Cobimetinib (Cotellic®)/vemurafenib (Zelboraf®) combination therapy is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Cobimetinib is a MEK1 and MEK2 inhibitor, and vemurafenib is an inhibitor of some mutated forms of BRAF kinase, including BRAF V600E. About half of patients with melanoma have a mutated form of the BRAF protein in their tumors. Combination MEK/BRAF inhibitor therapy is associated with superior tumor response and improved patient survival compared with single-agent BRAF inhibitory therapy. Using the combination also decreases the high rates of secondary cutaneous malignancies associated with single-agent BRAF inhibitory therapy.

This document is part of an overall nursing toolkit intended to assist nurses in optimizing care of melanoma patients receiving newer anti-melanoma therapies.
For advanced melanoma, both cobimetinib and vemurafenib are orally administered drugs. Cobimetinib is administered as 60 mg (three 20-mg tablets) once daily for 3 weeks, followed by a 1-week break, and vemurafenib as 960 mg (four 240-mg tablets) twice daily for a total daily dosage of 1920 mg, each according to the regimens outlined below. The cobimetinib dose can be taken at the same time as one of the vemurafenib tablets. If a missed dose of vemurafenib occurs within 4 hours of the scheduled dosing time, take the dose. If the patient misses a dose of cobimetinib or vemurafenib, adjust as follows:

- If the patient misses a dose of cobimetinib or vemurafenib, adjust as follows:
  - Cobimetinib: if ≤4 hours from scheduled dosing time, take the dose. If >4 hours, hold that dose and take the next scheduled dose at the normal time.
  - Vemurafenib: a double dose of either cobimetinib or vemurafenib should NOT be taken to make up for a missed dose.

- If the patient misses a dose of cobimetinib or vemurafenib, adjust as follows:
  - Cobimetinib: if >4 hours from scheduled dosing time, take the dose. If ≤4 hours, hold that dose and take the next scheduled dose at the normal time.
  - Vemurafenib: a missed dose can be taken up to 4 hours prior to next dose.

- Vemurafenib tablets should not be chewed or crushed.

- In general, strong or moderate CYP3A4 inhibitors may be administered with or without food. Vemurafenib tablets should not be crushed or chewed.

- In general, strong CYP3A4 inhibitors should be avoided while taking vemurafenib. If short-term concomitant use of a moderate CYP3A4 inhibitor is unavoidable, reduce the vemurafenib dose from 60 to 20 mg. After discontinuation of the CYP3A4 inhibitor, resume previous dose of vemurafenib.

- In general, strong CYP3A4 inducers should be avoided while taking vemurafenib. If concomitant use of a strong CYP3A4 inducer is unavoidable, increase the vemurafenib dose by 240 mg (one tablet) every 2 weeks. After discontinuation of the CYP3A4 inducer, the vemurafenib dose can be reduced to the dose taken before initiating the strong CYP3A4 inducer.
SIDE EFFECTS AND THEIR MANAGEMENT

• Possible treatment-related adverse events (AEs) should be discussed with patients before initiation of cobimetinib/vemurafenib therapy. Patients should be informed of the importance of immediately reporting any health changes that may reflect a treatment-related AE.

• AEs associated with cobimetinib/vemurafenib therapy can be generally categorized into those that are most common (but typically mild-to-moderate in severity) and less common but serious AEs. Table 1 shows the common and less common but serious AEs associated with cobimetinib/vemurafenib as well as other AEs (Appendices 1 and 2).

Table 1. AEs Associated With Cobimetinib/Vemurafenib

<table>
<thead>
<tr>
<th>irAE category</th>
<th>Examples</th>
<th>Treatment guidance (Appendix number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less common but serious</td>
<td>New primary cancers. - Cutaneous (eg, basal cell or squamous cell carcinoma, keratocanthoma, new melanoma). - Non-cutaneous. Ocular toxicity. Cardiovascular. - Cardiomyopathy (↓ LVEF). - Hemorrhage. - Venous thromboembolism (pulmonary embolism, deep vein thrombosis). - Hemolytic anemia. Colitis and gastrointestinal perforation. Interstitial lung disease/pneumonitis. Renal toxicity.</td>
<td>1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE  1SHARE</td>
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SIDE EFFECTS AND THEIR MANAGEMENT

(continued)

• Severe and sometimes moderate AEs are commonly managed by dose interruptions or withdrawal. In certain cases, referral to a cardiology, dermatology, or ophthalmology specialist is warranted.

