

## An Overview of Newer Non Hormonal Oral Chemotherapy Agents



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### Introduction

Oncology is the most heavily studied therapeutic area, as measured by research dollars and volume of drug candidates. When considering all current pipeline medications, 40% are being studied for oncology purposes, and of these, 35% are oral formulations. It is projected that 25% of chemotherapy will be delivered in oral formulation by 2013. Thus, oral chemotherapy will continue to create the need for knowledgeable practitioners outside of the oncologist's office and will accentuate the need to connect the payer, patients and pharmacy providers. These therapies are complex, with complex dosing regimens and toxicity profiles. In addition, the new oral chemotherapy drugs are costly, and as the list of approved drugs and indications grows, it will be increasingly important to develop an understanding of the clinical issues that encompass oral chemotherapy agents. This newsletter provides a review of some basic information about the newer non hormonal oral chemotherapies.

### Potential Advantages of Oral Chemotherapy

Providing chemotherapy as an oral and portable formulation offers patients obvious advantages over infused therapies. Oral chemotherapy can offer some flexibility in start of treatment timing, and the pharmacokinetics of some oral chemotherapy also offers an advantage of prolonged drug exposure. As measured by patient convenience and

patient preference, oral therapy is seen as an advantage compared to infused therapy.<sup>1</sup> Another potential advantage of oral chemotherapy is that, even with the high cost of the new drugs, oral administration offers the potential for reduced use of health care resources compared to infused therapies.

### Potential Problems with Oral Chemotherapy

However, oral chemotherapy is not a panacea for patients who have cancer. There are many challenges associated with oral chemotherapy, one being high out-of-pocket expense. High copayments or high deductibles frequently make oral drug therapy unaffordable. A second barrier may be availability and ease of access, as some manufacturers contract with a limited number of dispensing pharmacies.

Adherence may also pose a problem. Patients may not understand how to take their medicine according to their chemotherapy cycle or in association with their concomitant infused chemotherapy. Additionally, some patients' reluctance to accept a cancer diagnosis and treatment regimen may cause them to avoid taking oral chemotherapy because it is an intrusive daily reminder of the disease that they are fighting.

Other disadvantages related to the oral formulation center on adverse drug reactions, drug-disease interactions, and drug-drug interactions. Because patients are not coming into a clinic setting for an infusion, there may be less frequent patient monitoring for oral chemotherapy. Several weeks may elapse between patient visits to the prescriber, and without outbound patient phone calls, monitoring

## An Overview (continued)

for adverse effects does not occur and patient misconceptions about the proper use of the drug can go undetected and uncorrected.<sup>2</sup> Inherent to any oral drug molecule is bioavailability, which is compounded in cancer by nausea and vomiting and can be particularly problematic if an oral chemotherapy drug dose is expelled by vomiting. Lastly, nearly all of the oral kinase inhibitors are metabolized thru the CYP3A4 system, and are affected by CYP3A4 inhibitors and CYP3A4 inducers, some significantly. These drug-drug interactions create the potential for dangerously high levels, or the need for an increase in the dose of these already costly medications. These features highlight the complicated clinical aspects of the oral chemotherapy drugs, and the benefit of a multi-disciplined and high-touch approach to patient care.



## Summary of the Products

Tables 1 and 2 provide a summary of some of the currently available non hormonal oral chemotherapy drugs. The information provided is not intended to be clinical guidance, but only to offer a categorization of the newer oral chemotherapy drugs, and provide an idea of the unique qualities of each product. The tables do not include complete product information. Please see the respective full prescribing information sheets for more complete product information. Please note that this is a rapidly changing area, and the information provided is current as of the date of publication.

One of the main areas where research has found successful drug candidates is within the kinase receptors, which are proteins and are important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism and cell death in response to external and internal stimuli. Though their activity is tightly regulated in normal cells, over expression or aberrant activity is a hallmark of malignant cells, and they may acquire transforming functions due to mutations, overexpression, and autocrine paracrine stimulation, leading to malignancy.<sup>3</sup> A commonality among the drugs that inhibit tyrosine kinases or other kinases is that they can be thought of as “cancer growth inhibitors” or a drug that blocks the growth factors that trigger the cancer cells to divide and grow.

