ELIGIBILITY:

- Locoregionally recurrent/metastatic head and neck cancer (squamous cell, sinonasal undifferentiated carcinoma) with ECOG status 0-2
- normal hepatic and renal function
- adequate marrow function
- Intravascular device (e.g. PORT-A-CATH or PICC line) is highly recommended
- If there is a contraindication to CIPlatin (e.g. deafness, intolerance to fluid overload, neuropathy), consideration should be given to using CARBOplatin.

TESTS:

- Baseline: CBC & diff, platelets, creatinine, sodium, potassium, serum calcium, serum magnesium, serum albumin, ALT, bilirubin, DPYD test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Before each treatment: CBC & diff, creatinine
- If indicated: bilirubin

PREMEDICATION:

- For CIPlatin use antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- For CARBOplatin use antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA)
TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISplatin</td>
<td>25 mg/m² Daily for 3 to 4 days</td>
<td>IV in 100 to 250 mL NS over 30 min (use 250 mL NS if greater than 60 mg)</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>1,000 mg/m² /day for 4 days (total dose = 4,000 mg/m² over 96 h)</td>
<td>IV in D5W to a total volume of 480 mL by continuous infusion at 5 mL/h via appropriate infusor device*</td>
</tr>
</tbody>
</table>

*Inpatients: 1,000 mg/m²/day in 1,000 mL D5W by continuous infusion daily over 24 h for 4 days
  - The cycle is repeated every 4 weeks.

Alternatively, CARBOplatin may be used instead of CISplatin:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>BC Cancer Administration Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBOplatin</td>
<td>AUC 5 or 6 DAY 1 only Dose = AUC† x (GFR* + 25)</td>
<td>IV in 100 to 250 mL NS over 30 minutes.</td>
</tr>
</tbody>
</table>

† determined at discretion of the attending medical oncologist.

*GFR preferably from nuclear renogram, if not possible use:

\[
GFR = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}
\]

N = 1.04 (women) or 1.23 (men)

The estimated GFR should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

DURATION OF THERAPY:
Treatment may continue for a total of 6 cycles or to patience tolerance.
DOSE MODIFICATIONS:

Fluorourail Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

1. Hematological
   - Modify fluorouracil ONLY:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose (fluorouracil only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 to 1.5 or</td>
<td>75 to 100</td>
<td>750 mg/m^2 /d x 4 days</td>
</tr>
<tr>
<td>less than 1.0 or</td>
<td>less than 75</td>
<td>375 mg/m^2 /d x 4 days</td>
</tr>
</tbody>
</table>

2. Renal Toxicity
   - Modify CISplatin dose according to renal function

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Dose (CISplatin only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>100%</td>
</tr>
<tr>
<td>45 to 59</td>
<td>50%</td>
</tr>
<tr>
<td>less than 45</td>
<td>Hold CISplatin or delay with additional fluids or go to CARBOplatin option.</td>
</tr>
</tbody>
</table>

Calculation of the creatinine clearance rate (estimated using standard formula) should be done every cycle because patients who have lost weight may have normal serum creatinine, but have abnormal estimated creatinine clearance. If estimated creatinine clearance changes to less than 60 mL/min, dose reduction should be considered.

Creatinine clearance = $N^* \times (140\text{-age}) \times \text{weight (kg)}$

Serum Creatinine micromol/L

* for males $N = 1.23$, for females $N = 1.04$
3. **Neurotoxicity:**

- Tinnitus, mild high frequency hearing loss, and delayed peripheral neuropathy may occur secondary to CISplatin. The latter are generally reversible with time. If clinically significant hearing loss or functionally significant peripheral neuropathy occurs, discontinue CISplatin only.
- CNS toxicity due to fluorouracil is infrequent, but would necessitate cessation of treatment.

4. **GI Toxicity:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade</th>
<th>Description</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and Vomiting</td>
<td>4</td>
<td>greater than 10 episodes in 24 h or needs parenteral support, dehydration</td>
<td>If not controlled by antiemetics, give 75% dose CISplatin, change to CARBOplatin, or stop treatment</td>
</tr>
</tbody>
</table>

G.I. tract toxicity consisting of stomatitis or diarrhea and cramps suggestive of drug toxicity and is indication to stop therapy.

**PRECAUTIONS:**

1. **Nausea and vomiting** are common and patients should be treated with ondansetron and dexamethasone before and at least every 12 hours regularly during this treatment; netupitant-palonosetron may be substituted for ondansetron (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 or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient’s allergy profile.
4. Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).

Contact Dr. Cheryl Ho or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References: