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

- **Weingart et al. *BMJ,* 2007; 334: 407-109**
- 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

- **Walsh et al, *J Clin Oncol*, 2009; 27:891-896**
- 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

- **Weingart et al, *Cancer*, 2010; 116:2455-2464**
  - 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

- **Simchowitz, et al. *Clin J Oncol Nurs.* 2010; 14:447-453**
- 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

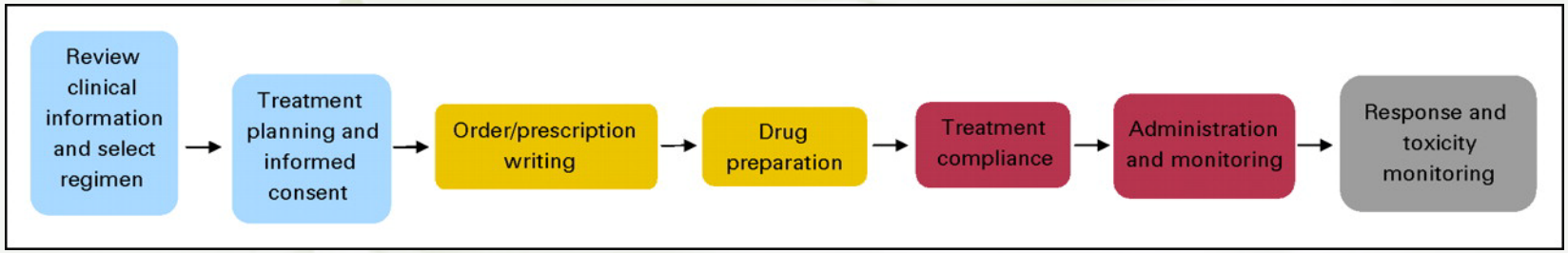
- **Weingart et al. J *Natl Compr Canc Netw*. 2008; Suppl 3:S1-S14**
- Following the Weingart 2007 article, NCCN convened a multidisciplinary task force consisting of oncologists, nurses, pharmacists, and payor representatives to discuss the impact of the increasing use of oral chemotherapy
- **Safety 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
- Critical issues had been identified by Weingart et al (2007, *BMJ;* 2008, *JNCCN*)
- 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

ASCO=American Society of Clinical Oncology; ONS=Oncology Nursing Society

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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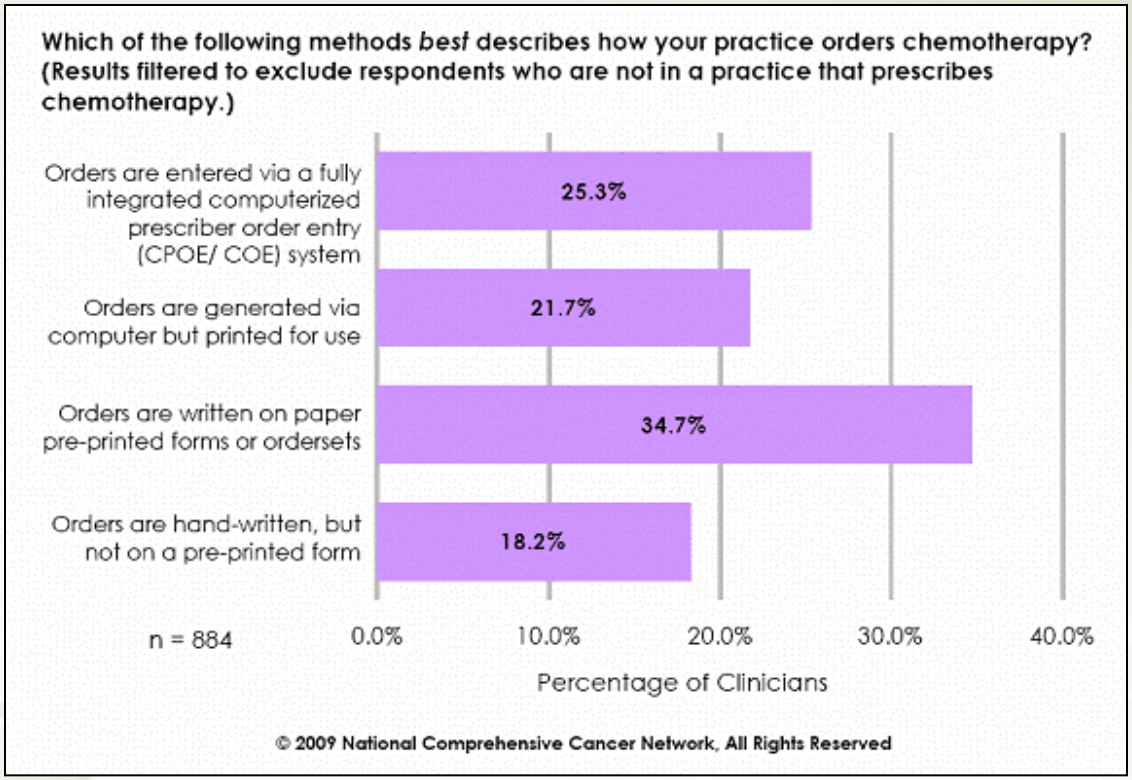
Jacobson et al, 2009