One way we can begin to understand tyrosine kinase inhibitors is by categorizing the tyrosine kinase affected. For example, the epidermal growth factor receptor (EGFR) inhibitors are associated with some of the dermal adverse events, such as rash and hand and foot disease. The vascular endothelial growth factor (VEGF) inhibitors are associated with some of the vascular events, such as edema or hypertension. Interestingly, if a patient experiences more pronounced dermal adverse effects, it may be a signal that the drug is working for that patient. Other targets of kinase inhibitors include platelet derived growth factor receptor (PDGFR), Breakpoint cluster region-Abelson (BCR-Abl), and the B-Raf protein (BRAF). There are also several others (e.g., SRC, STAT, cMYC, RAS, FLT3, cKIT). These targets of the kinase inhibitor may be located intracellularly or extracellularly. There are many drugs in Table 1 that block one or more kinases. ■

**Table 1. Newer Non Hormonal Oral Chemotherapy Drugs: Kinase Inhibitors**

	<b>Generic name   Brand name Manufacturer</b>	<b>Cancer type* (as general categories)</b>	<b>Usual Dosage^ [Available strengths]</b>
<b>Tyrosine Kinase Inhibitors</b>			
EGFR inhibitors	<b>Erlotinib   Tarceva® Genentech and OSI</b>	NSCLC Pancreatic	100 mg -150 mg/dose. Once daily [available as: 25, 100, 150 mg tablets]
	<b>Gefitinib   Iressa® AstraZeneca</b>	NSCLC Limited distribution Use limited to current patients	250 mg/dose. Once daily [available as: 250 mg tablets]
EGFR and HER2 inhibitor	<b>Lapatinib   Tykerb® GlaxoSmithKline</b>	HER2(+) Metastatic breast cancer	1250 mg/dose. Once daily [available only as: 250 mg tablets]
BCR-Abl kinase inhibitors	<b>Dasatinib   Sprycel® BristolMyersSquibb</b>	Ph+ CML, newly diagnosed Ph+ ALL	100 -140 mg/dose. Once daily [available as: 20, 50, 70, 80, 100, 140 mg tablets]
	<b>Nilotinib   Tasigna® Novartis</b>	Ph+ CML, newly diagnosed	300 mg/dose. Twice daily. [available as: 150 and 200 mg capsules]
Multiple tyrosine kinase inhibitors (PDGFR, VEGFR, KIT, FLT-3 and others)	<b>Sunitinib   Sutent® Pfizer</b>	Gastrointestinal (GIST) Renal cell Pancreatic (pNET)	37.5 mg -50 mg/dose. Once daily [available as: 12.5, 25, 50 mg capsules]
	<b>Sorafenib   Nexavar® Onyx and Bayer HealthCare</b>	Renal cell Hepatocellular	400 mg/dose. Twice daily [available as: 200 mg tablets]
	<b>Pazopanib   Votrient™ GlaxoSmithKline</b>	Renal cell	800 mg/dose. Once daily [available as: 200 mg tablets]
	<b>Imatinib   Gleevec® Novartis</b>	Ph+ CML Gastrointestinal (GIST) Dermatofibrosarcoma protuberans Chronic eosinophilic leukemia	400 mg or 600 mg/dose. Once daily [available as: 100, 400 mg tablets, scored]
	<b>Vandetanib   Caprelsa® Astra Zeneca</b>	Medullary thyroid cancer	300 mg/dose. Once daily [available as: 100, 300 mg tablets]
<b>Other Kinase Inhibitors</b>			
Serine/threonine-protein kinase	<b>Vemurafenib   Zelboraf™ Genentech</b>	Metastatic melanoma with BRAF mutation	960 mg/dose (4 tablets). Twice daily [available as: 240 mg tablets]
mTOR kinase inhibitor	<b>Everolimus   Afinitor® Novartis</b>	Renal cell Pancreatic (PNET) Subependymal giant cell astrocytoma	10 mg/dose. Once daily [available as: 2.5, 5, 7.5, 10 mg tablets, not scored]

\*Cancer type listed is not inclusive of place in therapy

^ Dose modifications may be required for renal/hepatic impairment, drug interactions.

NSCLC= non small cell lung cancer; HER2 =Human Epidermal Growth Factor Receptor 2; Ph+ CML =Philadelphia chromosome positive chronic myeloid leukemia; PNET=Progressive neuroendocrine tumors of pancreatic origin; GIST= Gastrointestinal stromal tumor ; LVEF = left ventricular ejection fraction; mTOR= mammalian target of rapamycin  
Please see the most recently published complete prescribing information for each product.

