The Cost and Clinical Impact of Drug Shortages

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Objectives

1. Review the causes of drug shortages
2. Evaluate the clinical impact of drug shortages
3. Discuss the financial impact of oncology medication shortages

Disclosure

- I do not intend to discuss an off-label use of a product during this activity.
- I currently have relevant financial relations during the past 12 months to disclose:
  - Commercial Interests in Pharmacyclics

Drug Shortages in the Press
Headlines

• “Genzyme Drug Shortage Leaves Users Feeling Betrayed” - NY Times 3/15/2010 - Production Plant Contamination

• “Teva Propofol Recall Leads to FDA Warning, Drug Shortage”

• “Generic chemotherapy drugs are in particularly tight supply at the nation’s hospitals, including mainstay cancer treatments such as cisplatin, doxorubicin, cytarabine and leucovorin”

• “Dire shortages of two critical cancer drugs — shortfalls that have threatened the lives and care of thousands of patients...Doxil and methotrexate”

National Medication Shortages

Data from University of Utah Drug Information Service

Medication Shortages in 2011

• Total of 267 drug shortages
  - 157 reported in 2009
  - 211 reported in 2010

• Over 77% were parenteral products

• 2011 marked the largest increase in antimicrobial and chemotherapy agent shortages since being reported

Data from University of Utah Drug Information Service
Reasons for Shortages in 2010

- Regulatory 1%
- Raw Materials 3%
- Discontinuation 7%
- Supply Chain 14%
- Manufacturing 28%
- Unknown 47%

Medication Shortages

Listed Drug Shortage in 2010

Data from University of Utah Drug Information Service

Medication Shortages

Number of Reported Drug Shortages

Data from University of Utah Drug Information Service
Reasons for Shortages

- Manufacturing
- Regulation and enforcement
- Distribution and use
- Changes in clinical practice
- Emergency situations
- Global market demand
- Economics
- Unknown

Pharmaceutical Supply Chain

Causes of Shortages

- Raw Materials
  - Sole source
    - Required time to develop or purchase raw materials
    - Often not disclosed to the public
    - Noted as the “greatest vulnerability to our supply”
  - Over 70% of raw materials obtained overseas
  - Few manufacturers for parenteral injections
  - One production line for multiple items
  - Batch failures
Causes of Shortages

• Manufacturer
  – Consolidation of the market
  – Developing business decisions
    • Economic profitability
    • Production quota
    • Source allotments
  – Shutdowns
    • Lead to 45 individual products impacted in 2010
    • Amikacin, Bactrim drug shortages are still unresolved

Causes of Shortages

• Regulatory Issues
  – Develop into immediate shortages
    • Examples: fosphenytoin, propofol, TMP/SMX, cytarabine
  – Q & A measures demanding tighter regulations
  – Unapproved drugs
    • DESI* drugs
  – Develops uncertainty in the market
    • Examples: phenylephrine, thiopental

*Drug Efficacy Study Implementation

Manufacture & Release Timeline
Causes of Shortages

- Regional Variances
  - Wholesaler
  - GPO
  - Patient population/patient characteristics

- Clinical Use
  - Vary, depending on practice setting

- Gray Market

- Stockpiling
  - “Feeling Safe”

Causes of Shortages

- Supply Chain
  - Global market economy
  - Consolidation of companies (brand & generic)
  - Tighter inventories
  - Failure to recapture market share
    - Lack of ability by companies to produce drug at the market demand

Medication Shortages
FDA’s Role in Drug Shortages

• FDA can expedite solutions related to drug shortages (e.g., new manufacturers, increased expiration, increased capacity)
• Develop contracts for temporary importation (e.g., propofol, foscarnet, cytarabine)
• Manufacturing /Quality
• Encourage firms to ramp up production

FDA Identification of Issues

• Notification from firms is important for all shortage issues
• Early notification leads to better chance of timely resolution
  – FDA prevented 195 shortages in 2011
  – Almost 100 shortages during the first half of 2012

Clinical Impact of Drug Shortages
Clinical Impact of Drug Shortages

- Prevent appropriate care for patients
  - Withholding or delay in medical treatments
  - Reduced dose for efficacy with unknown results
  - Lack of guidelines for alternative therapies
- Potential to lead to increase in medication errors
- Clinical trials being delayed or halted due to shortages