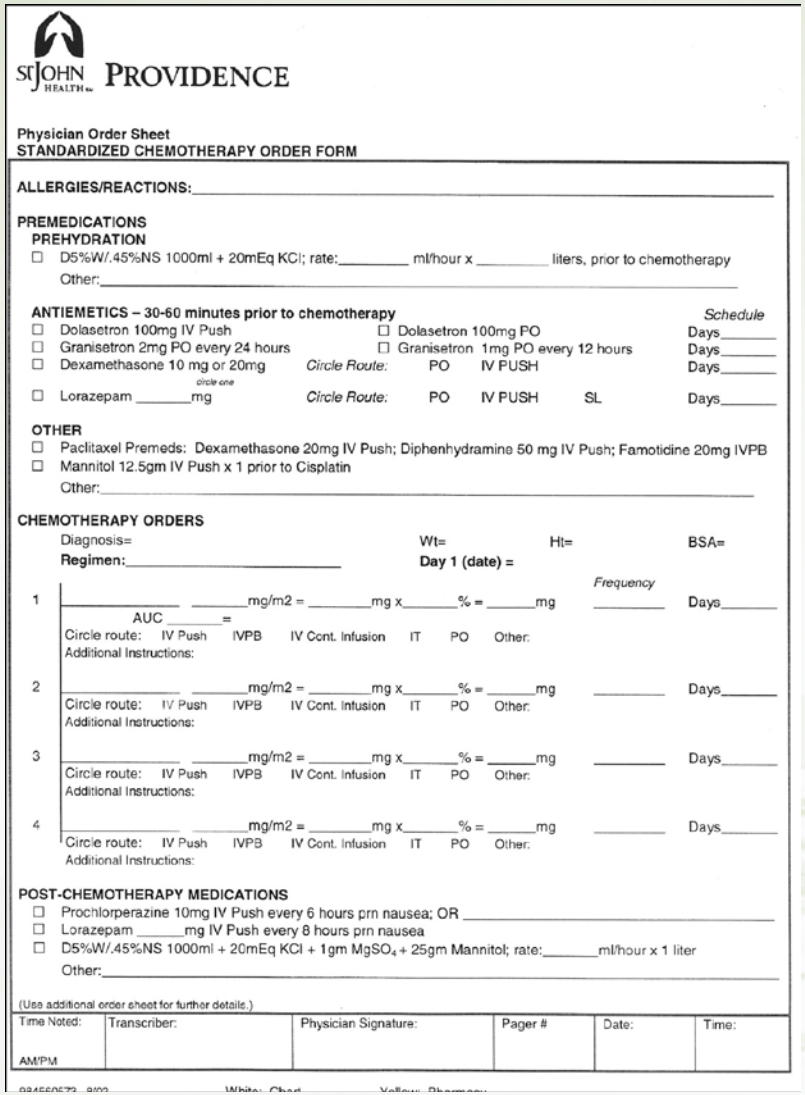
Strategies for Safe Use of Oral Oncolytics

NCCN Trends™ Survey on Chemotherapy Prescribing Practices (2009)



http://www.nccn.org/about/news/ebulletin/2009-12-21/compendium_use.asp

Standardized Pre-printed (IV) Chemotherapy Order



ST JOHN HEALTH PROVIDENCE

Physician Order Sheet
STANDARDIZED CHEMOTHERAPY ORDER FORM

ALLERGIES/REACTIONS:_____

PREMEDICATIONS
PREHYDRATION
☐ D5%W/.45%NS 1000ml + 20mEq KCl; rate:_____ ml/hour x _____ liters, prior to chemotherapy
Other:_____