**Table 2. Newer Oral Chemotherapy Drugs: Non Kinase Inhibitors**

	<b>Generic name   Brand name Manufacturer</b>	<b>Cancer type* (as general categories)</b>	<b>Usual Dosage^ [Available strengths]</b>
	<b>Capecitabine   Xeloda® Genentech</b>	Duke's C colon cancer Metastatic colorectal cancer Metastatic breast cancer	1250 mg/m <sup>2</sup> /dose. Twice daily given in combination and as part of a cycle [available as: 150, 500 mg tablets]
	<b>Temozolomide   Temodar® Merck</b>	Glioblastoma multiforme (GBM) Refractory anaplastic astrocytoma	75 mg/m <sup>2</sup> - 150 mg/m <sup>2</sup> /dose. Once daily. Dosing is cyclical and depends on diagnosis [available as: 5, 20, 100, 140, 180, 250 mg capsules]
	<b>Lenalidomide   Revlimid® Celgene</b>	Multiple myeloma (MM) Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS)	MM: 25 mg/dose Once daily, as part of a cycle [available as: 5, 10, 15, 25 mg capsules]
	<b>Thalidomide   Thalomid® Celgene</b>	Multiple myeloma (MM) Erythema Nodosum Leprosum (acute)	MM: 200 mg/dose Once daily [available as: 50, 100, 150, 200 mg capsules]
	<b>Fludarabine phosphate   Oforta™ sanofi-aventis</b>	B-cell chronic lymphocytic leukemia (CLL)	40 mg/m <sup>2</sup> /dose Once daily x5 days as part of a cycle [available as 10 mg tablets]
	<b>Vorinostat   Zolinza® Merck</b>	Cutaneous T-cell lymphoma (CTCL)	400 mg /dose Once daily [available as 100 mg capsules]

\*Cancer type listed is not inclusive of place in therapy

^ Dose modifications may be required for renal/hepatic impairment, drug interactions.

Please see the most recently published complete prescribing information for each product.



With the complexities of oral chemotherapy, patients need a partner in specialty pharmacy. For our patients who require financial assistance to meet insurance requirements, or who need to meet prior authorization criteria, our Patient Financial Advocates (PFAs) complete the tasks needed and navigate the labyrinth of insurance and financial aspects to help them obtain and maintain their oral chemotherapy.

## Effects of Cost on Adherence

A study presented at the Academy of Managed Care Pharmacy 2010 annual meeting found that 1 in 6 patients (16.6%) with an oral oncology out-of-pocket expense of greater than \$200 on their first claim abandoned therapy and were at least 3 times more likely to abandon their oral oncology therapy than patients with an out-of-pocket cost of \$100 or less on the first claim.<sup>4</sup> Conversely, the abandonment rate was 4.9% if the out-of-pocket expense was \$0-\$100. Strikingly, nearly 1 in 3 patients (28.8%) abandoned their oral chemotherapy if the out-of-pocket expense was \$500. ■

## Fairview Specialty Pharmacy Approach

Fairview Specialty Pharmacy has found that many patients face financial and logistical barriers in the form of prior authorization criteria, high copayments, high deductibles, or non formulary medications. Thus, each of our patients is assigned a Patient Financial Advocate (PFA), who facilitates care by helping patients obtain the drug prescribed. Our PFAs submit clinical information to payers and request prior authorizations, and once a prior authorization request is approved, they identify alternative sources of funding for copayments, co-insurance, or sometimes the full cost of the drug therapy. Some of the financial resources that they tap into are manufacturer programs, copay assistance cards, foundation grants and charity care programs. Our PFAs are truly patient-centric, and they provide a level of service that is welcomed by patients and prescribers.

To help patients maintain their oral chemotherapy, Fairview Specialty Pharmacy's Oral Chemotherapy Program is designed to help patients safely and successfully take oral medications for cancer. Our Therapy Management program provides regular telephone calls from nurses and pharmacists who have special training in cancer treatment. During these calls, we provide common sense ways to stay on schedule with oral oncology medications and to manage and reduce side effects. In addition, Fairview patients also have access to a medication therapy management (MTM) pharmacist who is board certified in oncology. The MTM pharmacist is able to provide a comprehensive review of drug-drug and drug-disease interactions, including a review of supplements and dietary factors (such as grapefruit juice, a CYP3A4 inhibitor) that could affect the patient's treatment. ■

### References

- <sup>1</sup> Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health Syst Pharm.* 2007;64 (Suppl 5):S4-7.
- <sup>2</sup> Bartel S. Safe practices and financial considerations in using oral chemotherapeutic agents. *Am J Health Syst Pharm.* 2007; 64(Suppl 5): S8-14.
- <sup>3</sup> Paul M, Mukhopadhyay A. Tyrosine kinase – Role and significance in Cancer. *Int J Med Sci.* 2004; 1(2): 101–115.
- <sup>4</sup> Starner CI, Gleason PP, Gunderson BW. Oral Oncology Prescription Abandonment Association with High Out-of-Pocket Member Expense. *J Manag Care Pharm.* 2010;16(2):161-162.

**Fairview Specialty Pharmacy** provides comprehensive specialty pharmacy services. As part of Fairview Health Services, a nonprofit healthcare system including the University of Minnesota Medical Center, we have expertise across the full spectrum of specialty diseases and provide a personalized approach that builds trust with our patients. We leverage our relationships with clinical experts and key opinion leaders at the University of Minnesota Medical Center and its affiliated Masonic Cancer Clinic.



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