Effective Symptom Management to Optimize Care with Oral Cancer Therapy

Peg Esper, DNP, ANP-BC, AOCN
Nurse Practitioner
University of Michigan Comprehensive Cancer Center
Thank you to......

• ONS Awards Committee
• My colleagues who nominated or provided letters of recommendation for me:
  – Christopher Friese
  – Lisa Schulmleister
  – Lita Smith
  – Suzette Walker
• My patients
• My husband and family
What Do We Know?

• In 2010, 10% of cancer therapy was given as oral agents
• This year, it is estimated that 25% of all oncology agents will be provided as an oral formulation
• There has been little in the way of national guidelines to provide direction on how to best manage oncology patients receiving oral therapies

Halfdanarson & Jatoi, Curr Oncol Rep, 2010; Moody & Jackowski, CJON, 2010
Advantages of Oral Agents

- Possible enhanced blood levels of drug and sustained tumor exposure to drug
- No IV access needed!
- Possible decrease in trips to clinic
- Less issues with transportation (drivers)
- Can help maintain work schedules for those patients wishing to work
Oral Therapeutics Trivia

• 5% of all hospital visits due to drug non-compliance [Est. $100 Billion/year]
• 69% of hospital visits for adverse drug reactions are secondary to incorrect self administration
• After 4 years of hormonal treatment, adherence rate drops to 50% in breast cancer patients
• Medicare beneficiaries abandon medications almost 2x more than those with commercial insurance

Streeter et al., JOP, 2011
Oral Agents Currently Used In Oncology

• Hormonal Therapy (i.e. - Aromatase Inhibitors)
• Chemotherapy (i.e. - Cyclophosphamide, Temozolamide, Chlorambucil)
• Small Molecule Inhibitors of EGFR, VEGF, BRAF, etc. (i.e. – erlotinib, imatinib, sunitinib, pazopanib, laptatinib, vemurafenib, cabozantinib, vandetanib)
• mTOR Inhibitors (i.e. – everolimus)
Issues Surrounding Oral Cancer Therapy

Maintaining Patients On Treatment

Toxicity Management

Finances

Education

Adherence
Definition of Adherence:
“The degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to timing, dosage and frequency.”

*International Society for Pharmacoeconomics and Outcome Research [ISPOR]*

- Patient Related
  - Cognitive
  - Depression
  - Support
  - Belief in Value
- Treatment Related
  - Stage of disease
  - Side effects of treatment
  - Complexity of treatment
  - Drug interactions
  - Label warnings
- Overadherence and Underadherence
- Range of 16-100%
• Evaluate coverage at time prescription written
  – Tier of agent [Often a “Specialty Tier”]
  – Preauthorization
  – Partial prescription authorization
  – Medicare Part D
    • % Copay
    • Donut hole

• Drug costs $1000-$80,000
• Most companies have patient assistance programs in place
• Pre-authorizations frequently required
• Two week start up prescriptions are common
• Assistance programs follow a calendar year
• Oral oncology agents present a multitude of educational challenges for providers
  – Rationale for use
  – Mechanism of action
  – Drug Interactions
  – How to administer
    • Number of pills/times per day
    • With or without food
    • With or without other meds
    • Safe Handling
• Who provides the patient education
  – Nursing staff may not see patients who are given prescriptions for oral agents during a clinic visit
  – Patient teaching visits may not be scheduled prior to a new therapy being initiated
  – Education can take considerable time and involve multiple issues
    • i.e. – How to take blood pressure readings
  – Patients get information from family, friends, websites and often misinformed individuals

• All non-reimbursable activities
Patients Get Info From Many Sources
• Many patients and family members perceive oral cancer therapy to have minimal to no side effects
• Estimates of 1 to 19% or more reported for patients who stopped taking their oral cancer therapy because of side effects
Toxicities Associated With Targeted Therapies

- Can result in decreased QOL for patients
- Can result in decreased compliance with therapy
- Can result in interruptions, dose reductions or discontinuation of therapy
- Require ongoing monitoring by healthcare providers
Monitoring Toxicity Challenges

- Visit frequency often less with oral agents
- Patients may not provide information about toxicities experienced between cycles of therapy [even in person]
- When to hold treatment
- Communication gaps
- Nonadherence to keeping diaries / logs
- E-mail use/abuse
- Interactions!!!!
Side Effects Based On Class of Agent

- Chemotherapy
- EGFR Inhibitors
- VEGF Inhibitors
- mTOR Inhibitors
- Others
Taking a Look at Common Toxicities