ANTIEMETICS – 30-60 minutes prior to chemotherapy — Schedule
☐ Dolasetron 100mg IV Push ☐ Dolasetron 100mg PO Days_____
☐ Granisetron 2mg PO every 24 hours ☐ Granisetron 1mg PO every 12 hours Days_____
☐ Dexamethasone 10 mg or 20mg (circle one) Circle Route: PO IV PUSH Days_____
☐ Lorazepam _____mg Circle Route: PO IV PUSH SL Days_____

OTHER
☐ Paclitaxel Premeds: Dexamethasone 20mg IV Push; Diphenhydramine 50 mg IV Push; Famotidine 20mg IVPB
☐ Mannitol 12.5gm IV Push x 1 prior to Cisplatin
Other:_____

CHEMOTHERAPY ORDERS
Diagnosis= Wt= Ht= BSA=
Regimen:_____ Day 1 (date) =

		Frequency	
1	_____ _____mg/m2 = _____mg x_____% = _____mg AUC _____= Circle route: IV Push IVPB IV Cont. Infusion IT PO Other: Additional Instructions:	_____	Days_____
2	_____ _____mg/m2 = _____mg x_____% = _____mg Circle route: IV Push IVPB IV Cont. Infusion IT PO Other: Additional Instructions:	_____	Days_____
3	_____ _____mg/m2 = _____mg x_____% = _____mg Circle route: IV Push IVPB IV Cont. Infusion IT PO Other: Additional Instructions:	_____	Days_____
4	_____ _____mg/m2 = _____mg x_____% = _____mg Circle route: IV Push IVPB IV Cont. Infusion IT PO Other: Additional Instructions:	_____	Days_____

POST-CHEMOTHERAPY MEDICATIONS
☐ Prochlorperazine 10mg IV Push every 6 hours prn nausea; OR _____
☐ Lorazepam _____mg IV Push every 8 hours prn nausea
☐ D5%W/.45%NS 1000ml + 20mEq KCl + 1gm $MgSO_4$ + 25gm Mannitol; rate:_____ml/hour x 1 liter
Other:_____

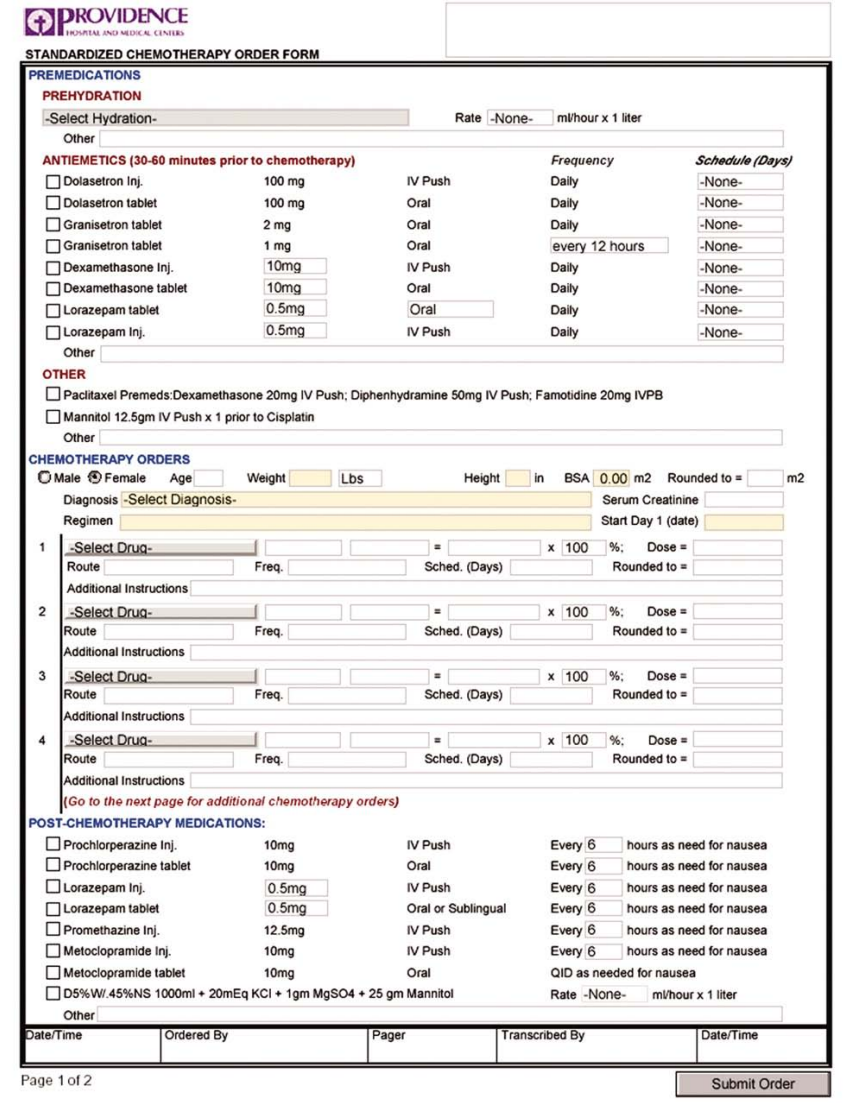
(Use additional order sheet for further details.)