Table 2: Recommended Dose Reductions for Cobimetinib/Vemurafenib

<table>
<thead>
<tr>
<th>Cobimetinib</th>
<th>Dose Reduction From 60 mg Orally Once Daily To</th>
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<tbody>
<tr>
<td>First dose reduction</td>
<td>40 mg orally once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>20 mg orally once daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue if unable to tolerate 20 mg once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vemurafenib</th>
<th>Dose Reduction From 960 mg Orally Twice Daily To</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>720 mg orally twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>480 mg orally twice daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue if unable to tolerate 480 mg twice daily</td>
</tr>
</tbody>
</table>
Before beginning targeted therapy, patients who previously received immunotherapy should be monitored carefully for possible overlapping toxicities. Several AEs are observed with both targeted and immunotherapy and may result in cumulative toxicities.

Potential drug-drug interactions are an important component of cobimetinib/vemurafenib therapy for melanoma:

- In addition to interactions with CYP3A4 inhibitors/inducers, cobimetinib/vemurafenib may adversely interact with other drugs to prolong the QT interval. It is important to identify these medications so they are not used concomitantly and/or drugs doses are appropriately modified.
- Patients should be encouraged to have all their medications filled by a single pharmacy to ensure familiarity with the full medication list and to avoid polypharmacy issues.

Patients should be seen by a dermatologist before beginning treatment, every 2 months during treatment, and as many as 7 months after treatment discontinuation.

New skin cancers often initially present as a new wart, skin sore or reddish bump that bleeds or does not heal, and/or as a change in size or color of a mole. Patients should be made aware of this association and advised to immediately report any skin changes to the healthcare team.

Advise patients to take pictures of any skin lesions for documentation.
**QUESTIONS & ANSWERS**

**Q.** Patients often ask me how to tell if the medication is working. What can I tell them?

**A.** You can advise patients that the oncology team will be seeing them on a regular basis, usually at least monthly, to perform a physical exam and review the labs and symptoms. In addition, your team will perform restaging scans every 8–12 weeks to assess response to therapy. A member of the oncology team will be ordering a LDH level, which is a lab test that acts as a marker for melanoma and can help assess the patient’s response to treatment.

Ask your patients to keep a diary of their symptoms and possible adverse events that they might be experiencing with this therapy. Tell the patients that they may also notice certain symptoms, such as pain, starting to lessen, which could mean that their tumor(s) is/are starting to shrink.

**Q.** How long will patients stay on BRAF/MEK inhibitor therapy?

**A.** Most likely, patients will continue therapy if their disease is responding to therapy and they are tolerating the side effects. During the clinical trials, the patients who had to stop therapy were those who had disease progression or had moderate to severe drug toxicities that affected their quality of life and required persistent drug holidays, dose reduction, or discontinuation.
PATIENT RESOURCES

Financial Assistance
Cotellic and Zelboraf Access Solutions
888-249-4918
http://www.genentech-access.com/cotellic/patients

COTELLIC® (cobimetinib)/ZELBORAF® (vemurafenib)
Information Resources
For more information about this therapy and support:
Nursing Hotline
855-MY-COTELLIC (855-692-6835)

Additional Information Resources
AIM at Melanoma Foundation (Nurse on Call, patient symposia, drug resources, etc)
http://www.AIMatMelanoma.org
American Cancer Society: Targeted therapy for melanoma skin cancer
ADDITIONAL RESOURCES


Click here for downloadable action plans to customize for your patients
**Pyrexia**

Care Step Pathway - Pyrexia

### Grading Toxicity

- **Grade 1 (Mild)**: Asymptomatic; mild, low-grade fevers (99.0°F–101.2°F [37.2°C–38.4°C])
- **Grade 2 (Moderate)**: Potentially symptomatic (chills, etc) (101.3°F–104.0°F [38.5°C–40.0°C])
- **Grade 3 (Severe)**: Grade 3 (Severe or Life-threatening); limiting self-care ADLs (40.0°C [104.0°F])
- **Grade 4 (Potentially Life-threatening)**: Grade 4 (Potentially Life-threatening)

