BC Cancer Protocol Summary for Palliative Third Line Treatment of Metastatic Colorectal Cancer Using PANitumumab

Protocol Code: GIAVPANI

Tumour Group: Gastrointestinal

Contact Physician: GI Systemic Therapy

ELIGIBILITY:

Patients with:
- metastatic colorectal adenocarcinoma previously treated with fluorouracil, irinotecan and oxaliplatin,
- wild type RAS (tested on primary or metastatic tumour*)
- ECOG performance status 0-2
- Adequate marrow reserve (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L
- Adequate renal (creatinine less than or equal to 1.5x ULN) and liver function (has not been studied in patients with hepatic impairment)
- **Note:** Approvals will only be given for one of GIAVPANI or GIACETIR – not both.
* [www.bccancer.bc.ca/health-professionals/professional-resources/laboratory-services/pathology](http://www.bccancer.bc.ca/health-professionals/professional-resources/laboratory-services/pathology)

EXCLUSIONS:

Patients with:
- mutant RAS tumours
- Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis

TESTS:

- Baseline: CBC and differential, sodium, potassium, magnesium, calcium, serum creatinine, LFTs (bilirubin, ALT, alkaline phosphatase)
- Prior to each cycle: sodium, potassium, magnesium, calcium
- Post-treatment: monthly sodium, potassium, magnesium, calcium for 2 months after last PANitumumab treatment
- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.
- If clinically indicated: CEA
PREMEDICATIONS:

- Antiemetic protocol for low emetogenicity (see SCNAUSEA). Antiemetics are not usually required.
- Consider preemptive therapy for PANitumumab-induced dermatologic toxicity (see below).

TREATMENT:

A cycle equals -

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANitumumab</td>
<td>6 mg/kg</td>
<td>IV in 100 mL NS over 1 hour using a 0.22 micron in-line filter.*</td>
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<tr>
<td></td>
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<td>If tolerated, administer over 30 minutes in subsequent cycles.</td>
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</tbody>
</table>

* For PANitumumab dose greater than 1000 mg, use 150 mL NS and infuse over 1 hour 30 min each cycle.

Repeat every 2 weeks until either toxicity or disease progression.

DOSE MODIFICATIONS:

1. Dermatologic toxicities:

As a class, EGFR Inhibitors are characterized by cutaneous adverse effects, most commonly a papulopustular reaction involving the skin of the face and upper torso. This can leave the skin vulnerable to bacterial overgrowth and serious infection which may require aggressive interventions.

A well characterized clinical course has been identified. Within week 1 of treatment patients experience sensory disturbance with erythema and edema. During weeks 1 to 3 (median time of 14 days after start of therapy) the papulopustular eruption manifests, followed by crusting at week 4. Despite effective treatment for rash, erythema and dry skin may persist in the areas previously affected during weeks 4 to 6. Most patients exhibit some degree of partial improvement during therapy and the rash generally resolves completely and without scarring following cessation of therapy (median time of 84 days after the last dose.)
Consideration should be given to preemptive or reactive treatment of EGFR Inhibitor skin toxicity. **Preemptive therapy** includes doxycycline (or minocycline) 100 mg po bid and clindamycin 2%/hydrocortisone 1% skin lotion at cycle 1. Preemptive therapy was compared to reactive management and resulted in decreased grade ≥ 2 skin toxicity and decreased impairment in quality of life.

Reactive management is summarized below.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
<th>PANitumumab dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Macular or papular eruption or erythema with no associated symptoms</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2</td>
<td>Macular or papular eruption or erythema with pruritus or other symptoms that are tolerable or interfere with daily life</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>3</td>
<td>Severe, generalised erythroderma or macular, papular or vesicular eruption</td>
<td>Withhold infusion for 2 to 4 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ When improvement to Grade 2 or less, continue at 50% of original dose (3mg/kg); If toxicities do not worsen, escalate by 25% increments of original dose (4.5 mg/kg, then 6 mg/kg) until recommended starting dose is reached</td>
</tr>
<tr>
<td>4</td>
<td>Generalized exfoliative, ulcerative or blistering skin toxicity</td>
<td>Discontinue treatment.</td>
</tr>
</tbody>
</table>

The prevention or management of EGFR inhibitor related skin toxicities not only improves or maintains patient quality of life, it prevents dose reduction or discontinuation of potentially effective therapy.

