Managing Toxicities of Oral Antineoplastic Agents

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Disclosure

• I have no conflicts of interest to disclose

• I will be discussing off-label use of medications
Learning Objectives for Pharmacists

1. Identify common oral antineoplastic agents
2. Review key toxicities of oral antineoplastic agents
3. Describe interventions to manage toxicities
4. Formulate recommendations to manage toxicities
Learning Objectives for Pharmacy Technicians

1. Recognize common oral antineoplastic agents

2. Review special handling processes involved in filling prescriptions for oral antineoplastic agents

3. Formulate dispensing regimens using available dosage strengths
Background
Cancer Trends in the United States

New Cases, Deaths and 5-Year Relative Survival

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<tbody>
<tr>
<td>5-Year Relative Survival</td>
<td>48.7%</td>
<td>49.1%</td>
<td>52.5%</td>
<td>57.7%</td>
<td>61.6%</td>
<td>66.0%</td>
<td>67.3%</td>
<td>68.9%</td>
</tr>
</tbody>
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Strides Made in Molecular Biology
Development of Oral Antineoplastic Agents

- Mercaptopurine (1953)
- Methotrexate (1953)
- Capecitabine (1998)
- Lenvatinib (2016)

< 20 approved

>> 20 approved

OAA Approved Before 1998

- 6-mercaptopurine
- Methotrexate
- Busulfan
- Chlorambucil
- Cyclophosphamide
- Melphalan
- Thioguanine
- Hydrea
- Procarbazine

- Mitotane
- Lomustine
- Tamoxifen
- Etoposide
- Eulexin
- Bicalutamide
- Nilutamide
- Letrozole
OAA Approved Since 1998

- Capecitabine
- Thalidomide
- Exemestane
- Temozolomide
- Bexarotene
- Imatinib
- Gefitinib
- Erlotinib
- ATRA
- Sorafenib
- Lenalidomide
- Dasatinib
- Sunitinib
- Vorinostat
- Topotecan
- Nilotinib
- Lapatinib
- Everolimus
- Pazopanib
- Ruxolitinib
- Vandetanib
- Crizotinib
- Vemurafenib
- Abiraterone
- Enzalutamide
- Pazopanib
- Regorafenib
- Axitinib
- Ponatinib
- Vismodegib
- Cabozantinib
- Bosutinib
- Dabrafenib
- Pomalidomide
- Trametinib
- Ibrutinib
- Afatinib
- Ceritinib
- Idelalisib
- Olaparib
- Osimertinib
- Sonidegib
- Ixazomib
- Trifluridine &Tipiracil
- Lenvatinib
- Palbociclib
- Panobinostat
- Cobimetinib
- Alectinib
No OAA approved for the following cancer types: anal, bladder, bone, esophageal, Kaposi’s sarcoma, malignant mesothelioma, Multicentric Castleman Disease, neuroblastoma, penile, retinoblastoma, rhabdosarcoma, testicular, vaginal, vulvar, Wilms’ Tumor
Advantages of OAA

- Increased survival
- Acceptability among patients
- Prolonged exposure
- Cost savings?
Changing Landscape

- Parenteral cytotoxic chemotherapy
  - Intravenous infusion
  - Cyclic administration
  - Healthcare facility

- Oral cytostatic anti-cancer therapy
  - Low-dose regimen
  - Chronic, prolonged treatment
  - Home-based
Changing Roles

• Patients and outpatient providers now have a greater larger in ensuring proper use of oral antineoplastic agents

• Challenges
  • Access to medication
  • Adherence
  • Toxicities
  • Drug interactions
  • Cost
  • Misconceptions
Oral Antineoplastic Agents
Audience Question 1

Which is an oral antineoplastic agent?

A. Bevacizumab (Avastin®)
B. Ondansetron (Zofran®)
C. Paclitaxel (Taxol®)
D. Pegfilgrastim (Neulasta®)
E. Temozolomide (Temodar®)
Biggest Selling Oral Oncology Drugs

REPORTED FOR 2014

• Lenalidomide
• Imatinib
• Abiraterone
• Everolimus
• Nilotinib
• Dasatinib
• Erlotinib
• Enzalutamide
• Sunitinib
• Sorafenib

PREDICTED FOR 2020

• Lenalidomide
• Ibrutinib
• Enzalutamide
• Palbociclib
• Pomalidomide
• Nilotinib
• Abiraterone
Review of Select OAA

1990’s
- Capectiabine (1998),
- Temozolomide (1999)