### Pyrexia Page 1 of 2

**Grading Toxicity**

- **Relevant Information or National Level**
  - Recent exposure to animals?
  - Recent sick contacts?
  - Symptoms suggestive of infectious etiology
- **Recognize**
  - Recent infection or recent splenectomy
  - Recent splenectomy or recent splenectomy
  - Recent infection or recent splenectomy
  - Recent sick contacts?
  - Symptoms suggestive of infectious etiology
  - Releva
- **Diagnosis**
  - Elevated body temperature in the absence of clinical or microbiological evidence of infection
  - Potential infection in the absence of clinical or microbiological evidence of infection
  - Potential infection in the absence of clinical or microbiological evidence of infection
  - Potential infection in the absence of clinical or microbiological evidence of infection

### Potential Infectious Causes

- **Recent exposure to animals?**
- **Recent sick contacts?**
- **Symptoms suggestive of infectious etiology**
- **Method of temperature assessment (oral, axillary, temporal)**
- **Onset and duration of fevers**
- **Grading Toxicity**
  - **Relevant Information or National Level**
  - **Recognize**
  - **Diagnosis**
  - **Potential Infectious Causes**
  - **Listen:**
Pyrexia

Management

- Identify barriers to adherence
- Assess patient & family understanding of recommendations and rationale
- Identify patient factors contributing to adherence barriers
- Appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)
- Change to different targeted therapy regimen if clinically indicated
- For recurrent pyrexia, CS with prednisone or equivalent will be used (25 mg/d, with downward titration); consider change in targeted therapy regimen, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)
- Oral corticosteroid premedication (10 mg/d) to be used for oral, advise fluids: water, rehydration drinks (Pedialyte), juices, sports drinks (Gatorade, Powerade), popsicles
- For pyrexia refractory to antipyretics, CS with prednisone or equivalent will be used, 25 mg/d, with downward titration; consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib)
- Monitor renal and hepatic function during antipyretic treatment
- Review medication profile with patient and family, including prescriptions, OTCs, herbs, supplements, or other complementary therapies
- Look for causative infectious etiology
- Culture, urinalysis, throat cultures, blood cultures, etc
- Hyperthermia causing moderate changes in the patient’s condition or function
- Fever of 101.3°F–104.0°F (38.5°C–40.0°C); mildly symptomatic (chills, etc)
- Hypotension, dehydration, or renal failure, prompting medical and supportive care interventions
- Respiratory distress, agitation, or brief loss of consciousness
- Seizures
- Grade 1 (Mild)
- Temperature of 99.0°F–101.2°F (37.2°C–38.4°C)
- Asymptomatic; mild, low-grade fevers (99.0°F–101.2°F [37.2°C–38.4°C])
- Grade 2 (Moderate)
- Temperature of 39.8°C–40.7°C (103.6°F–105.5°F)
- Other symptoms, such as dehydration, rigors, hypotension, malaise, fatigue, GI or respiratory symptoms
- Pale?
- Diaphoretic?
- Grade 3 (Severe)
- Temperature of 40.0°C–40.3°C (104.0°F–104.5°F)
- Any fever >101.3°F (38.5°C) that is moderately symptomatic (chills, etc)
- Fever of 104.0°F (40.0°C) or any fever accompanied by chills
- High risk of life-threatening or severe disease
- Temperature of 39.8°C–40.3°C (103.6°F–104.5°F)
- Risk of injury, self-harm, or death
- Grade 4 (Potentially Life Threatening)
- Temperature of 40.3°C–40.6°C (104.5°F–104.8°F)
- Any fever >104.0°F (40.0°C)
- Moderately or highly symptomatic
- Potential high risk of life-threatening or severe disease
- Temperature of 40.6°C–41.0°C (104.8°F–105.8°F)
- Life-threatening, emergent intervention
- Signs of severe illness
- Grade 5 (Life Threatening)
- Temperature of 41.0°C–41.3°C (105.8°F–106.3°F)
- Life-threatening conditions
- Rapid heart rate, respiratory distress, hypotension, altered mental status
- Signs of severe illness
Skin Toxicities  Page 1 of 2

Grade 5 (Death)

Definition: A disorder characterized by an intense itching sensation.

