BC Cancer Protocol Summary for Treatment of Locally Advanced Squamous Cell Carcinoma of the Head and Neck with DOCEtaxel, CISplatin and Infusional Fluorouracil

***Protocol Code**:* *HNLADCF*

***Tumour Group**:* *Head and Neck*

Contact Physician: *Cheryl Ho*

ELIGIBILITY:
- Locally advanced (unresectable) squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx, including primary unknown with cervical lymphadenopathy
- ECOG 0-1
- Adequate hepatic, renal, marrow and cardiac function
- Age 65 years or younger recommended. Caution should be used for patients over 65 years of age
- Caution: This regimen has been associated with a high rate (25%) of febrile neutropenia and should only be administered in settings with appropriate support
- To be followed by HNLAPRT

EXCLUSIONS:
- 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, platelets, serum Creatinine, Bilirubin, ALT, Alkaline Phosphatase, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Before each treatment: CBC & diff, platelets, serum Creatinine, ALT, Alkaline Phosphatase

PREMEDICATIONS:
- dexamethasone 8 mg PO bid for 3 days starting one day prior to each administration of DOCEtaxel
- A minimum of 3 doses of dexamethasone pre-treatment are required
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA protocol)
- DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
DOCEtaxel	75 mg/m^2	IV in NS 250 to 500 mL* over 1 hour (use non-DEHP equipment)
CISplatin	75 mg/m^2	Prehydrate with NS 1000 mL over 1 hour, then give CISplatin IV in NS 500 mL with potassium chloride 20 mEq, magnesium sulfate 1 g, mannitol 30 g over 1 hour
fluorouracil	750 mg/m^2/day for 5 days (total dose = 3750 mg/m^2 over 120 h)	IV in D5W to a total volume of 240 mL by continuous infusion at 2 mL/h via appropriate infusor device*

*Inpatients: 750 mg/m^2/day in D5W 1000 mL by continuous infusion daily over 24 h for 5 days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

- Repeat every 21 days x 3 cycles

DOSE MODIFICATIONS:

Fluorouracil 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. **Hematology** For DOCEtaxel and fluorouracil

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose*
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to less than 1.5	or	75 to less than 100	75%
less than 1.0	or	less than 75	**Delay**
*Consider decreasing to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment			

2. **Gastrointestinal toxicity**: For fluorouracil

Grade	Stomatitis	Diarrhea	Dose Fluorouracil
Grade 1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output	100%
Grade 2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	75%
Grade 3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Increase of greater than 7 stools/day or grossly bloody diarrhea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Discontinue or delay until toxicity resolved then resume at 50%

3. Hand-Foot Syndrome for fluorouracil

Grade	Hand-Foot Syndrome	Dose
Grade 1	Skin changes or dermatitis without pain e.g. erythema, peeling	100%
Grade 2	Skin changes with pain not interfering with function	75% until resolved then consider increasing dose by 10%
Grade 3	Skin changes with pain, interfering with function	Delay until resolved then resume at 75%

4. Hepatic dysfunction: for DOCEtaxel

Alkaline phosphatase		AST and/or ALT	Dose
less than 2.5 x ULN	**and**	less than 1.5 x ULN	100%
2.5 to 5 x ULN	**and**	1.5 to 5 x ULN	75%
greater than 5 x ULN	**or**	greater than 5 x ULN	**Delay**

5. **Renal dysfunction**: for CISplatin

Calculated Cr Clearance (mL/min) by Cockcroft/Gault formula	CISplatin dose
greater than or equal to 60	100%
45 to less than 60	80%
less than 45	Hold CISplatin or delay with additional IV fluids

Cockcroft/Gault formula:

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

Where N = 1.04 for females, and 1.23 for males

PRECAUTIONS:

1. **Fluid retention**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
2. **Hypersensitivity** reactions to DOCEtaxel are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer Hypersensitivity Guidelines.
3. **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.
6. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
7. **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.
8. **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.
9. **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
10. **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).

Call Cheryl Ho or tumour group delegate at (604) 877-6000 with any problems or questions regarding this treatment program.

Reference:

1. Posner M, et al. Phase III trial of cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-15.
2. Vermorken M, et al. Phase II study of cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-704.
3. Lorch JH, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011;12(2):153-9.