- Hypertension
- Hand Foot Skin Reaction
- Diarrhea
- Rash
- Mucositis
- Fatigue
Case Study #1

• 49 y/o female presents with chest pain, pleural effusion and L renal mass Jan, 2011
• Feb, 2011: Bx chest wall mass + for kidney cancer (PAX 8+ IHC)
• Sept, 2011: R lung nodule increased with new hilar and subcarinal adenopathy
• Feb, 2012: VEGF inhibitor tx
• Current antihypertensive medication:
  – Lisinopril 40 mg po bid
• Week 2: Seen for follow up toxicity evaluation
  – Complains of increasing headaches last several days
  – BP Log shows last 3 days systolic BPs 150 to 170 and diastolic BPs 90 to 104
  – Sphygmomanometer checked and is accurate
• Add amlodipine 5 mg to lisinopril 40 mg bid for worsening HTN
• Week 4: Amlodipine increase to 10 mg qd and Losartan 50 mg daily was added to maintain BP
Hypertension

- Class effect of VEGF inhibitors [9-30% incidence]
- Proposed Mechanism of Action:
  - Inhibition of endothelial nitric oxide synthase path
  - Increased vascular tone and peripheral resistance
- Grading
  - JNC7

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

Larkin et al., 2013, Amer J Clin Onc; Appleby et al., 2011; Hematol Oncol Clin N Am
Sprouting angiogenesis

- Tumor cells
- Hypoxia
- Release of soluble factors: cytokines, growth factors, guidance molecules and MMPs
- ECM remodeling
- Intravasation
- EPC

Vasculogenesis

- Recruitment of EPCs
- Stem cells, EPCs
- Notch1, VEGFR2
- VEGF
- Cancer stem cell differentiation
- Notch ligand, Ang-2
- Vascular mimicry

Weis & Cheresh, Nature Medicine, 17, 1359–1370 (2011) doi:10.1038/nm.2537
2 Weeks Later: Grade 2/3 HFSR
Rx for 40% Urea OINTMENT started
3 Weeks Later: Still with HFSR (slight improvement but very painful)
Increase in analgesics (oxycodone/APAP)
May, 2012 CT: marked decrease in adenopathy
  – Continues with all supportive measures
Hand Food Skin Reactions [HFSR]

• Another class effect of VEGF inhibitors
  – Incidence as high as 30% or more based on agent
  – Thickened skin with patchy hyperkeratodermia seen mostly over pressure areas
  – Discomfort can be severe and prevent ambulation

• Proposed mechanism of action:
  – Possibly a purely mechanical phenomenon
  – Postulated as related to increased eccrine sweat glands in extremities and blockage of receptor tyrosine kinases by VEGF inhibitors (ie. c-kit)
  – Hypothesized to be potentially related to affects of agents on keratinocyte differentiation
HFSR Management

- Evidence based practice strategies lacking
- Intervention recommendations largely based on anecdotal and “common sense” approaches
  - Avoid activities that lead to increased pressure
  - Gel inserts in shoes
  - Pre-treatment management of skin problems
  - Frequent application of emollient creams
  - Analgesic support
  - Treatment holidays for high grade toxicity
Additional EBP

• Limited trials have been completed to evaluate efficacy of interventions for HFSR
• Some success noted with use of 40% urea cream in addition to 0.1% tazarotene or 5% fluorouracil cream bid
• Evidence for break in therapy to allow symptoms to resolve followed by reinitiating treatment
Dermatologic Toxicities Observed With VEGF Inhibitor/MKI Therapy

- Hand Foot Skin Reaction
- Rash / desquamation
- Hair depigmentation
- Trichomegaly
- Paronychia / Subungal hemorrhages
- Xerosis
- Mucositis
- Pruritis
- Bullae
- Yellowing of skin
- Impaired wound healing

Bonny et al., 2011; Esper et al, 2007.
• RL is a 69 y/o male diagnosed with NSCLC and placed on an EGFR inhibitor therapy
• He contacts the clinic 8 days into treatment complaining of a pruritic and papular rash
• He indicates he hadn’t been using any cream on his skin, but states it really isn’t bothering him that much
• You request that RL come to clinic so that you can evaluate his rash, but advise that he can take diphenhydramine if the pruritis is bothering him
• RL comes to clinic and has a rash covering much of his face as well as his chest and upper arms
• The rash is erythematous and small papules are present – some are fluid filled
• No evidence of infection is seen
Grading of Dermatologic Toxicities

• Some debate continues regarding the most effective way to grade dermatologic toxicities associated with the various targeted therapies

• The NCI/CTC has been the standard

• Problems with this criteria have been identified based on the use of coverage of body by % as the determinant of grade
CTCAE v4.02

Grading is based on percentage of BSA covered by macules/papules

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>&lt;10% BSA with or without symptoms (eg, pruritus, burning, tightness)</td>
</tr>
<tr>
<td>2</td>
<td>10-30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL</td>
</tr>
<tr>
<td>3</td>
<td>&gt;30% BSA with or without associated symptoms; limiting self-care ADL</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
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Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.