Sampling of Chemotherapy /Supportive Medication Shortages

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>Leucovorin</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Mesna</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Methylene Blue</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Doxorubicin, Liposomal Doxorubicin</td>
<td>Sodium thiosulfate</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Thiotaque</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Vinblastine</td>
</tr>
</tbody>
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Clinical Impact of Drug Shortages

- Chemotherapy agents are indicated for a limited number of disease states
- One agent’s loss in supply may effect several different disease states
  - Liposomal doxorubicin (Doxil®) shortage
    - Breast cancer, ovarian cancer, and multiple myeloma
- Lack of clinical studies evaluating comparative efficacy in disease states
Clinical Impact of Drug Shortages

- Drugs in shortages may be rationed to specific patients
  - Ethical decisions on who gets what
- Doses may be reduced for continued therapy
  - Potential for disease relapse
- Alternative therapies may be utilized with little data for efficacy

Clinical Impact of Drug Shortages

Guideline Recommendation

- Lack of guideline references for equivalent therapy
- NCCN has made mention of drugs shortages in its guidelines, but has not created alternative guidelines for comparative use
- Lack of uniformity as to what to do next in oncology
  - AML Consolidation
    - Cytarabine Sensitive Genotypes: Inv(16), t(8;21)?

http://aishealth.com/archive/nspn0312-07

ASHP/ISMP Survey

- In 2010 ASHP/ISMP developed a survey to evaluate the current state of drug shortages
- Focus on issues related to drug shortages and patient safety
- Over 1,800 healthcare practitioners – 68% Pharmacists

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Percent Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No information about duration of shortage</td>
<td>85</td>
</tr>
<tr>
<td>No advanced warning and suggested alternatives</td>
<td>84</td>
</tr>
<tr>
<td>No information about cause of shortage</td>
<td>83</td>
</tr>
<tr>
<td>Substantial resources developing plan of action</td>
<td>82</td>
</tr>
<tr>
<td>Difficulty obtaining suitable alternative</td>
<td>80</td>
</tr>
<tr>
<td>Experience significant financial impact</td>
<td>78</td>
</tr>
<tr>
<td>Lack of suitable alternative product</td>
<td>70</td>
</tr>
<tr>
<td>Substantial resources preparing alternative</td>
<td>69</td>
</tr>
<tr>
<td>Risk of adverse patient outcome</td>
<td>64</td>
</tr>
<tr>
<td>Internal hoarding of product</td>
<td>58</td>
</tr>
</tbody>
</table>

ASHP/ISMP Survey

- Near Misses
  - 35% reported a near miss at their facility due to a drug shortage
  - 20% reported errors associated with the drug shortage
  - 19.2% reported an adverse patient outcome
    - 33% reported by physicians
    - 21% reported by pharmacists
    - 16% reported by nurses
Dosing Errors on the Front Lines

- Chemotherapy
  - Delays in transplants
  - Errors in dosing conversion in patients with IV to oral chemotherapy
  - Changes in chemotherapy among antineoplastic classes
  - Maximum efficacy with minimal dosing

Caveats

- Alternatives to drugs with superior efficacy and/or lower risk profile
  - Propofol
- Alternative medications vulnerable to shortage when supply and demand picks up suddenly
  - HYDROMorphone
  - Bumetanide
- Enhanced risk of errors and/or adverse outcomes
  - Cannot remember all drugs and alternatives, how to safely prescribe, dispense, administer

Caveats

- Drugs with no viable alternatives
  - Foscarnet
  - Amikacin
    - A patient with a pseudomonas infection sensitive only to amikacin died when the drug could not be provided
    - Inability to treat with amikacin in a patient with established resistance caused readmission due to treatment failure with ineffective alternatives
  - Acyclovir
  - Pancreatic Enzymes
Clinical Trials

Clinical Studies
- Trials are being put on hold due to issues with obtaining concomitant medication and continued maintenance therapy
- Studies have been switched to alternative agents, therefore leading to potential bias of outcome data
- Protocols have been closed due to prolonged delays of drug shortages

Financial Impact of Drug Shortages

- Financial consequences of shortages
  - Expends tremendous resources
- Utilizing non-pedigree medications from “Gray Market” Suppliers
- Costly alternative medications for provider and patient
- Additional costs associated with treatment of adverse outcomes
Financial Impact of Drug Shortages

Drug shortages cost U.S. hospitals at least $200 million annually.

