Oral Oncolytics: Consensus Standards to Increase Patient Safety

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Objectives

• Identify the extent, scope and risks of oral oncolytic errors
• Review ASCO/ONS oral oncolytic consensus safety standards
• List multidisciplinary strategies for the safe use of oral oncolytics
Primum Non Nocere

First, do no harm...
A (very) Short History of Oral Oncolytics

• Oral oncolytics have been available for nearly 6 decades
  - Methotrexate, cyclophosphamide, mercaptopurine, busulfan approved 1950s
  - Capecitabine received FDA approval in April 1998, ushering in a new era of oral chemotherapy
  - And nothing has been the same since...

• More than 40 oral oncolytics are currently FDA-approved in the US
  - At least 25% of 400 drugs in the pipeline are for oral administration
  - The number of commercially available oral oncolytics is expected to more than double by 2020
Defining *Medication Error*

- Any error occurring in the medication use process
- Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer
- Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use

Bates et al, 1995
What’s Wrong with this Rx?

ABC Cancer Center
123 Main Street
Happy Village, USA
555.555.5555

Date 1/18/11

For **Mary Smith** Lacks identifiers, BSA, diagnosis

Xeloda 4000mg twice daily

Serious dose calculation error
Signature overlaps mg (0 vs 6)

Illegible signature; no printed name

6 refills  **Prescribe only 1 cycle until stable**
Substitution permitted  ____  **Complete all items on Rx form**
A Decade Ago…

- 2001: Institute of Medicine (IOM) advocated the use of an electronic ordering system to ensure safety and accuracy in medication ordering
- Full electronic medical record (EMR), including all types of patient information, is not necessary to benefit from automated clinical data
- Use of medication order entry systems using data on patient diagnoses, current medications, and history of drug interactions or allergies can result in sizable reductions in prescribing errors

Institute of Medicine, 2001
A Wake-up Call

- Written survey of pharmacy directors at NCI comprehensive cancer centers on safety practices for prescribing, coordinating, monitoring, and educating patients about oral chemotherapy
  - Surveys completed by 42 (78%) of 54 eligible centers
- Few of the safeguards routinely used for infusion chemotherapy had been adopted for oral chemotherapy at US cancer centers
- Nearly 25% (10) of centers had no formal process for monitoring patients’ adherence
- The majority of errors resulted in a near miss
  - 39.3% of reports involving the wrong number of days supplied resulted in adverse drug events
  - Incidents derived from the literature search and hospital incident reporting system included a larger percentage of adverse drug events (73.1% and 58.8%, respectively) compared with other sources
Medication Errors in the Oncology Outpatient & Home Settings

- Determine rates and types of medication errors and systems factors associated with error in outpatients with cancer
- Retrospective review records from visits to three adult and one pediatric oncology clinic in the SE, SW, NE, and NW
  - Of 1,262 adult patient visits involving 10,995 medications, 7.1% (n = 90) were associated with a medication error
  - Of 117 pediatric visits involving 913 medications, 18.8% (n = 22) were associated with a medication error
  - > 70% of errors in children occurred in the home setting
  - 64 of the 112 errors had the potential to cause harm, and 15 errors resulted in injury
  - Errors most commonly occurred in administration (56%).
- Authors suggest improved communication about medication administration in the clinic and home can decrease errors
Oral Chemotherapy Medication Errors

  - Reports were collected of oral chemotherapy-associated medication errors from a medical literature and Internet search and review of reports to the Medication Errors Reporting Program and MEDMARX
  - The authors identified 99 adverse drug events, 322 near misses, and 87 medical errors with low risk of harm
    - Of the 99 adverse drug events, 20 were serious or life-threatening, 52 were significant, and 25 were minor
    - The most common medication errors involved wrong dose (38.8%), wrong drug (13.6%), wrong number of days supplied (11%), and missed dose (10%)
    - The majority of errors resulted in a near miss; however, 39.3% of reports involving the wrong number of days supplied resulted in adverse drug events.
  - Standardizing chemotherapy regimens and improving the functionality of computerized order entry so it can be used for oral chemotherapy drugs may help curb these errors
Parents’ Concerns about Administration of Oral Oncolytics to Children

- Explored perceptions and experiences of oral chemotherapy users and their caregivers to assess vulnerabilities and improvement opportunities at each stage of the medication process: choosing oral chemotherapy, prescribing, dispensing, administering, and monitoring
- N = 15, included 3 parents of pediatric patients with cancer
  - “In addition to being their parent, you have to be their caregiver”
  - “Retail pharmacists are very, very unfamiliar with pediatric chemotherapy”
  - A dose miscalculation resulted in too much chemotherapy being administered to a child
  - A parent described administering her child’s chemotherapy ungloved while pregnant
NCCN Task Force Report: Oral Chemotherapy

• Weingart et al. J Natl Compr Canc Netw. 2008; Suppl 3:S1-S14
• Following the Weingart 2007 article, NCCN convened a multidisciplinary task force consisting of oncologists, nurses, pharmacists, and payor representatives to discuss the impact of the increasing use of oral chemotherapy

• Safety issues identified:
  - The lack of checks and balances to avoid medication errors
  - Lack of evidence-based monitoring techniques
  - Patient non-adherence
  - A shift in the responsibility for managing a potentially complicated oral regimen from the clinician to the patient

• Problems were identified but no standards were established
Do We Need Safety Standards?

