PHARMACY LEARNING NETWORK 1-DAY REGIONAL MEETINGS

A Changing Paradigm in Cancer Care:

The Migration to Oral Oncolytic Agents

ICHP

Presented in partnership with the ICHP Annual Meeting

Faculty

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Disclosures

Christopher A. Fausel, PharmD, MHA, BCOP has no financial relationships to disclose relating to the subject matter of this presentation.

Learning Objectives

- Describe the pharmacologic mechanisms and indications of newly available oral agents to treat various cancers
- Evaluate the reported toxicities for newer oral oncolytic drugs and discuss the therapeutic implications of these toxicities
- Review the factors that impact the potential success of treatment with oral oncolytic drugs such as adherence and drug procurement

Oral Chemotherapy Circa 2002

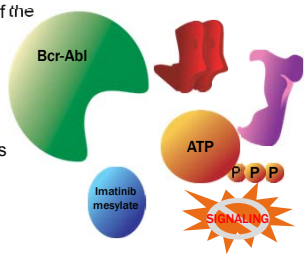
Drug	Class
Cyclophosphamide, Melphalan	Nitrogen mustard alkylating agent
Estramustine	Alkylating agent/estrogen
Lomustine	Nitrosourea alkylating agent
Methotrexate	Antifolate antimetabolite
Capecitabine	Pyrimidine antimetabolite
Mercaptopurine, Thioguanine	Purine antimetabolite
Etoposide	Epipodophyllotoxin
Hydroxyurea	Substituted ureas
Procarbazine	Methylhydrazine derivative
Temozolomide	Imidazotetrazine derivative
Tretinoin, Bexarotene	Retinoids
Tamoxifen/Letrozole/Flutamide/Nilutamide	Hormonal therapy
Imatinib	Tyrosine kinase inhibitor

***Drug Facts and Comparisons*. Facts and Comparisons; 2002:1957.**

Pharmacology 101 for Oral Chemotherapy Drugs

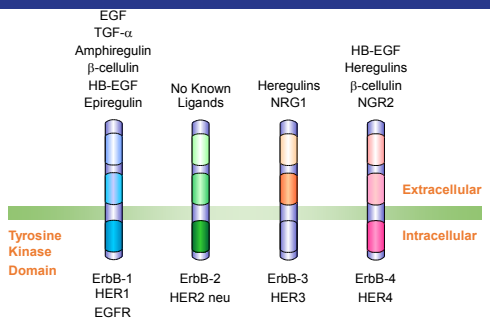
Pharmacodynamics of Imatinib

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



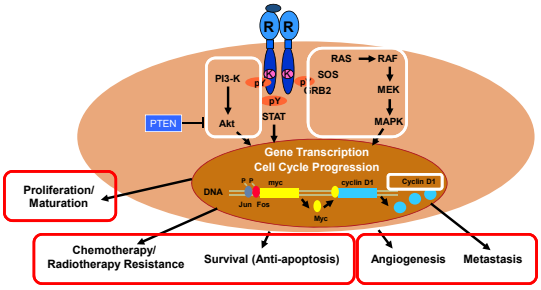
ATP = adenosine triphosphate; P = phosphate.
Savage DG, et al. *N Engl J Med*. 2002;346(9):683-693.

HER Family Receptors and Ligands



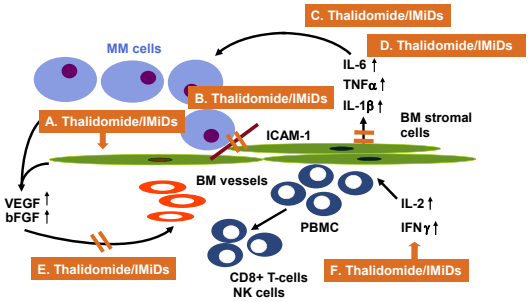
Yarden Y, et al. *Nat Rev Mol Cell Biol*. 2001;2(2):127-137.

Activated EGFR-TK: A Promoter of Malignancy



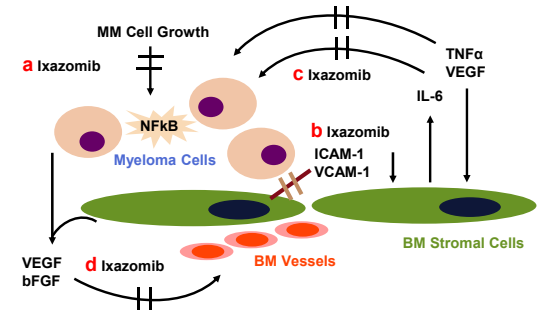
EGFR-TK = epidermal growth factor receptor tyrosine kinase.
Harari PM, et al. *Clin Cancer Res*. 2000;6(2):323-325. Herbst RS. *Int J Radiat Oncol Biol Phys*. 2004;59(2 Suppl):21-26.