Time Noted: AM/PM	Transcriber:	Physician Signature:	Pager #	Date:	Time:

- **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

Dumasia L et al, 2006

Standardized Electronic (IV) Chemotherapy Order



PROVIDENCE
HOSPITAL AND MEDICAL CENTERS

STANDARDIZED CHEMOTHERAPY ORDER FORM

PREMEDICATIONS

PREHYDRATION

-Select Hydration- Rate -None- ml/hour x 1 liter

Other

ANTIEMETICS (30-60 minutes prior to chemotherapy)

			Frequency	Schedule (Days)
☐ Dolasetron Inj.	100 mg	IV Push	Daily	-None-
☐ Dolasetron tablet	100 mg	Oral	Daily	-None-
☐ Granisetron tablet	2 mg	Oral	Daily	-None-
☐ Granisetron tablet	1 mg	Oral	every 12 hours	-None-
☐ Dexamethasone Inj.	10mg	IV Push	Daily	-None-
☐ Dexamethasone tablet	10mg	Oral	Daily	-None-
☐ Lorazepam tablet	0.5mg	Oral	Daily	-None-
☐ Lorazepam Inj.	0.5mg	IV Push	Daily	-None-

Other

OTHER

☐ Paclitaxel Premeds:Dexamethasone 20mg IV Push; Diphenhydramine 50mg IV Push; Famotidine 20mg IVPB

☐ Mannitol 12.5gm IV Push x 1 prior to Cisplatin

Other

CHEMOTHERAPY ORDERS

◯ Male ◉ Female Age Weight Lbs Height in BSA 0.00 m2 Rounded to = m2

Diagnosis -Select Diagnosis- Serum Creatinine

Regimen Start Day 1 (date)

1 -Select Drug- = x 100 %; Dose =

Route Freq. Sched. (Days) Rounded to =

Additional Instructions

2 -Select Drug- = x 100 %; Dose =

Route Freq. Sched. (Days) Rounded to =

Additional Instructions

3 -Select Drug- = x 100 %; Dose =

Route Freq. Sched. (Days) Rounded to =

Additional Instructions

4 -Select Drug- = x 100 %; Dose =

Route Freq. Sched. (Days) Rounded to =

Additional Instructions

(Go to the next page for additional chemotherapy orders)

POST-CHEMOTHERAPY MEDICATIONS:

☐ Prochlorperazine Inj.	10mg	IV Push	Every 6 hours as need for nausea
☐ Prochlorperazine tablet	10mg	Oral	Every 6 hours as need for nausea
☐ Lorazepam Inj.	0.5mg	IV Push	Every 6 hours as need for nausea
☐ Lorazepam tablet	0.5mg	Oral or Sublingual	Every 6 hours as need for nausea
☐ Promethazine Inj.	12.5mg	IV Push	Every 6 hours as need for nausea
☐ Metoclopramide Inj.	10mg	IV Push	Every 6 hours as need for nausea
☐ Metoclopramide tablet	10mg	Oral	QID as needed for nausea
☐ D5%W/.45%NS 1000ml + 20mEq KCl + 1gm MgSO4 + 25 gm Mannitol			Rate -None- ml/hour x 1 liter

Other

Date/Time	Ordered By	Pager	Transcribed By	Date/Time

Page 1 of 2

Submit Order

Dumasia L et al, 2006

- **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

Provide All Components for Safety

John Smith MD
123 Main Street
Any Village, USA
555.555.5555

Date 1/18/11

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


MD


RN

John Smith MD **DEA** JSxxxxxxxxx

SECURITY WATERMARK

Monitoring Adherence

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

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

- **Garber et al. *Medical Care,* 2004; 42:649-652**
- 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?

YES!

- 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?