BC Cancer Agency
CARE + RESEARCH
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RATIONALIZING THE USE OF AUXILIARY LABES FOR ORAL ONCOLOGY DRUGS

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Objective

To develop a systematic approach to standardize the use of auxiliary labels for oral oncology drugs in the ambulatory setting

Background

Auxiliary labels provide supplemental information on safe administration, storage and drug interactions.[1,2]
- Effectiveness[3-5] depends on the label design, number and positioning on medication vial.[6-9]
- Patients may pay little attention to auxiliary labels,[6,10] particularly in the second and third positions on the limited space of the medication vial.[9]
- Effective use is important with increasing number of oral oncology drugs which often have a narrow therapeutic index.
- No legal guidance or "best practice" approach has been identified from:
  - Pharmacist licensing body (College of Pharmacists of British Columbia)
  - Institute of Safe Medication Practice
  - Large healthcare organizations (Lower Mainland Pharmacy Services of British Columbia)
  - Standard drug information resources (Lexicomp®, RxList®).
- British National Formulary is the only standard resource which provides an authoritative list of auxiliary labels[11]

Methods

The multi-phased project was conducted at the BC Cancer Agency, British Columbia, Canada. The Agency is a government funded, non-profit, integrated provincial care organization with six regional centres.
- Phase I: an environmental scan at the centres to compile a list of the auxiliary labels for oral oncology drugs dispensed for outpatients.
- Phase II: guiding principles developed by pharmacy practice leaders, the medication safety pharmacist and a drug information pharmacist to standardize use of auxiliary labels.
- Phase III: inclusion criteria for common auxiliary labels developed by the Cancer Drug Manual© editor, the medication safety pharmacist and the drug information pharmacist.
- Phase IV: a list of auxiliary labels standardized and maintained for oral oncology drugs based on the guiding principles and literature.

Results

The project was initiated in July 2013 and completed in June 2014.

Phase I

Fifty-five drugs (table 1) and 22 auxiliary labels (table 2) were identified through the environmental scan.
- Universal warning to keep medicines out of reach of children was used in 83%
- Frequently used labels were not always based on drug specific evidence (e.g., swallow whole or do not chew/crush in 89%, avoid grapefruit in 70%)
- Only 9% of drugs were assigned with the same labels across the centres. Erlotinib was assigned 8 labels at one centre but only 2 labels by another.
- No explicit method on assigning labels was identified from the centres.

Table 1. Oral oncology drugs reviewed

abiraterone	everolimus	mercaptopurine
acitretin	exemestane	methotrexate
anastrozole	fludarabine	mitotane
bexarotene	fludrocortisone	nilotinib
bicalutamide	flutamide	nilutamide
bromocriptine	gefitinib	pazopanib
busulfan	hydrocortisone	prednisolone
cabergoline	hydroxyurea	prednisone
capecitabine	lmatinib	procarbazine
chlorambucil	isotretinoin	quinagolide
clodronate	lapatinib	sorafenib
cortisone	lenalidomide	sunitinib
cyclophosphamide	letrozole	tamoxifen
cyclosporine	leucovorin calcium	temozolomide
dasatinib	lomustine	thalidomide
dexamethasone	medroxyprogesterone	thioguanine
erlotinib	megestrol	tretinoin
estramustine	melphalan	vemurafenib
etoposide		

Table 2. Usage of auxiliary labels: pre- and post-standardization

Auxiliary labels	Usage (N=55)	
	Pre-standardization	Post-standardization
Do not chew or crush, swallow whole	49	2
Keep out of reach of children	46	0
Avoid grapefruit or grapefruit juice	38	15
Take with plenty of water	28	8
Chemotherapy dispose of appropriately	26	N/A*
May cause drowsiness/dizziness	26	6
Take with food	22	10
Take on an empty stomach	19	16
Avoid prolonged exposure to sun	14	1
Keep in refrigerator	8	2
Avoid ASA	7	0
Avoid alcohol	7	4
Do not take if pregnant	7	3
Do not take with dairy/antacid/iron within 1 hour	2	0
Do not take within 2 hours of antacids	4	6
Do not drink milk or dairy or dairy products	0	2
Do not take with iron	0	0
Finish all medication	2	0
May cause discoloration of urine	2	2
Return to pharmacy	2	0
Hazardous drug label	1	N/A*