IMiD Pharmacodynamics



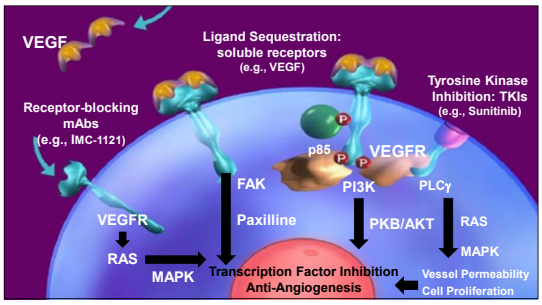
BM = bone marrow; IMiD = immunomodulatory derivative of thalidomide; MM = multiple myeloma; PBMC = peripheral blood mononuclear cell.
Richardson PG, et al. *Blood*. 2002;100(9):3063-3067. Hideshima T, et al. *Blood*. 2000;96(9):2943-2950.

Proteasome Inhibitor Pharmacodynamics



Cavo M. *Leukemia*. 2006;20(8):1341-1352.

Anti-Angiogenesis Pharmacology

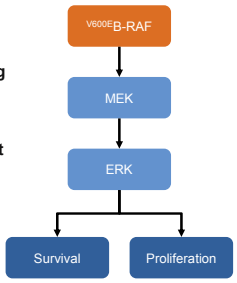


Croce CM. *N Engl J Med*. 2008;358(5):502-511.

Oncogenic B-RAF Promotes Stimulation and Survival

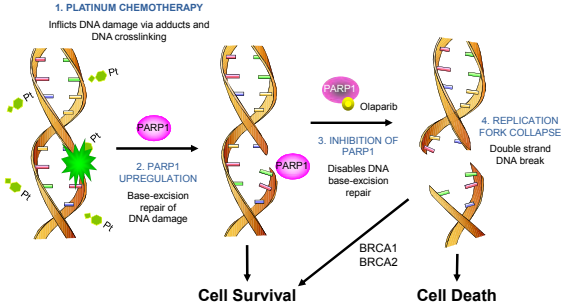
^{V600E}B-RAF

- **500-fold** activated
- Stimulates **constitutive signaling**
- Stimulates **proliferation**
- Stimulates **survival**
- Is an excellent **therapeutic target**



Garnett MJ, et al. *Cancer Cell*. 2004;6(4):313-319. Karasarides M, et al. *Oncogene*. 2004;23(37):6292-6298. Wan PT, et al. *Cell*. 2004;116(6):855-867. Wellbrock C, et al. *Nat Rev Mol Cell Biol*. 2004;5(11):875-885.

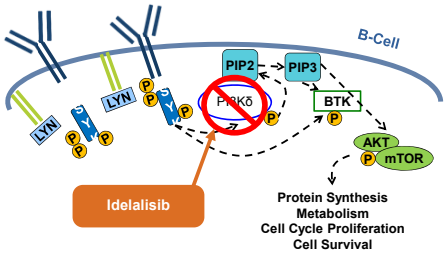
PARP Inhibitor Pharmacodynamics



PARP = poly ADP ribose polymerase.

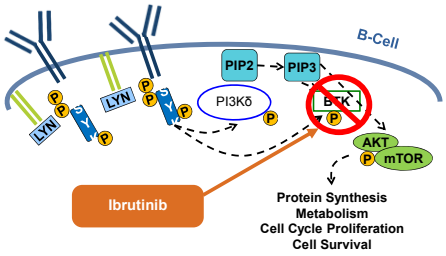
McLornan DP, et al. *N Engl J Med*. 2014;371(18):1725-1735.

Idelalisib Pharmacodynamics



Fruman DA, et al. *N Engl J Med*. 2014;370(11):1061-1062.

Ibrutinib Pharmacokinetics



Fruman DA, et al. *N Engl J Med*. 2014;370(11):1061-1062.

Oral Oncolytic Agents in Clinical Use

FDA Approvals Oral Oncolytics 2006-2008

Drug	Indication	Year
Imatinib	Dermatofibrosarcoma proturberans, HES, MDS/MPD, systemic mastocytosis	2006
Vorinostat	Cutaneous T-cell lymphoma – 3rd line	2006
Lenalidomide	Myeloma – 2nd line with dexamethasone	2006
Dasatinib	CML – 2nd line	2006
Sorafenib	Advanced hepatocellular carcinoma	2007
Nilotinib	CML – 2nd line	2007
Lapatinib (+capecitabine)	HER-2 +, metastatic breast; post trastuzumab/anthracycline/taxane	2007
Sunitinib	Advanced renal cell carcinoma	2007
Imatinib	Adjuvant gastrointestinal stromal tumor	2008

CML = chronic myeloid leukemia; HES = hypereosinophilic syndrome; MDS/MPD = myelodysplastic/myeloproliferative diseases.