- Oral chemotherapy drugs are no less hazardous than other types of chemotherapy
- Chemotherapy agents have narrower therapeutic indices
  - Less margin for error
  - Consequences of error may be more devastating
- Primary stakeholders: ASCO & ONS
ASCO/ONS Chemotherapy Safety Standards Task Force

• **Goal**: Develop chemotherapy administration safety standards using a multidisciplinary, consensus-building process

• A volunteer ASCO/ONS Steering Group was assembled. Consensus was reached by a structured workshop, open public comment period, and systematic review of collated data.

• The scope of the project was chemotherapy administration.

• Oral chemotherapy was considered equivalent to parenteral in terms of risk and safety requirements.

ASCO=American Society of Clinical Oncology; ONS=Oncology Nursing Society
Jacobson et al, 2009
ASCO/ONS Chemotherapy Safety Standards Task Force

- Workshop was convened in December 2008
  - 40 participants
  - Medical oncologists, nurses, pharmacists, social workers, practice administrators, and patient advocates

- Draft standards refined to prepare a version for public comment:
  - Focused on patient safety
  - Relevant to diverse outpatient practice settings providing chemotherapy to adult patients with cancer
  - Actionable
  - Measurable

- Draft standards were posted for public comment from January 27, 2009 to March 13, 2009

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Jacobson et al, 2009
ASCO/ONS Chemotherapy Safety Standards: Oral Chemotherapy

- All patients who are prescribed oral chemotherapy are provided written or electronic patient education materials about oral chemotherapy before or at the time of prescription
  - Patient education should be appropriate for the patient’s reading level/literacy and patient/caregiver understanding
- The practice maintains and uses standardized, regimen-level, preprinted or electronic forms for chemotherapy prescription writing
- Frequency of office visits and monitoring that is appropriate to the agent and is defined in the treatment plan
  - Orders for oral chemotherapy should be written with a time limitation to ensure appropriate evaluation at predetermined intervals
- The practice establishes a procedure for documentation and follow-up for patients who miss office visits and treatments

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Jacobson et al, 2009
Strategies for Safe Use of Oral Oncolytics

Which of the following methods best describes how your practice orders chemotherapy? (Results filtered to exclude respondents who are not in a practice that prescribes chemotherapy.)

- Orders are entered via a fully integrated computerized prescriber order entry (CPOE/COE) system: 25.3%
- Orders are generated via computer but printed for use: 21.7%
- Orders are written on paper pre-printed forms or ordersets: 34.7%
- Orders are hand-written, but not on a pre-printed form: 18.2%

n = 884

Percentage of Clinicians

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Standardized Pre-printed (IV) Chemotherapy Order

- **Advantages**
  - Most components legible
  - Approved regimens pre-populated
  - Includes safety cues such as double check

- **Disadvantages**
  - Requires computer & printer
  - Must be revised for frequent drug changes
  - Prescriber can choose not to complete certain sections
  - Illegibility still a concern
  - May not be accepted at retail, mail-order or specialty pharmacies
Standardized Electronic (IV) Chemotherapy Order

- **Advantages**
  - Legibility of all components
  - Approved regimens pre-populated
  - Includes safety cues such as dose calculation, double check, lab values, check against standard doses
  - May be transmitted to outside pharmacy

- **Disadvantages**
  - Requires electronic prescribing or EMR
  - May not be accepted at retail, mail-order or specialty pharmacies

Dumasia L et al, 2006
For Mary Smith  DOB 1/16/1942

Ht 66 inches, Wt 145 lbs, BSA = 1.74, dose 1250 mg/m2 BID = 2000 mg BID, rounded. Dx: metastatic breast cancer, ICD 9 = 174.2;197.7

Xeloda 2000mg PO twice daily X 14 days, followed by 7 days off medicine. Take with food.