Grading Toxicity

RASH (maculopapular rash, acneiform rash, or dermatitis)

Care Step Pathway - Skin Toxicities

Nursing Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear noncompliant?
- Does the patient appear confused?
- Is the patient wearing any occlusive clothing?
- Are the patient's eyes red and watery?
- Are the patient's ears red and irritated?
- Are the patient's hands red and swollen?
- Are the patient's feet red and swollen?
- Are the patient's mouth red and swollen?
- Are the patient's nails red and swollen?
- Are the patient's toes red and swollen?
- Are the patient's abdomen red and swollen?
- Are the patient's chest red and swollen?
- Are the patient's back red and swollen?
- Are the patient's legs red and swollen?
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**Concern for Superinfection**

**RED FLAGS:**
- Extensive rash (>50% BSA), or rapidly progressive
- Identify barriers to adherence
- Anticipate treatment with higher-potency topical or oral possible treatment interruption for persistent or worsening adverse events
- Antihistamines and analgesics as needed
- Sun avoidance/sunscreen
- Refer to dermatologist
- Introduce concept of treatment interruption and possible dose reduction when educating patients prior to initiation of therapy

**Management**

**Grade 5 (Death)**
- Persistent Grade 2: therapy to be held until Grade 0-1
- Possible use of oral antihistamines and analgesics
- Delegation only

**Grade 4 (Potentially Life Threatening)**
- Oral corticosteroid or immunosuppressive therapy to be held until Grade 0-1
- Immediate referral to dermatologist
- Consider hospitalization for IV electrolyte replacement and IV hydration

**Grade 3 (Severe)**
- Antihistamines and analgesics
- Moderate to high-potency topical steroids
- Consider referral to dermatologist

**Grade 2 (Moderate)**
- Low-potency topical steroid
- Referral to dermatologist
- Daily applications of nonsteroidal moisturizers or emollients containing humectants (urea, glycerin)

**Grade 1 (Mild)**
- Intensive moisturization
- Antihistamines and analgesics
- Low-potency topical steroids

**Definition:**
- A disorder characterized by the presence of macules (flat) and papules (elevated). Maculopapular rash typically appears on the face, scalp, upper chest, and back.

**Potentially Life Changing**
- Identify barriers to adherence
- Underlying or alternative diagnosis
- Pain and discomfort
- Multidisciplinary approach
- sun exposure
- sun avoidance/sunscreen
- Antihistamines/sunscreen
- Use of UV-protective clothing, sunscreen
- Stopping or reducing immunosuppressive therapy
- Referral to dermatologist or provider trained in managing toxicities from targeted therapy

**Patient Counseling:**
- Anticipatory guidance regarding treatment discontinuation or possible hospitalization for steroids and/or hydration
- Oral steroid taper no longer than 7 days
- Consider hospitalization for IV electrolyte replacement
- Avoid hot baths
- Keep fingernails short (to avoid scratching)
- Limit instrumental ADLs
- Help with hygiene
- Limit sun exposure/sunscreen
- Use of UV-protective clothing, sunscreen
- Antihistamines/sunscreen

**Supportive Measures:**
- Maintain development of follicular rash
- Reintroduce or initiate new medications, herbal supplements, alternative/complementary therapies
- Concomitant xerosis (oily dermatitis)
- Provide anticipatory guidance
- Patient education
- Provide anticipatory guidance
- Sun exposure
- Sun avoidance/sunscreen
- Use of UV-protective clothing, sunscreen

**Adverse Events**
- Antihistamines and analgesics
- Moderate to high-potency topical steroids
- Consider referral to dermatologist
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**Concern for Superinfection**
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- Pain and discomfort
- Multidisciplinary approach
- Sun exposure
- Sun avoidance/sunscreen
- Antihistamines/sunscreen
- Use of UV-protective clothing, sunscreen
- Stopping or reducing immunosuppressive therapy
- Referral to dermatologist or provider trained in managing toxicities from targeted therapy

**Patient Counseling:**
- Anticipatory guidance regarding treatment discontinuation or possible hospitalization for steroids and/or hydration
- Oral steroid taper no longer than 7 days
- Consider hospitalization for IV electrolyte replacement
- Avoid hot baths
- Keep fingernails short (to avoid scratching)
- Limit instrumental ADLs
- Help with hygiene
- Limit sun exposure/sunscreen
- Use of UV-protective clothing, sunscreen
- Antihistamines/sunscreen

**Supportive Measures:**
- Maintain development of follicular rash
- Reintroduce or initiate new medications, herbal supplements, alternative/complementary therapies
- Concomitant xerosis (oily dermatitis)
- Provide anticipatory guidance
- Patient education
- Provide anticipatory guidance
- Sun exposure
- Sun avoidance/sunscreen
- Use of UV-protective clothing, sunscreen