US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2009-2010

Drug	Indication	Year
Pazopanib	Advanced renal cell carcinoma	2009
Everolimus	Renal cell carcinoma; post sorafenib or sunitinib	2009
Everolimus	Giant cell astrocytoma	2010
Dasatinib	CML – Front line	2010
Nilotinib	CML – Front line	2010
Lapatinib	Hormone receptor +, metastatic breast cancer (with letrozole)	2010

US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2011

Drug	Indication
Ruxolitinib	Primary myelofibrosis; PV or ET associated myelofibrosis
Crizotinib	ALK+ NSCLC
Vemurafenib	BRAF V600E metastatic melanoma
Abiraterone	Metastatic castration-resistant prostate cancer; post docetaxel
Vandetanib	Metastatic medullary thyroid cancer
Everolimus	Progressive neuroendocrine tumors of pancreatic origin

ALK = anaplastic lymphoma kinase; ET = essential thrombocythemia; NSCLC = non-small cell lung cancer; PV = polycythemia vera.
US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2012

Drug	Indication
Ponatinib	Refractory CML; Ph+ ALL
Abiraterone	Metastatic castration-resistant prostate cancer
Cabozantinib	Progressive medullary thyroid cancer
Regorafenib	Metastatic colorectal cancer, previous irinotecan, VEGF inhibitor therapy
Bosutinib	CML
Enzalutamide	Metastatic castration-resistant prostate cancer (post docetaxel)
Everolimus	Hormone receptor + breast cancer post letrozole/anastrazole; HER-2 negative
Pazopanib	Soft tissue sarcoma; post chemotherapy
Vismodegib	Basal cell carcinoma
Axitinib	Renal cell carcinoma – 2nd line

Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukemia.
US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2013

Drug	Indication
Sorafenib	Metastatic differentiated thyroid carcinoma
Afatinib	1st line NSCLC EGFR+ exon 19 or 21 deletions
Erlotinib	1st line NSCLC EGFR+ exon 19 or 21 deletions
Lenalidomide	Third-line mantle cell lymphoma
Dabrafenib	BRAF V600E metastatic melanoma
Trametinib	BRAF V600E or V600K metastatic melanoma
Pomalidomide	Myeloma – 3rd line

US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2014

Drug	Indication
Idelalisib	CLL/follicular NHL
Ceritinib	ALK + NSCLC post crizotinib
Mercaptopurine suspension	Pediatric ALL
Ibrutinib	CLL, including 17p deletions
Trametinib/dabrafenib	Combination therapy for BRAF V600E or V600K metastatic melanoma
Olaparib	BRCA mutated advanced ovarian cancer

CLL = chronic lymphocytic leukemia; NHL = Non-Hodgkin lymphoma.
US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

FDA Approvals
Oral Oncolytics 2015

Drug	Indication
Palbociclib	ER+, HER-2-Neu negative metastatic breast cancer
Lenvatinib	Metastatic thyroid cancer
Panobinostat	Multiple myeloma
Sonidegib	Basal cell carcinoma
Trifluridine/tipiracil	Metastatic colon cancer
Cobimetinib	Metastatic melanoma
Osimertinib	Metastatic NSCLC - EGFR
Alectinib	Metastatic NSCLC – ALK +
Ixazomib	Multiple myeloma

US Food and Drug Administration. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed on February 17, 2016.

Practical Matters in Managing Oral Oncolytics for Pharmacists

Drug-Drug Interactions

- How to navigate the complexity of drug interactions with oral oncolytics
  - Assume **all** targeted agents have numerous CYP450-mediated drug-drug interactions (because most of them do)
  - Use proven resources to review a patient medication profile
    - IUSM Clinical Pharmacology interactions table
    - Online drug information database: Lexicomp, Micromedex
    - Call people like us

Indiana University Department of Medicine. http://medicine.iupui.edu/clinpharm/ddis/clinical-table/. Accessed on February 16, 2016.