2000’s
- Imatinib (2001),
- Erlotinib (2004),
- Lenalidomide (2005),
- Sunitinib (2006),
- Nilotinib (2007)

Since 2010
- Abiraterone (2011),
- Enzalutamide (2012),
- Ibrutinib (2013),
- Palbociclib (2015)

Classification of OAA

- Traditional
- Hormonal
- Targeted
Traditional OAA

- Interferes with cellular division
  - Cell cycle or non-cell cycle specific

- Class side effects
  - Gastrointestinal toxicity
  - Pyrexia
  - Fatigue
  - Hair damage
  - Nephrotoxicity
  - Pulmonary toxicity
Capecitabine (Xeloda®)

- Pro-drug of 5-fluorouracil
- Approved for colorectal cancer, breast cancer
- Available as a tablet (mg): 150, 500
  - Take within 30 minutes after a meal
- BSA-dosing at 1250 mg/m² twice daily x 2 weeks then 1 week off
- Select side effects
  - Diarrhea, myelosuppression, hand-and-foot syndrome

Chemotherapy-Induced Diarrhea

• Reported in 50 to 80% of patients
  • Depending on chemotherapy
  • Common with capecitabine
  • BSA-dosing at 1250 mg/m² twice daily x2 weeks then 1 week off

• Management
  • Initial – consider dietary modifications
  • Mild to moderate – loperamide, diphenoxylate/atropine, tincture of opium, paregoric, octreotide, budesonide
  • Severe – hospital admission

A patient drops off a prescription to fill Xeloda® 2000 mg p.o. twice daily for a 3-week cycle (2 weeks on then 1 week off). Using 500 mg strength tables, what quantity should be dispensed?

A. 56  
B. 84  
C. 112  
D. 168
Temozolomide (Temodar®)

- Approved for glioblastoma multiforme (GBM), anaplastic astrocytoma (AA)

- Available as a capsule (mg): 5, 20, 100, 140, 180, 250
  - Take on an empty stomach

- BSA-dosing
  - GBM: 75 mg/m\(^2\) x 42 days with radiation therapy, then 150 mg/m\(^2\) once daily for D1-5 of 28d cycle
  - AA: 150 mg/m\(^2\) once daily x 5 days for 28d cycle

- Select Side Effects
  - Myelosuppression, *Pneumocystis* pneumonia
Pneumocystis pneumonia

- Opportunistic infection
  - Caution with concurrent steroids

- Antibiotic prophylaxis
  - Required for concurrent temozolomide and radiation therapy
  - Trimethoprim-sulfamethoxazole
Palbociclib (Ibrance®)

- Cyclin-dependent kinase inhibitor (4 and 6)
- Approved for breast cancer
  - Combination with letrozole/fulvestrant
- Available as a capsule (mg): 75, 100, 125
  - Take with food
- Dose is 125 mg once daily x3 weeks then 1 week off
- Substrate of CYP 3A4
- Side effects
  - Neutropenia, fatigue
Classification of OAA

- Traditional
- Hormonal
- Targeted
Hormonal OAA

• Used in breast cancer, prostate cancer
• Prevent hormone activation or suppress hormone production
• Class side effects
  • Fatigue
  • Hot flushes
  • Mood swings
  • Decreased libido
  • Bone effects
Hormonal Agents for Breast Cancer

• SERMs block estrogen receptors
  • Tamoxifen (Nolvadex®), toremifene (Fareston®), raloxifene (Evista®)
  • Thromboses (Boxed Warning), hypercalcemia, bone effects

• AIs stop estrogen production
  • Letrozole (Femara®), anastrazole (Arimedex®), exemestane (Aromasin®)
  • Arthralgia, osteoporosis

• Side effects
  • Vaginal dryness, night sweats, irregular menstrual periods, cardiovascular risk

AI: aromatase inhibitor; SERM: selective estrogen receptor modulator
Hormonal Agents for Prostate Cancer

• Anti-androgens
  • Flutamide (Eulexin®), bicalutamide (Casodex®), nilutamide (Nilandron®), enzalutamide (Xtandi®), abiraterone (Zytiga®)

• Side effects
  • Gynecomastia: tamoxifen
  • Diarrhea: anti-diarrheals
  • Erectile dysfunction: sildenafil, tadalafil, vardenafil

Muscle and Bone Pain

• Potential risk factors
  • Joint disease, myalgia, obesity, osteoporosis, vitamin D deficiency, PPIs, ACE-I, quinolones, statins

• Pharmacological
  • Acetaminophen, NSAIDs, opiates, capsaicin, tiger balm
  • Daily calcium and vitamin D