**Adverse Events**
- Antihistamines and analgesics
- Moderate to high-potency topical steroids
- Consider referral to dermatologist
- Daily applications of nonsteroidal moisturizers or emollients containing humectants (urea, glycerin)

**Concern for Superinfection**
- Identify barriers to adherence
- Underlying diagnosis
- Pain and discomfort
- Multidisciplinary approach
- Sun exposure
- Sun avoidance/sunscreen
- Antihistamines/sunscreen
- Use of UV-protective clothing, sunscreen
- Stopping or reducing immunosuppressive therapy
- Referral to dermatologist or provider trained in managing toxicities from targeted therapy

**Patient Counseling:**
- Anticipatory guidance regarding treatment discontinuation or possible hospitalization for steroids and/or hydration
- Oral steroid taper no longer than 7 days
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- Moderate to high-potency topical steroids
- Consider referral to dermatologist
- Daily applications of nonsteroidal moisturizers or emollients containing humectants (urea, glycerin)
Clinical Toxicity: Ocular Toxicity

Ocular Toxicity is a potential adverse effect of targeted therapy. It is defined as any observed or self-reported problem that affects vision or eye comfort. Ocular toxicities can range from mild to severe and may include:

- Blindness or severe visual loss
- Photosensitivity
- Rashes that affect the eye(s)
- Retinal vein occlusion
- Conjunctivitis
- Keratitis
- Serous retinal detachment
- Uveitis
- Keratoconjunctivitis

Nursing Assessment:

1. Basic information:
   - Age
   - Gender
   -民族
   - Occupation
   - History of eye disease
   - Family history of eye disease
   - Medical history
   - Current medications
   - Allergies

2. History of ophthalmology:
   - Previous ophthalmology treatment
   - Previous eye surgery
   - History of eye trauma
   - History of contact lens use
   - History of dry eye syndrome

3. History of diabetes:
   - Duration of diabetes
   - Control of blood glucose levels

4. History of cardiovascular disease:
   - Hypertension
   - Obesity
   - History of smoking

5. History of vision changes:
   - Change in vision
   - Change in color vision
   - Change in visual field

6. History of eye symptoms:
   - Headache
   - Vomiting
   - Nausea
   - Photophobia
   - Eye pain
   - Redness
   - Swelling
   - Decrease in visual acuity
   - Decrease in visual field

Care Plan: Pathway - Ocular Toxicity

1. Identify and closely monitor at-risk patients, including those with:
   - A history of glaucoma
   - Dry eyes
   - Uveitis
   - Retinal disease
   - Macular degeneration

2. Refer for baseline ophthalmic examination before beginning therapy. The ophthalmologist should be made aware that the patient is to start combination therapy.

3. Overall Strategy:
   - Assessment: Determine the grade of ocular toxicity.
   - Management: Implement targeted therapy dose modifications or discontinue therapy if necessary.

4. Specific targeted therapy dose modifications:
   - Retinal pigment epithelial detachment: Hold trametinib;
   - Serous retinal detachment: Hold MEKi;
   - Conjunctivitis: Use antihistamines, CS, cool compresses, artificial tears, antibiotics if needed;
   - Keratitis: Use artificial tears, lubricants, or CS drops, antibiotics;
   - Uveitis: Use CS drops, beta blockers, alpha antagonists, mydriatic ophthalmic drops;
   - Identifying and closely monitoring at-risk patients;
   - Refer for baseline ophthalmic examination before beginning therapy;
   - High-risk (severe) ocular toxicities; marked decrease in visual acuity;
   - Highly symptomatic (pain, irritation, threatening);
   - Grade 4 (potentially life-threatening);
   - Grade 3 (severe);
   - Grade 2 (moderate);
   - Grade 1 (mild);

5. Key points:
   - When ocular issues are identified, anticipate management by the treating ophthalmologist.
   - In general, anticipate referral to ophthalmology.
   - Electronic management of the patient's ophthalmology history is encouraged.
   - Ocular toxicities can be preventable with precautions such as:
     - Use of sunglasses and reduction in sun exposure;
     - Encourage use of sunglasses and reduction in sun exposure;
     - Diet (potentially including dietary supplements containing omega-3 and omega-6 fatty acids for dry eye syndrome);
     - Identifying and closely monitoring at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration);
     - In patients with diabetes, promote good control of blood glucose levels since it reduces the risk of retinal disease.