CYP450-Mediated Drug Interactions

- Enzymes of relevance
  - 1A2, 2B6, 2C8, 2C9, 2D6, 3A4/5/7
- Remember the inducer drugs
  - Antiepileptics: carbamazepine, phenobarbitol, phenytoin, primidone
  - Anti-tuberculin agents: rifampin, rifabutin
  - HIV drugs: efavirenz, nevirapine, ritonavir
  - Others: pioglitazone, troglitazone, St. John's Wort

Indiana University Department of Medicine. http://medicine.iupui.edu/clinpharm/ddis/clinical-table/. Accessed on February 16, 2016.

Select End-Organ Toxicities with Oral Chemotherapy Agents

Organ Toxicity	Drug
Cardiac	Afatinib, BCR-ABL TKIs, ceritinib, crizotinib, dabrafenib, ibrutinib, lapatinib, pazopanib, regorafenib, ruxolitinib, trametinib, vismodegib
Pulmonary	Afatinib, ceritinib, crizotinib, erlotinib, everolimus, idelalisib, lapatinib, trametinib
Hepatic	Abiraterone, afatinib, BCR-ABL TKIs, ceritinib, crizotinib, idelalisib, lapatinib, regorafenib
Renal	Everolimus, ibrutinib
Vascular	IMiDs, BCR-ABL TKIs, cabozantinib, everolimus, pazopanib
Endocrine	Ceritinib, crizotinib, pazopanib, sorafenib, sunitinib
Ocular	Afatinib, crizotinib, dabrafenib, trametinib
Secondary malignancies	IMIDs, dabrafenib, trametinib, vemurafenib, everolimus, vismodegib

Carcelero E, et al. *Expert Opin Drug Saf*. 2013;12(3):403-420.

Barriers to Adherence

Patient-specific Factors	Provider-related Factors	Treatment-related Factors
Health beliefs	Relationships	Complexity of regimen
Patient history	Satisfaction with care	Behavioral changes required for treatment
Social support	Insurance coverage	Cost
Socioeconomic status	Convenience of care	Duration of therapy
Age	Continuity of care	Adverse effects
Comorbid conditions and polypharmacy		Immediacy of evidence of benefit

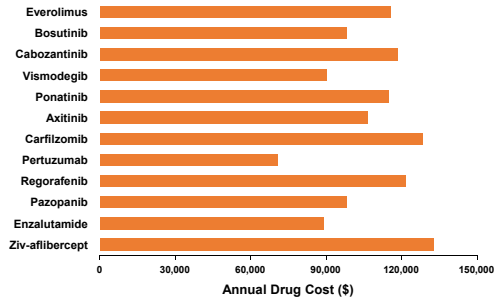
Hartigan K. *Clin J Oncol Nurs*. 2003;7(6 Suppl):21-24. Patridge AH, et al. *J Natl Cancer Inst*. 2002; 94(9):652-661. Winkeljohn DL. Clin *J Oncol Nurs*. 2007;11(6):793-796. Ruddy K, et al. *CA Cancer J Clin*. 2009;59(1):56-66.

Patient/Caregiver Safety

Dos for Oral Oncolytics	Don'ts for Oral Oncolytics
Review Rx and ensure understanding of directions	Leave medications in open area
Use gloves and wash hands when handling	Store med where food/drink are
Keep list of ADEs	Crush, break, or chew
Return unused, expired, damaged, discontinued med to pharm or hospital	Double up on doses
Minimize number of people administering	Assume oral is safer than IV
Wash pts clothes and linen separately	Skip doses
Double-flush toilet after use, during use and 4 to 7 days after d/c	Discard med down toilet or in garbage
Report all medications/OTC/herbals you are taking	

ADEs = adverse drug events; OTC = over-the-counter.
Goodin S, et al. *J Oncol Pract*. 2011;7(1):7-12.

Annual Cost for Selected Oncolytics



Hirsch BR, et al. *Health Aff*. 2014;33(10):1714-1720.

Financial Toxicity

Grade	Description
1	Lifestyle modification (deferral of large purchases or reduced spending on vacation and leisure activities) because of medical expenditures. Use of charity/grants/fundraising/copayment program mechanisms to meet costs of care.
2	Temporary loss of employment resulting from medical treatment. Need to sell stocks/investments for medical expenditures. Use of savings accounts, disability income, or retirement funds for medical expenditures.
3	Need to mortgage/refinance home to pay medical bills. Permanent loss of a job as a result of medical treatment. Current debts > household income. Inability to pay for necessities such as food or utilities.
4	Need to sell home to pay for medical bills. Declaration of bankruptcy because of medical treatment. Need to stop treatment because of financial burden. Consideration of suicide because of financial burden of care.

Khera N. *J Clin Oncol*. 2014;32(29):3337-3338.

Questions?