- Providers are paying an average of 11 percent more for shortage products.
- Gray Market products are expensive – 10 to 1000 x usual cost.
- Data does not include indirect costs such as added labor needed to manage shortages and secure alternative supplies.

Drug shortage survey

- ASHP/AHA surveyed directors of pharmacy in the United States and its territories.
- Participants were provided with a list of 30 recent drug shortages.

Results

- Overall, 70% of the respondents felt that the information resources available to manage drug shortages were not good.
- The labor costs associated with managing shortages in the United States is an estimated $216 million annually.
- Of these drugs evaluated, only three were oncology drugs (Dacarbazine, Mesna, Idarubicin).
Gray Market

• Companies procure specific medications, stockpile inventory, then offer them to institution at increased markups.
• The average markup on drugs is 650%

Gray Market

Premier analyzed 636 unsolicited sales offers from gray market vendors:
• Average markup was 650%
• Highest markup was more than 4,500%
• 45% were marked up at least 1,000%
• More than 25% were marked up at least 2,000%
Gray Market

“Gray Market” Drug Distribution Shipment
Two Vials of Cytarabine 1gm

Shortage: Heparin 5,000 unit/dose

Shortage Dates: 9/22/09 to 11/20/09

Alternative Agent: Enoxaparin 40 mg

Additional Expenditure: $122,307

Cost of Alternative Therapies

Primary CNS lymphoma
• 3% of all primary brain tumors
• High-grade malignant non-Hodgkin’s B-cell lymphoma in more than 90% of cases
• Treatment regimens vary by physician and patient
  – High-dose methotrexate
  – Whole Brain Radiation Therapy
  – Stem Cell Transplant

Cost of Alternative Therapies

http://www.ichpnet.org/resources/events/AM10/10-049.pdf
Cost of Alternative Therapies

High Dose Methotrexate
- Leucovorin
  * 25 mg q 6 hours (Cost 50mg $20.85*)
  * 3 days leucovorin rescue - Cost $125.10
- Levoleucovorin
  * 7.5 mg q 6 hours (Cost 50mg $176.44*)
  * 3 days leucovorin rescue - Cost $1056.60
  » If delayed elimination, increase to 75 mg q 3 hours
- Carboxypeptidase G2
  * One Dose (Cost Approximately $55,000 (Phase II/III Compassionate Use))

Cost of Alternative Therapies

Colorectal Cancer
- FolFox6 Regimen
  - Leucovorin 400 mg/m² or Levoleucovorin 200 mg/m²
  - Oxaliplatin 100 mg/m² a 2-hour IV infusion
  - Fluorouracil 400 mg/m² as an IV injection
  - Fluorouracil 1200 mg/m²/day as a continuous IV infusion over 23 hours on days 1 and 2
  - Cycle repeated every 2 weeks
  - Infusions centers are not being reimbursed for the added cost of Levoleucovorin

Cost of Alternative Therapies

Colorectal Cancer
- CapeOx Regimen
  Day +1
  - Oxaliplatin 130 mg/m² Day 1
  - Capecitabine 850-1000 mg/m² twice daily PO for 14 days
  - Cycle repeated every three weeks
- Patients unable to afford oral chemotherapy
- Increased side effect profiles with capecitabine
Cost of Alternative Therapies

Testicular Cancer/Germ Cell Tumors

- Bleomycin Containing Regimens were switched to VIP (VP-16, Ifosfamide, Cisplatin)
- Outpatient-based regimens were switched to inpatient
- Overall increased costs to institutions and healthcare for prolonged inpatient stays

Financial Impact of Drug Shortages

- Financial effects of shortages
  - Expends tremendous resources
- Costly alternative medications for provider and patient
- Reimbursement may not be enough for alternative therapies
  - Lack of resources to cover importations costs
- Costs associated with adverse outcomes

Conclusions

- Drug shortages have taken a foothold in oncology practice
- Therapeutic alternatives are often limited due to the lack of comparative studies and guidelines
- The financial cost of drug shortages has taken a toll on clinical practice sites, institutions and the U.S. Health Care System
Questions

"You can observe a lot just by watching."

-Yogi