ADL = activities of daily living; BSA = body surface area.
• EGFR is found in keratinocytes in the epidermis
  - Inhibits inflammation and is important in wound healing
  - In adults, high levels of EGFR are found in the basal and suprabasal layers of the epidermis as well as the outer root sheath of hair follicles
• EGFR has an important role in the development and maintenance of the epidermis
• Dermatologic toxicity is an anticipated effect of EGFR inhibition

Lacouture et al, 2011.
### Incidence of EGFR Dermatologic Toxicities

- **Rash (papulopustular)**: 60%–80%  
  Onset: 1-2 weeks
- **Xerosis**: 4% - 35%  
  Onset: 2-3 weeks
- **Paronychia**: 6%–12%  
  Onset: 2-8 weeks
- **Hair changes**: 5%–6%  
  Onset: 12-24 weeks
- **Hypertrichosis/trichomegaly**: 20%  
  Onset: 4-8 weeks

Lynch et al., 2007; Wu et al., 2011.
Prophylactic Treatment of EGFRI Rash

• Skin moisturizer creams / ointments
• Avoidance of excessive sun exposure
• Avoidance of hot showers or hot water on hands
• Avoid any products having an alcohol base
• Based on recent randomized clinical trials:
  – Minocycline (or Doxycycline)
  – Skin moisturizer
  – Sunscreen (PABA free, > 15 SPF, UVA/UVB)
  – 1% Hydrocortisone Cream

Balagula et al., 2011; Lacouture et al., 2011
• Grade 3
  – Modify dose of agent
  – Consider cultures to evaluate for infection
  – Consider addition of oral steroid

• Grade 4
  – Discontinue treatment
Rash Management: BRAF Inhibitors

• Rash
  – May occur with or without pruritis
  – Start as mild erythematous macular rash that progresses to a papular or even pustular level
  – Moisturizing creams are recommended for grade I/II rashes, but should be free of alcohol base or fragrance
  – Use of minocycline for papular/pustular rashes
  – Hold/discontinue treatment per protocol guidelines
  – Pruritis can be managed with antihistamines such as diphendydramine ATC
  – Patients should be instructed to take cool/tepid showers
  – Avoid introduction of perfumes, new laundry detergents, or soaps
  – Steroids may be required for severe (grade 3/4) rashes
Rash Management: mTOR Inhibitors

- Onset typically within one month
- Supportive measures
- Usually associated with pruritus
- Topical steroids for higher grade rashes
- Dose modification infrequent

Rash Management: VEGFRIs, MKIs

- Significantly less research on rash management in this patient population
- Rash typically is not as severe as that seen with EGFR inhibitors and occurs in smaller percent of patients
- Antibiotics and steroids are not usually recommended
- Treat based on grade of rash
  - Emollient creams prophylactically
  - Dose reduction and treatment discontinuation when indicated
- More significant skin toxicity typically Hand Foot Skin Reaction (HFSR)
• 61 y/o male who stays in Florida during winter months. Progressive disease on CT at last visit
• Change in therapy to another oral targeted agent
• Returns to Michigan for two week toxicity check
• "I can't tolerate this medication." On Day 10 he developed fatigue, all over joint pain, and profuse diarrhea. Not improved despite loperamide and diphenoxylate-atropine
• Treatment has been on hold for two days following a call to clinic to notify of symptoms
Gastrointestinal Toxicities of Oral Targeted Agents

- Diarrhea
- Nausea
- Vomiting
- Dyspepsia
- Stomatitis / Mucositis
- Anorexia
- Altered taste

Diarrhea

- Incidence completely variable based on patient characteristics, agent and other comorbidities

- Mechanism of Action: Unclear
  - Possible direct damage to intestinal mucosa
  - Possible changes to normal intestinal microflora and effect on Cajal cells leading to dysmotilllity
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces. Entirely Liquid</td>
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Diarrhea Management

• Careful consideration when treating patients with history of chronic GI syndromes (IBS, etc.)
• Patient education re: use of loperamide, pepto bismol and when to contact HCP
• Maintain adequate hydration, evaluate need for additional IV hydration, dietary modifications
• Increase use of psyllium products
• Evaluate need for prescription anti-diarrheals
• New evidence for use of Probiotics (lactobacillus rhamnous GG)
• Evaluate need for interruption of therapy
FATIGUE

• Prevalence as high as 99% in the general cancer population
• Multidimensional etiology
• Potential Causes Include:
  – Anemia
  – Endocrinopathies
  – Treatment Induced
  – Depression
• Fatigue Research
Evidence?