It is recommended that patients wear sunscreen and a hat and limit sun exposure as sunlight can exacerbate any skin reactions.
Activities and skin care products that dry the skin should be avoided such as long, hot showers, alcohol-based or perfumed skin care products. Greasy ointments should be avoided. Frequent moisturizing with alcohol-free emollient creams is recommended.

This rash is distinct from acne vulgaris and therefore, other topical acne treatments should not be applied.

Other less frequent manifestations are: dry skin, pruritus, fissures, palmar-plantar rash, hyperkeratosis, telangiectasia, hyperpigmentation, and blisters.

2. Hypomagnesemia

Serious cases may be asymptomatic and have been reported greater than 6 weeks after initiation of treatment. Symptoms include severe weakness and fatigue. Concern is cardiac arrhythmias which may be associated with hypokalemia. Magnesium levels should be monitored closely and regular infusions of Magnesium Sulfate as well as oral supplementation may be required. Monitoring of potassium and calcium may also be required.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Serum Magnesium</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mmol/L to less than LLN</td>
<td>Continue PANitumumab. Consider daily oral magnesium replacement</td>
</tr>
<tr>
<td>2</td>
<td>0.4 to less than 0.5 mmol/L</td>
<td>Continue PANitumumab and initiate daily oral magnesium replacement and magnesium sulfate 5 G IV in 100 mL NS over 3 hours every 2 weeks</td>
</tr>
<tr>
<td>3</td>
<td>0.3 to less than 0.4 mmol/L</td>
<td>if symptomatic - hold PANitumumab until improved to Grade 2. If asymptomatic – increase supplementation to magnesium sulfate 5G IV in 100 mL NS over 3 hours weekly</td>
</tr>
<tr>
<td>4</td>
<td>Less than 0.3 mmol/L</td>
<td>Hold PANitumumab until asymptomatic and improved to Grade 2 – increase supplementation to magnesium sulfate 5G IV in 100 mL NS over 3 hours twice weekly.</td>
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Oral preparations of magnesium may be poorly tolerated resulting in poor compliance due to potential for diarrhea. Diarrhea is dose dependent. Combination product with calcium may reduce incidence of diarrhea.
### Magnesium Preparation

<table>
<thead>
<tr>
<th>Magnesium Preparation</th>
<th>Elemental Magnesium content</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Magnesium complex</td>
<td>Each 250 mg tablet contains 250 mg</td>
<td>1 tablet twice daily</td>
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<tr>
<td>Magnesium glucoheptonate</td>
<td>Each 15ml of 100 mg/mL solution contains 76.8 mg</td>
<td>15 – 30 mL up to 4 times daily</td>
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<tr>
<td>Magnesium oxide</td>
<td>Each 420 mg tablet contains 252 mg</td>
<td>1 tablet twice daily</td>
</tr>
<tr>
<td>Calcium/Magnesium</td>
<td>Each 333/167 tablet contains 167 mg</td>
<td>1 tablet 3 times daily</td>
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</table>

### PRECAUTIONS:

1. **PANitumumab Hypersensitivity Reactions (HSR):** severe infusion reactions, including anaphylactic reactions, bronchospasm and hypotension have occurred with the administration of PANitumumab in approximately 1% of patients, very rarely with a fatal outcome. Late onset HSR have also occurred and it is recommended that patients be warned of this possibility.

2. **Interstitial Lung Disease:** has been observed with EGFR inhibitors. Interstitial lung disease and interstitial pneumonitis are rare (<1% for PANitumumab). Worsening of preexisting lung conditions is also reported with PANitumumab. Investigation of acute symptoms is warranted and PANitumumab should be withheld in the event of onset or worsening of respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.

3. **Severe Diarrhea and Dehydration:** PANitumumab should be withheld until resolution. Acute renal failure has been observed in patients with severe diarrhea and dehydration receiving PANitumumab. In addition to the risk of diarrhea induced dehydration, patients on warfarin are at risk for an elevation in INR and an increased risk of bleeding.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

### References: