BCCA Protocol Summary for Combined Modality Therapy for Locally Advanced Esophageal Cancer using CISplatin, Infusional Fluorouracil and Radiation Therapy

Protocol Code: GIEFUPRT

Tumour Group: Gastrointestinal

Contact Physician: GI Systemic Therapy

ELIGIBILITY:
- Locally advanced squamous cell cancer or adenocarcinoma of the esophagus suitable for curative therapy.
- In cases where surgery is not appropriate (e.g. by virtue of the high tumour position above the carina), where local surgical clearance is not possible, or where patient is medically unfit or refuses surgery.
- As an alternative to surgery, depending on local Cancer Centre policy and availability of specialized surgical expertise.
- Any age - patients over 69 to be assessed individually
- ECOG 0-2

EXCLUSIONS:
- Distant metastases
- Hearing impairment
- Inadequate renal function (creatinine clearance less than 45 mL/min as calculated by Cockcroft/Gault formula - see page 3).
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia.

TESTS:
- Baseline: CBC, diff and platelets, creatinine, serum albumin, bilirubin, SGOT and alkaline phosphatase.
- Prior to each cycle: CBC, diff and platelets, creatinine
- If clinically indicated: bilirubin, liver enzymes
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.

PREMEDICATIONS:
- Antiemetic protocol for High Moderate emetogenic chemotherapy as long as CISplatin dose is not greater than 50 mg. If CISplatin is greater than 50 mg use antiemetic protocol for Highly emetogenic chemotherapy protocols.

TREATMENT:

Chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluorouracil (5FU)</td>
<td>1000 mg/m²/day for 4 days (total dose = 4000 mg/m² over 96 h)</td>
<td>IV in D5W to a total volume of 192 mL by continuous infusion at 2 mL/h via appropriate infusor device*</td>
</tr>
<tr>
<td>CISplatin</td>
<td>25 mg/m² Daily x 3 days **</td>
<td>In 100 mL normal saline, over 30 min</td>
</tr>
</tbody>
</table>

*Inpatients: 1000 mg/m²/day in 1000 mL D5W by continuous infusion daily over 24 h for 4 days.
**For patients with an excellent performance status who are being treated before radiation therapy has begun, the CISplatin total dose may be increased to 100 mg/m² given as 25 mg/m² daily for 4 days (cycles 1-4). In some circumstances the total dose of CISplatin may be given as a single dose with appropriate pre and post hydration.**

Radiation Therapy:
5000 cGy in 25 fractions over 5 weeks. Note: Some patients may receive additional brachytherapy as part of a toxicity trial. This does not alter the chemotherapy dosage or schedules.

**Duration of chemotherapy:** Four cycles of chemotherapy are given as follows:

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo Cycle</td>
<td>1</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Cycle 1:** Given concurrent with the first week of radiation therapy. This is usually started on the first day of the radiation therapy.

**Cycle 2:** Given concurrent with the fifth week of radiation therapy. This cycle may be eliminated if the patient is experiencing major toxicity.

**Cycle 3:** Given approximately 3 weeks after the end of radiation therapy.

**Cycle 4:** Given 3 weeks after day 1 of cycle 3.

**Alternative Schedule**

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chemo Cycle</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>(3)</td>
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</tr>
</tbody>
</table>

**Cycle 1:** Given three weeks prior to initiation of radiation therapy, to allow for planning and wait list for radiation, if this is the best management for the individual patient.

**Cycle 2:** Given concurrent with the first week of radiation therapy. This is usually started on the first day of the radiation therapy.

**Cycle 3:** Given concurrent with the fifth week of radiation therapy. This cycle may be eliminated if the patient is experiencing major toxicity.

**Cycle 4:** Given approximately 3 weeks after the end of radiation therapy.

**DOSE MODIFICATIONS:**

1. **Hematological**
   **Day 1 counts:**
   - ANC (x10⁹/L) and Platelets (x10⁹/L) and Dose - Fluorouracil only
   - greater than 1.5 greater than 100 100%
   - less than 1.5 or less than 100 Delay x 1 week then reassess

2. **Renal**
   Delay for one week if serum creatinine greater than 3 x ULN. If serum creatinine less than 3 x ULN adjust CISplatin dose as follows:

<table>
<thead>
<tr>
<th>CrCl (By Cockcroft/Gault formula)</th>
<th>Dose - CISplatin only</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60 mL/min</td>
<td>100%</td>
</tr>
<tr>
<td>45 – 59 mL/min</td>
<td>50%</td>
</tr>
<tr>
<td>less than 45 mL/min</td>
<td>Delay x 1 week then reassess</td>
</tr>
</tbody>
</table>
Cockcroft/Gault formula:

\[
CrCl = \frac{N \times (140-\text{age}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}}
\]

Where \( N = 1.04 \) for females, and 1.23 for males

3. **Neurotoxicity**: If clinically significant hearing loss or functionally significant peripheral neuropathy occurs, omit CISplatin and replace with mitomycin 10 mg/m\(^2\) on day 1 of Cycles 1 and 3 OR Cycles 2 and 4 (maximum cumulative dose 20 mg/m\(^2\)). (See BCCA Cancer Drug Manual for administration guidelines).

4. **GI Toxicity**
   
   (a) **Nausea and vomiting**: Grade 4 (greater than 10 episodes in 24 h or requires parenteral support, dehydration) - not helped by antiemetics. Decrease CISplatin dose to 80%, or **discontinue therapy**.
   
   (b) **Stomatitis**: Grade 3-4 (painful erythema, edema or ulcers and cannot eat). Decrease dose of Fluorouracil infusion by 25%.
   
   (c) **Diarrhea**: Grade 4 (increase of greater than or equal to 10 stools/day or grossly bloody diarrhea; dehydration). dose of Fluorouracil infusion by 25%.

**PRECAUTIONS:**

1. **Nausea and vomiting** are common and patients should be treated with ondansetron and dexamethasone before each dose of CISplatin (see premedication section).

2. **Renal toxicity** may occur with a salt and water losing nephropathy. Patients should be encouraged to maintain good oral hydration.

3. **Myocardial ischemia and angina** occurs rarely in patients receiving fluorouracil or capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient’s allergy profile.

4. **Diarrhea**: Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer’s directions or per the BCCA Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.

5. **CNS toxicity** such as tinnitus, mild high frequency hearing loss and delayed peripheral neuropathy may occur secondary to CISplatin.

6. **Nutrition**: It is important to maintain weight if possible and early consultation with a nutritionist to advise about aggressive oral nutritional support and/or an enteral feeding tube is recommended.

7. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.

8. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of fluorouracil, repeat INR weekly for one month.

9. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.
Call the GI Systemic Therapy physician at your regional cancer centre or Dr. JP McGhie at (250) 519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

Date activated: 22 Sept 1998 (as GIEFUP)
Date revised: 1 Nov 2015 (addition of Diarrhea Precaution)