6. Clinical Toxicity: Ocular Toxicity

7. Nursing Assessment:
   - Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration);
   - Refer for baseline ophthalmic examination before beginning therapy. The ophthalmologist should be made aware that the patient is to start combination therapy;
   - Overall Strategy:
     - Assessment: Determine the grade of ocular toxicity.
     - Management: Implement targeted therapy dose modifications or discontinue therapy if necessary.

8. Specific targeted therapy dose modifications:
   - Retinal pigment epithelial detachment: Hold trametinib;
   - Serous retinal detachment: Hold MEKi until visual symptoms improve. Use dose reduction scheme based on severity;
   - Conjunctivitis: Use antihistamines, CS, cool compresses, artificial tears, antibiotics if needed;
   - Keratitis: Use artificial tears, lubricants, or CS drops, antibiotics;
   - Uveitis: Use CS drops, beta blockers, alpha antagonists, mydriatic ophthalmic drops;
   - Identifying and closely monitoring at-risk patients;
   - Refer for baseline ophthalmic examination before beginning therapy;
   - High-risk (severe) ocular toxicities; marked decrease in visual acuity;
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   - Grade 4 (potentially life-threatening);
   - Grade 3 (severe);
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9. Key points:
   - When ocular issues are identified, anticipate management by the treating ophthalmologist.
   - In general, anticipate referral to ophthalmology.
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     - Identifying and closely monitoring at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration);
     - In patients with diabetes, promote good control of blood glucose levels since it reduces the risk of retinal disease.
### Ocular Toxicity

#### Management

**Overall Strategy:**

- Patient is unable to perform regular ADLs because of ocular issues
- Sudden vision disturbances such as photosensitivity, eye pain, and redness

**RED FLAGS:**

- Obtain ophthalmology clearance prior to restarting therapy
- Assess adherence to eye drops/topical therapy
- Anticipate drug holds/dose modifications of targeted therapy
- Observe dose of combination therapy
- Obtain drug clearance and provide anticipatory guidance/assistance, as appropriate

**Specific Ocular Issues:**

- Retinal pigment epithelial detachment (bilateral or multifocal separation of the retina from back of eye, leading to sudden vision changes): drug hold/dose reduction/discontinuation
- Retinal vein occlusion (vascular event leading to vision changes, macular edema, glaucoma): anti-VEGF and steroid injection in addition to drug discontinuation
- Serous retinal detachment (fluid accumulation under layers of retina): drug hold/dose reduction/discontinuation
- Conjunctivitis (inflammation of the interior eyelids): antihistamines, CS, cool compresses, artificial tears, antibiotics if needed
- Keratitis (inflammation of cornea): artificial tears, lubricants, or CS drops, antibiotics

**Anticipate Permanent Discontinuation of Targeted Therapy for Other Severe Ocular Toxicities, Per Prescribing Information:**

- Grade 1 (Mild):
  - Conjunctivitis
  - Keratitis

- Grade 2 (Moderate):
  - Uveitis (severe): hold dabrafenib, permanently discontinue

- Grade 3 or 4 (Severe):
  - Uveitis (persistent Grade 2 or >6 weeks duration): hold BRAFi therapy

**Grading System:**

- Grade 1 (Mild): symptoms improve. Use dose reduction scheme based on severity
- Grade 2 (Moderate): symptoms improve. Use dose reduction scheme based on severity
- Grade 3 or 4 (Severe): symptoms improve. Use dose reduction scheme based on severity

**Specific Targeted Therapy Dose Modifications/Holds/Discontinuations:**

- Retinal pigment epithelial detachment: hold trametinib; reduce dose or discontinue if no improvement after 3 weeks.
- Retinal vein occlusion: permanently discontinue.
- Serous retinal detachment: drug hold/dose reduction/discontinuation.
- Conjunctivitis: antihistamines, CS, cool compresses, artificial tears, antibiotics if needed.
- Keratitis: artificial tears, lubricants, or CS drops, antibiotics.

**Identify and Closely Monitor at-Risk Patients:**

- Patients at risk: those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration
- Advise patients to promptly report any changes in vision or any eye symptoms (and anticipate treatment hold pending further evaluation)
- Refer for baseline ophthalmic examination before beginning therapy.

