival in adult AML patients by year of transplant

SURVIVAL (%) vs MONTHS AFTER TRANSPLANT

- 2012–2014 (n=4035)
- 2008–2011 (n=4036)
- 2003–2007 (n=2740)
- 1987–2002 (n=1858)

SOURCE: CIBMTR®, the research program of NMDP/Be The Match
Conclusion

- Costs of HCT are likely to continue to increase

- Financial burden of HCT for patients is in large part driven by medications

- Identifying novel strategies to help mitigate the financial burden of HCT for patients and healthcare systems remains critical
Acknowledgements

- Donna Capozzi
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