Evidence Suggests Benefit.....
Exercise       Relaxation       Massage
Screen for contributing factors
Measures to improve sleep patterns

Balance Benefit With Potential Harm: ESA’s

Mixed Reviews:
Acupuncture  Methylphenidate  Modafinil

No Effectiveness Has Been Proven.....
Hypnosis      Paroxetine      Reiki
Yoga          Chinese medicinal herbs

ONS PEP, Lower, 2009
Expert Opinions

• Increase Hydration
  – Cytokine production may be increased as a result of both disease and treatment [i.e. diarrhea]
  – This can lead to patients being “dry”
  – A known symptom of dehydration is fatigue
  – Cells that are well hydrated are able to function at a more normal capacity
  – Research is needed in this area!!!!
Management of Oral Mucositis/Ulcers

• Nonpharmacologic
  – Avoid harsh agents such as hydrogen peroxide, iodine and thyme derivates, as well as alcohol-containing mouthwashes
  – Oral care with a soft toothbrush and mild toothpaste in addition to saline rinses
  – Bioadherent oral gels can be applied to lesions to reduce discomfort during eating

• Pharmacologic
  – Avoid antifungal agents unless a fungal infection is diagnosed
  – Analgesics may be required

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Cochrane Review - Mucositis

• Most effective: ICE CHIPS / Cryotherapy

• Specific circumstances
  – Keratinocyte Growth Factor

• Less effective
  – GMCSF
  – Honey
  – Low intensity laser

Worthington, Cochrane Review, 2013
Drug-Drug Interactions of Targeted Therapies

• CYP3A4 metabolic pathway
  – CYP3A4 inhibitors & inducers
  – Dose adjustment may be indicated
  – Avoid grapefruit juice (CYP3A4 inhibitor)
  – Avoid St. John’s Wort (CYP3A4 inducer)

• Warfarin
  – Monitor PT/PTT and INR
  – Monitor for bleeding

• H2 antagonists

• Others!!!
New ASCO/ONS Guidelines

• For oral chemotherapy, the frequency of office visits and monitoring that is appropriate for the individual and the antineoplastic agent and is defined in the treatment plan.

• Before initiation of an oral chemotherapy regimen, assessment of the patient’s ability to obtain the drug and administer it according to the treatment plan is documented, along with a plan to address any identified issues.

• Assessment includes socioeconomic, psychosocial, financial, administrative and regulatory factors that may influence initiation and/or adherence to prescribed regimen.
Chemotherapy drugs are labeled immediately upon preparation, including, at minimum:

- Administration instructions (oral agents)
- Number of refills (oral agents)
- Prescriber name (oral agents)

The practice/institution maintains a plan for ongoing and regimen-specific assessment of each patient’s oral chemotherapy adherence and toxicity. The policy includes, at minimum, patient assessment for adherence and toxicity at each clinical encounter at the practice/institution, as well as a plan for clinical staff to address any issues identified.
Strategies To Improve Care
For Patients Receiving Oral Oncology Agents

• Increase frequency of visits when starting a new oral therapy
• Provide phone support
• No more than one cycle of therapy on a prescription
• Patient diaries, logs
• Educational materials for symptom management strategies
More Pearls......

• Be certain patient gets the drug after Rx written
• Patient education on side effects and their management with 24/7 number to call for problems
• Thorough evaluation of con meds – if toxicity out of what is expected, check again
• Check home blood pressure monitoring equipment for accuracy
• Early and aggressive management of toxicities of targeted therapies can help to maintain patients not only on treatment, but at optimal dosing levels
Never Forget the Patient Perspective
The Future

• Oral therapies have resulted in a transformation of cancer care

• Future treatment will continue to be customized for individual patients and take into consideration such factors as specific genetic alterations, metabolic factors and unique histologic features

• It is an amazing time to be an oncology nurse!
References