• Non-pharmacological
  • Exercise, relaxation techniques, supportive devices
HOT FLUSHES

- Best benefit
  - SSRI antidepressants
  - Caution CYP 2D6
  - Venlafaxine, citalopram
  - Gabapentin
  - Megestrol acetate
- Modest benefit with clonidine

MOOD CHANGES

- Antidepressants most commonly prescribed
  - Start at half dose of expected therapeutic dose
  - Takes several weeks to work
- Caution interactions
  - SSRI and tamoxifen
Enzalutamide (Xtandi®)

• Approved for prostate cancer
  • Dose is 160 mg orally once daily
    • Available as 40 mg capsule

• Select Side Effects
  • Fatigue, diarrhea, myalgia, seizure (Boxed Warning)

• Drug Interactions
  • CYP 2C8 inhibitors: gemfibrozil, ritonavir, irbesartan, rabeprazole, trimethoprim
  • CYP 3A4 or CYP2C8 inducers: warfarin (additional INR monitoring)
Abiraterone (Zytiga®)

• Approved for prostate cancer
  • Dose is 1000 mg orally once daily, with prednisone
    • Available as 250 mg tablet
  • Take on empty stomach

• Select Side Effects
  • Hepatotoxicity (can be serious)
    • Start at lower dose per Child-Pugh Class
    • During treatment: hold, wait to normalize, restart
  • Hypertension, fluid retention, hypokalemia
Audience Question 3

Your opinion is sought about treatment for hot flushes in a breast cancer patient. The patient is taking tamoxifen. What do you recommend?

A. Venlafaxine  
B. Herbal supplements  
C. SSRI, such as paroxetine  
D. Stop taking tamoxifen
Classification of OAA

- Traditional
- Hormonal
- Targeted
TKIs Targeting BCR/ABL

- Used in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST), acute lymphoblastic leukemia (ALL)
  - Imatinib (Gleevec®), nilotinib (Tasigna®), dasatinib (Sprycel®)

- Common Side Effects
  - Low grade toxicity, myelosuppression, nausea, diarrhea, rash

- Effect on bioavailability
  - By food – check individual agents
    - Chronic acid suppression contraindicated with dasatanib

- Metabolized by CYP 3A4 – caution for drug interactions
Imatinib (Gleevec®)

• Used in Ph+ CML, myelodysplastic disease, GIST
  • Available as tablets (mg): 100, 400
  • Take with meal

• Dose ranges from 400 mg to 800 mg daily
  • 400 mg or 600 mg once daily, 800 mg as 400 mg twice daily

• Select side effects
  • Edema, dyspepsia, diarrhea, muscle cramping, rash

• P-gp substrate – caution drug interactions, i.e. PPIs
**Nilotinib (Tasigna®)**

- Used in Ph+ CML
- Dose is 300 to 400 mg twice daily
  - Take on an empty stomach
- Available as capsules (mg)
  - 150, 200
- QT prolongation (Boxed Warning), GI, rash, arthralgia

**Dasatinib (Sprycel®)**

- Used in Ph+ ALL, CML
- Once daily dosing
  - ALL: 140 mg
  - CML: 100 mg or 140 mg
  - Several strengths
- Take with our without food
- Edema, rash, bone marrow suppression
Audience Question 4

Which is the most common side effect of TKIs that target EGFR?

A. Nausea
B. Joint pain
C. Shortness of breath
D. Skin rash
TKIs Targeting EGFR

- Used in lung cancer, pancreatic cancer, breast cancer
  - Erlotinib (Tarceva®), gefitinib (Iressa®), lapatinib (Tykerb®)
    - Lapatinib also targets HER2
      - Take with capecitabine (high bill burden), letrozole, or trastuzumab

- Side Effects
  - Papulopustular rash, diarrhea, interstitial lung disease (rare)

- Bioavailability varies with food – check individual agents

- Metabolized by CYP 3A4 – caution for drug interactions
Erlotinib (Tarceva®)

• Used in non-small cell lung cancer (NSCLC) and pancreatic cancer (+ chemotherapy)
• Once daily dosing
  • NSCLC 150 mg; pancreatic cancer 100 mg
• Available as tablets (mg): 25, 100, 150
  • Take on an empty stomach
• Select side effects
  • Rash (dose-dependent), fatigue, gastrointestinal side effects
• Interactions
  • CYP1A2 minor pathway, warfarin (additional INR monitoring), pH dependent solubility, cigarette smoking
Papulopustular rash

