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Positive Quality Intervention: Afatinib (Gilotrif®) Management in Non-Small Cell Lung Cancer

Description: The purpose of this PQI is to provide information on the management of common adverse events, follow-up with patients, and dose modifications. Dose adjustments are common and greatly reduced frequency and severity of adverse reactions. In Lux-Lung 3, 43% maintained the 40 mg starting dose, 38% reduced to 30mg and 19% further reduced to 20 mg. Progression free survival remained consistent in patients with or without dose adjustments.

Background: Afatinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test. In addition, it is also indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy. Proper follow up including patient assessment is essential when new patients start on therapy. An increased number of patient touches are needed to ensure patients are being managed properly and are dose reduced appropriately. Weekly follow ups are ideal to assess adverse events.

PQI Process: Upon receipt of afatinib prescription

- Ensure appropriate indication and dose
  - Verify appropriateness by using Uncommon EGFR Mutations Patient Database
  - Recommended starting dose: 40 mg once daily
- Afatinib Dose Management
  - Adverse event management (Supplemental Information)
  - Dose Reduction
    - Renal impairment: 30 mg once daily
  - Hold therapy
    - ≥ Grade 3 adverse reactions
    - ≥ Grade 2 diarrhea (persisting for 2 or more consecutive days while taking anti-diarrheal)
    - Cutaneous reactions (prolonged, lasting more than 7 days, or intolerable)
    - Resume treatment when adverse reaction fully resolves/returns to baseline/improves to Grade 1; reduce dose by 10 mg per day less than dose at which adverse reaction began
  - Permanently Discontinue
    - Life-threatening bullous, blistering, or exfoliative skin lesions
    - Confirmed interstitial lung disease (ILD)
    - Severe drug-induced hepatic impairment
    - Gastrointestinal perforation
    - Persistent ulcerative keratitis
    - Symptomatic left ventricular dysfunction
    - Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
  - Day 1 – Initial Patient Counseling
    - Ensure patients are aware that dose modifications are common
    - Educate patients on adverse events, especially diarrhea and rash/acne are expected

        - Provide patients with loperamide. Advise patients to take loperamide and call the office at the onset and continue anti-diarrheal until loose stools cease for 12 hours
        - Advise patients to call office at the onset of rash
    - Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following: trouble breathing, shortness of breath, cough, fever
    - Advise patients to immediately report any symptoms of a liver problem: yellowing of skin and whites of eyes, dark or brown urine, pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy
- Days 7, 14, 21, 28– Add reminder in EMR to follow up with patient
    - Follow up on diarrhea and rash/acne
    - Follow up on other common reactions: stomatitis and paronychia
    - Follow up on less common reactions: dry skin, pruritus, keratitis, interstitial lung disease, hepatic toxicity

Reference:

1. Gilotrif® (afatinib) [prescribing information].

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Supplemental Information

Diarrhea	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	< 4 stools	4-6 stools	7 or more stools	Life-Threatening
	Increase of <4 stools/day over baseline, mild increase in ostomy output compared to baseline.	Increase of 4-6 stools/day over baseline; not interfering with daily activities; IV fluids indicated, 24 hrs; moderate increase in ostomy output compared to baseline.	Increase of +7 stools/day over baseline; incontinence; interfering with daily activities; IV fluid fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline.	Life-Threatening consequences (ex. hemodynamic collapse).
	Maintain dose	**Consider pausing**	**Hold**	**Hold**
	Continue same dose. Stop laxatives and advise patient to drink 8-10 glasses of water or clear fluids/day. Prescribe 4 mg loperamide taken immediately; followed by 2 mg after each loose stool (max. 16 mg/day) until bowel movements cease for 12 hours	Continue same dose unless grade 2 diarrhea continues for ≥ 48 hours, hold until reduced to grade 1 or below; resume with dose reduction; see grade 1; continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluid and electrolyte replacement.	Hold until recovered to grade 1 or below and follow with dose reduction. In addition to grade 2 interventions, an infection process should be ruled out with stool cultures; aggressive IV fluid replacement for ≥ 24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is neutropenic.	See Grade 3.
Rash/ Acne	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Macular or papular eruptions or erythema without associated symptoms.	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA.	Severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration.	Generalized exfoliative, ulcerative, or bullous dermatitis.
	Maintain dose	**Hold**	**Hold**	**Discontinued**
	Topical Steroids or tacrolimus ointment alternative. Consider topical antibiotics twice daily. Recommend cream for isolated scattered lesions, and lotion for multiple scattered areas.	Topical steroid treatment as for grade 1 oral antibiotic (6 weeks) ex. doxycycline 100 mg b.i.d., minocycline HCL 100 mg b.i.d., or, if available, oxytetracycline 500 mg b.i.d. Stop topical antibiotic if being used.	Topical and systemic treatment as for grade 2. If Infection suspected, switch oral antibiotic to broad spectrum/gram negative coverage and consider skin swab for bacterial culture.	Permanently discontinue for life-threatening bullous, blistering, or exfoliative skin lesions.

Paronychia (Nails)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Nail fold edema or erythema; disruption of the cuticle.	Localized intervention indicated; oral intervention indicated (ex. antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL.	Surgical intervention or IV antibiotics indicted; limiting self-care activities of daily living (ADL).	N/A
	Maintain dose	**Prolonged: Pause**	**Hold**	N/A
	Topical antibiotics/antiseptics, vinegar soaks, and topical ultrapotent steroids.	Topical antibiotics, vinegar soaks, silver nitrate application weekly, and topical ultrapotent steroids.	Topical antibiotics, vinegar soaks, silver nitrate application weekly/ consider nail avulsion and systemic antibiotics.	N/A
Stomatitis	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Erythema of the mucosa.	Patchy ulcerations or pseudomembranes.	Confluent ulcerations or pseudomembranes; bleeding with minor trauma.	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences.
	Maintain dose	**Prolonged: Hold**	**Hold**	**Hold**
	Oral rinses with agents such as non-alcoholic mouthwash, normal saline, diluted salt and baking soda solution.	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.