0 refills
Substitution permitted No

John Smith MD
DEA JSxxxxxxxxxx
# Monitoring Adherence

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly observed therapy</td>
<td>Most accurate</td>
<td>Patients can hide pills in their mouth, and then discard them; impractical for routine use</td>
</tr>
<tr>
<td>Measurement of the level of medicine or metabolite in blood</td>
<td>Objective</td>
<td>Variations in metabolism and “white coat adherence” can give a false impression of adherence; expensive</td>
</tr>
<tr>
<td>Measurement of biologic marker in blood</td>
<td>Objective</td>
<td>Requires expensive quantitative assays and collection of bodily fluids</td>
</tr>
<tr>
<td><strong>Indirect methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient questionnaires, patient self-reports</td>
<td>Simple; inexpensive; the most useful method in the clinical setting</td>
<td>Susceptible to error with increases in time between visits; results are easily distorted by the patient</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Objective, quantifiable, and easy to perform</td>
<td>Data easily altered by the patient (e.g., pill dumping)</td>
</tr>
<tr>
<td>Rates of prescription refills</td>
<td>Objective; easy to obtain data</td>
<td>A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system</td>
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<tr>
<td>Assessment of the patient’s clinical response</td>
<td>Simple; generally easy to perform</td>
<td>Factors other than medication adherence can affect clinical response</td>
</tr>
<tr>
<td>Electronic medication monitors</td>
<td>Precise; results are easily quantified; tracks patterns of taking medication</td>
<td>Expensive; requires return visits and downloading data from medication vials</td>
</tr>
<tr>
<td>Measurement of physiologic markers</td>
<td>Often easy to perform</td>
<td>Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)</td>
</tr>
<tr>
<td>Patient diaries</td>
<td>Helps to correct poor recall</td>
<td>Easily altered by the patient</td>
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Based on Osterberg & Blaschke, 2005; Peterson et al, 2003
Meta-analysis of Trials of Interventions to Improve Medication Adherence

- Various databases searched for articles published 1966-2000 (N = 484)
  - 61 articles met criteria for meta-analysis
- There were no significant differences among the behavioral or educational interventions
- Mail reminders had the largest impact
- Meta-analysis revealed an increase in adherence of 4-11%
- No single strategy appeared to be best

Peterson et al, 2003
Concordance of Self-Report with Other Measures of Adherence

- Literature search yielded 86 comparison studies
  - Self-report: questionnaires, diaries, interviews
  - Non-self-report: electronic measures, pill count, refill rates, plasma drug concentration
- 37 (43%) were categorized as highly concordant
- Self-report measures were highly concordant with electronic measures in only 17% of comparisons, whereas they were highly concordant with other types of non-self-report measures in 58% of comparisons ($P < 0.01$)
- Interviews had significantly lower concordance with non-self-report measures as compared with questionnaires or diaries ($P = 0.01$)
Safe Handling of Oral Oncolytics

- It is generally assumed that patients receive chemotherapy in traditional health care settings.
- With increased use of oral chemotherapy this paradigm is shifting from ambulatory infusion clinics and physicians offices, to include:
  - Self administration at home
  - Assisted living and long-term care facilities
  - Visiting nurses
- Home caregivers and staff in group facilities need education on safe administration practices.
- Oral chemotherapy drugs are hazardous, just as any type of chemotherapy.
- Increased risks apply for women who are:
  - Breastfeeding
  - Pregnant
  - Planning on becoming pregnant
Safe Administration of Oral Oncolytics in Residential Facilities

- Maintain list of drugs to be handled as hazardous (annual update)
- Store securely in clearly labeled original containers
- Establish dose-verification procedures
- Follow OSHA recommendations for safe work area
  - Do not manipulate (crush, cut, dissolve) unless approved in PI
  - If manipulation is permitted, use BSC; wear mask, gown & eyewear
  - Wear gloves to handle and administer oral chemotherapy
  - Wash hands before and after removing gloves
  - Dispose of unused oral cytotoxic drugs, PPE and packaging in approved container

OSHA = Occupational Safety and Health Administration; PI = prescribing information; BSC = biologic safety cabinet; PPE = personal protective equipment

Goodin S, 2007; Goodin et al, 2011
Oral Chemotherapy in the Home
Instructions for Patients & Caregivers

• Keep the medicine in its original container, in a safe place, away from other family medications and out of the reach of children or pets. Unused medications should be returned to the clinic for disposal.

• Double flush after using the toilet. Wash your hands well with soap and water after using the toilet, and wash your skin if urine, vomit or stool gets on other parts of your body.

• Caregivers should wear gloves when giving oral chemotherapy medications if the medicine is handled directly.

• Always wear gloves in disposing of urinal or commode waste and cleaning of equipment. Wash your skin if exposed to urine, vomit or stool.

• Caregivers should wear disposable gloves when handling linens or clothing that has been soiled with your body waste. Soiled items should be kept in a plastic bag prior to being washed, and should be washed separately from the other laundry.

Goodin et al, 2011
Recap: Do We Need Safety Standards?

- Development of and clinical indications for oral oncolytics continue to increase
- Adequate safety and support systems have not evolved as quickly as oral oncolytics
- There are unique safety issues related to oral oncolytics
  - Patient education
  - Staff education
  - Access to medication
  - Safe handling
  - Adherence
- Evidence-based recommendations can help minimize risk and maximize positive patient outcomes
Questions?