Multi-Targeted TKIs

• Used in several malignancies
  • Pazopanib (Votrient®) – renal cell carcinoma (RCC), sarcoma
  • Sorafenib (Nexavar®) – RCC, liver cancer, thyroid cancer
  • Sunitinib (Sutent®) – RCC, pancreatic neuroendocrine tumor (PNET), GIST
  • Axitinib (Inlyta®) – RCC

• Select side effects
  • Hypertension – interaction with verapamil, diltiazem
  • Hand-foot syndrome

• Bioavailability varies with food – check individual agents
• Metabolized by CYP 3A4 – caution for drug interactions
Hand-foot syndrome
Sunitinib (Sutent®)

- Used in GIST, RCC, PNET
- Available as a capsule (mg): 12.5, 25, 37.5, 50
  - Once daily dosing
  - GIST and RCC: 50 mg for 4 weeks then 2 weeks rest
  - PNET: 37.5 mg once daily continuously
- Select side effects
  - Fatigue, gastrointestinal side effects, mucositis, hand-foot syndrome, heart failure, yellowing of skin/hair, altered taste, QT prolongation

Angiogenesis Inhibitors

• Stop the process of new blood vessel formation

• Used in several malignancies
  • Everolimus (Afinitor®)
    • RCC, breast cancer, brain tumor, PNET
  • Lenalidomide (Revlimid®)
    • Multiple myeloma (MM), non-Hodgkin lymphoma
  • Thalidomide (Thalomid®)
    • MM
Wide Range of Side Effects

- High blood pressure
- Rash
- Hand-foot syndrome
- Diarrhea
- Fatigue
- Neutropenia
- Poor wound healing
Lenalidomide (Revlimid®)

- Used for MM, myelodysplastic syndrome (MDS), mantle cell lymphoma (MCL)
- REMS® program, formerly RevAssist®
- Available as capsules (mg): 2.5, 5, 10, 15, 20, 25
  - Once daily dosing
  - MDS 10 mg; MM and MCL: 25 mg on D1-21 of 28d cycle
- Boxed Warnings: embryo-fetal, hematologic, thromboses
- Common side effects
  - GI side effects, fatigue, edema, insomnia, muscle ache

Revlimid Package Insert. 2015; Image obtained from Lexicomp Online.
Human teratogen

• Females
  • Avoid pregnancy ≥4 weeks before starting lenalidomide, during treatment, and ≥4 weeks after stopping lenalidomide
  • Use two forms of birth control

• Males
  • Use condom for up to 28 days after stopping lenalidomide
  • Do not donate blood during treatment and for 1 month after stopping treatment

Ibrutinib (Imbruvica®)

- Used in chronic lymphocytic leukemia (CLL), MCL
- Inhibits Bruton’s tyrosine kinase
- Available as 140 mg capsule
  - Once daily dosing
  - CLL: 420 mg +/- bendamustine and rituximab
  - MCL: 560 mg
- Select side effects
  - Diarrhea, bleeding, atrial fibrillation
Handling OAA
- Contact with oral oncology therapies
- Accidental exposures
- Dispose cytotoxic medications

- Store separately from non-cytotoxic agents

- Dispose of personal protective equipment as hazardous waste
Protection from OAA

• Use correct personal protective equipment

• Work in a biological safety cabinet

• Keep equipment used for oral oncology agents separate

• Have a plan to handle accidental exposures
Audience Question 5

Which statement is true?

A. There is no concern for using the same counting tray for oral oncology agents and non-oncology agents

B. Oral oncology agents should be disposed of in the same way as hazardous waste

C. Wearing personal protective equipment is not needed while handling oral oncology agents

D. It is not necessary for staff who work with oral oncology agents to be trained about procedures to handle accidental exposure
Audience Question 6

Do you agree with the following?

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
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<tr>
<td>Diarrhea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>Alcohol-free emollient</td>
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<tr>
<td>Edema</td>
<td>Ondansetron</td>
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<tr>
<td>Bone pain</td>
<td>Opiate</td>
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<tr>
<td>Depression</td>
<td>Furosemide</td>
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<tr>
<td>Hand-foot syndrome</td>
<td>SSRI/SNRI</td>
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Now and Future

- Over 25 million doses administered per year in U.S.

- Estimated 400 antineoplastic agents are in the drug development pipeline

- More than 25% will be oral therapies
Conclusion

• OAA are shifting the practice model to the outpatient setting

• Patients and their caregivers need support and education

• Pharmacists
  • Safe prescribing
  • Appropriate counseling
  • Appropriate follow-up and management of toxicities
There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
Managing Toxicities of Oral Antineoplastic Agents

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