**Ocular Toxicity Quiz:**

- Does the patient wear contact lenses?
- Are there skin lesions surrounding the eye(s)?
- Any recent eye injury, new medications, or exposure to toxic chemicals?
- Is there lid or periocular edema?
- When did symptoms start?
- Reports of specific eye complaints: redness, watering, drainage, change in vision
- Other treatment-related symptoms
- Does the patient look uncomfortable?
- Does the patient look jaundiced?
- Are pupils reactive?
- Other treatment-related symptoms
- When did symptoms start?
- Reports of specific eye complaints: redness, watering, drainage, change in vision
- Other treatment-related symptoms
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Cardiotoxicity

**Nursing Assessment**

**Care Step Pathway - Cardiotoxicity**
Cardiotoxicity

Management

Grades 3-4 (Severe or Life-threatening)
- Cardiopulmonary arrest in emergency department for chest pain/pressure to evaluate for MI
- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI
- Anticipate urgent cardiology referral if condition worsens
- Full cardiac workup (including ECG for vemurafenib, ECHO/MUGA for any MEK-containing regimen, cardiac enzymes, CBC, CMP, BNP, creatinine, C-Reactive Protein, CXR) to be performed
- Repeat ECHO for MEK-containing regimen at 1 month and every 2-3 months while on treatment. If ECHO performed (on immunotherapy), repeat ECHO at 14 days, monthly, every 3 months, every 6 months, depending on the treatment regimen
- Re-evaluate ECHO for MEK-containing regimen if QTc >500 ms
- Full cardiac workup at baseline: ECHO for vemurafenib, ECHO/MUGA for any MEK-containing regimen, cardiac enzymes, CBC, CMP, BNP, creatinine, C-Reactive Protein, CXR
- Review cardiac treatment that may affect heart function, particularly the QTc interval
- Grade 3 (Severe)
- Symptoms of serious arrhythmia (ventricular tachycardia, or signs or symptoms of torsade de pointes, polymorphic ventricular tachycardia, or QTc ≥501 or >60 ms change from baseline
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Ventricular arrhythmia requiring intervention
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Grade 2 (Moderate)
- Symptoms of QT interval prolongation: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.
- Encourage evaluation of lipid panel to assess cardiovascular risk
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Grade 1 (Mild)
- Symptoms of QT interval prolongation: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Anticipate cardiology referral if QTc remains >500 ms and ≥20% from baseline
- Grade 0 (None)
- No symptoms of QT interval prolongation
- No evidence of cardiac dysrhythmia
- No evidence of QT interval prolongation
- No evidence of QT interval prolongation

Overall Strategy:
- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities
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- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities
- Smoking cessation, control of comorbidities