* Pending harmonization of safe handling procedures with other hospitals in British Columbia

Phase II

Major components of the guiding principles on assigning auxiliary labels:
1. They supplement but do not replace counselling and drug specific, patient information handout.
2. A maximum of four labels per drug to allow clarity and reduce alert fatigue.
3. Hazardous drugs is designated with an auxiliary label. Detailed safe handling is addressed by counselling and a separate patient handout (in development).
4. They are not intended for universal warnings (e.g., keep out of reach of children).
5. Label selection is prioritized, in decreasing importance of the caution:
   - Storage, which has immediate impact on drug potency
   - Efficacy, including proper administration (e.g., "Take with food")
   - Toxicity, including interactions, side effects, pregnancy warning
   - Any other relevant clinical issues.

Phase III

Inclusion criteria were developed for commonly used auxiliary labels to facilitate label assignment (table 3). The criteria were generally consistent with those used in the British National Formulary.

Table 3. Inclusion criteria for commonly used auxiliary labels

Label	Inclusion criteria
Do not take if pregnant	Health Canada or Food and Drug Administration mandated pregnancy monitoring programs (e.g., thalidomide, lenalidomide)
Do not chew or crush, swallow whole	Crushing may affect bioavailability (e.g., enteric coating, modified release)
Take with plenty of water	Nephrotoxic or with specific recommendations to consume large quantities of fluid (e.g., cyclophosphamide)
May cause drowsiness/dizziness	Strong cautions on somnolence or dizziness affecting functioning (confirm with BNF where possible)
Avoid alcohol	Interactions with alcohol (e.g., disulfiram-like reaction)
Avoid grapefruit or grapefruit juice	Evidence-based interactions based on: - CPS grapefruit interaction section, - Product monograph cautions, or - Lexicomp® citing clinical cases
Avoid prolonged exposure to sun	Strong phototoxic reactions OR black box or other strong warnings (confirm with BNF where possible)
Avoid Aspirin	Documented interaction with aspirin
Do not take within 2 hours of antacids	Evidence-based interactions with antacids

BNF = British National Formulary, CPS = Compendium of Pharmaceuticals and Specialties

Phase IV

A list of standardized auxiliary labels was developed and adopted by all six centres in June 2014.
Sources of information to support an auxiliary label included:
- Compendium of Pharmaceuticals and Specialties
- BC Cancer Agency Cancer Drug Manual©
- British National Formulary
- Other resources as needed (e.g., Lexicomp®, AHFS DI®, Micromedex®)
- Literature, including alerts from Health Canada and the US Food and Drug Administration.

After standardization:
- Number of auxiliary labels used was significantly reduced (table 2)
- .The auxiliary label list was posted as part of the Cancer Drug Manual© on the website (www.bccancer.bc.ca)
- BC Cancer Agency pharmacy directive was developed.
- Staff was educated through two 30-minute inservices and an emailed document summarizing the frequently asked questions and answers

Discussion

BC Cancer Agency has developed a systematic approach to standardize the use of auxiliary labels for oral oncology drugs dispensed for outpatients. The practice before standardization was highly inconsistent, similar to that reported in other studies.[15]

Standardization has led to practice changes that may improve the safe administration of oral agents:
- Labels are consistently applied, independent of the practitioner[12]
- Consistent messaging during patient counselling across centres
- Consistent assignment of similar cautions for similar situations for future drugs
- Label with multi-step instructions separated into labels with single-step instructions[10,13]
- Consistent order (positioning) in applying the labels on the medication vial[16]
- Prioritize auxiliary labels used by patients as the main information source (e.g., storage, proper administration)[14]
- Reduced number of auxiliary labels
  - Improve clarity by focusing on the more significant cautions[9,14]
  - Minimize alert fatigue[17]

Conclusion

A systematic approach was developed to standardize and prioritize the use of auxiliary labels for oral oncology drugs to improve their safe administration at the BC Cancer Agency. The consistency of our practice has been significantly improved following the development and implementation of a harmonized list for all regional centres' pharmacies.

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