Prevention (no known strategies), but encourage healthy lifestyle

Dizziness or syncope?
- Changes in BP?
- Changes in cardiac function: ECG changes, decreased EF, decreased 60 ms from pretreatment (after controlling for persistent arrhythmia)
- Heart failure or a LVEF value decreased >10% from baseline and below the institution's LLN
- Grade 5 (Life Threatening)
- Grade 4 (Potentially Life Threatening)
- Grade 3 (Severe)
- Grade 2 (Moderate)
- Grade 1 (Mild)
- Grade 0 (None)
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias/myalgias</td>
<td>Joint pain, swelling, or stiffness, feeling tired</td>
<td>* Query patients regarding joint symptoms; standard supportive care (analgesia and anti-inflammatory drugs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Anticipate treatment hold for intolerable Grade 2 (moderate pain, limiting instrumental ADLs) or Grade 3 (severe pain and self-care ADL limitations)</td>
</tr>
<tr>
<td>Chills</td>
<td>Shaking feeling/cold in absence of fever</td>
<td>* Query about symptoms, including symptoms related to serious febrile reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Anticipate treatment hold for intolerable Grade 2 (moderate tremors) or Grade 3 (severe or prolonged chills that are not responsive to narcotics)</td>
</tr>
<tr>
<td>Constipation/abdominal pain</td>
<td>Infrequent stools/difficulty stooling, abdominal pain</td>
<td>* Increase fluid; fiber; laxatives. Consider appropriate testing to evaluate bowel obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Anticipate treatment hold for intolerable Grade 2 (persistent symptoms of constipation or moderate pain limiting instrumental ADLs) or Grade 3/4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)</td>
</tr>
<tr>
<td>Edema</td>
<td>Swelling of limbs, etc</td>
<td>* Anticipate treatment hold for intolerable Grade 2 (moderate swelling, limiting instrumental ADLs) or Grade 3 (severe swelling, gross deviation from anatomic contour)</td>
</tr>
<tr>
<td>Embryo-Fetal Toxicity</td>
<td>—</td>
<td>* Cibimetinib and vemurafenib can cause fetal harm. Females and males of child-bearing potential should use effective birth control during cibimetinib/vemurafenib treatment and for 2 weeks after the final dose of cibimetinib or vemurafenib (whichever is taken later)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Unrelenting exhaustion not relieved by rest</td>
<td>* Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and biochemical abnormalities; standard supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Anticipate treatment hold for fatigue not relieved by rest and limiting ADLs (Grade 2/3)</td>
</tr>
<tr>
<td>Headache</td>
<td>Pain and/or change in vision</td>
<td>* May be multifactorial. For severe symptoms, could involve bleeding in the brain, uncontrolled hypertension, dehydration, new CNS disease, or other causes; consider brain MRI and evaluations for hypertension</td>
</tr>
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<td></td>
<td></td>
<td>* Anticipate treatment hold for intolerable Grade 2 (moderate pain) or Grade 3 (severe pain, limiting self-care ADLs)</td>
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<tr>
<td>Hemorrhage</td>
<td>Red or black/tarry stools, blood in urine, headaches, coughing or vomiting blood, abdominal pain, unusual vaginal bleeding, fatigue dizziness or weakness</td>
<td>* Standard supportive care; medical intervention as indicated</td>
</tr>
<tr>
<td></td>
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<td>* Anticipate treatment hold for intolerable Grade 2 (moderate bleeding) or Grade 3/4 (severe bleeding requiring transfusion or radiologic, endoscopic, or operative intervention or life-threatening consequences)</td>
</tr>
</tbody>
</table>
### Detection and management of AEs and laboratory abnormalities not included in care step pathways for cobimetinib/vemurafenib

(Continued)

<table>
<thead>
<tr>
<th>Adverse event</th>
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| Hepatotoxicity | Abdominal pain or swelling; yellowing of skin or eyes; dark urine; easy bruising, loss of appetite; feeling tired or weak | • Monitor LFTs at baseline and monthly during treatment or as clinically indicated  
• Anticipate treatment hold of cobimetinib at first occurrence of Grade 4 (>20× upper limit of normal [ULN] for transaminases and alkaline phosphatase; >10× ULN for bilirubin) and permanent discontinuation if not improved within 4 weeks  
• Anticipate treatment hold of vemurafenib for intolerable Grade 2 (transaminases >3× ULN, alkaline phosphatase >2.5× ULN, or bilirubin >1.5× ULN) or Grade 3/4 (transaminases or alkaline phosphatase >5× ULN, bilirubin >3× ULN) and permanent discontinuation if no recovery to Grade 0–1 or recurrent Grade 4 event |
| Hypersensitivity reaction | Swelling, feeling faint, rash, erythema, anaphylaxis | • Possible hospitalization  
• Anticipate immediate permanent discontinuation of vemurafenib for patients with severe hypersensitivity reactions |
| Nausea/vomiting | Vomiting, queasiness, RUQ or LUQ pain | • May indicate hepatotoxicity; check LFTs/lipase/amylase; provide standard supportive care  
• Anticipate treatment hold for intolerable Grade 2 (oral intake decreased or 3–5 vomiting episodes in 24 hours) or Grade 3/4 (inadequate oral intake or ≥6 vomiting episodes in 24 hours or life-threatening consequences) |
| Radiation sensitization/recall | Inflammatory skin reaction in areas treated with radiation | • Use vemurafenib with caution in patients with prior or ongoing radiotherapy or those who will be candidates for this treatment; advise patients to report if they have received radiation therapy or are planning to receive therapy |
| Renal toxicity | Decreased urine, blood in urine, swelling of ankles, decrease in appetite | • Measure serum creatinine before treatment initiation and periodically during treatment; monitor kidney function  
• Anticipate treatment hold with intolerable Grade 2 (eGFR or CrCl 59 to 30 mL/min/1.73 m²) or Grade 3/4 (eGFR or CrCl ≤29 mL/min/1.73 m²) |

*When treatment holds are required, resume therapy at a lower dose level following improvement to Grade 0 to 1. Permanently discontinue targeted therapies in case of persistent intolerable Grade 2 events, persistent Grade 3 events, and persistent or recurrent Grade 4 events unless otherwise specified.*