

BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using **DOCEtaxel** and Capecitabine

Protocol Code:
Tumour Group:
Contact Physician:

BRAVDCAP
Breast
Dr. Stephen Chia

ELIGIBILITY

- First line treatment of metastatic breast cancer after adjuvant anthracycline-based chemotherapy.
- Second or third line treatment of metastatic breast cancer after previous combination chemotherapy with an anthracycline in a patient who has an ECOG status of less than or equal to 2 and a life expectancy greater than three months.
- Progressive breast cancer after failure of previous combination chemotherapy in patient for whom anthracyclines are contraindicated and who has an ECOG status of less than or equal to 2 and a life expectancy greater than three months.
- patient must be able to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis
- A BCCA "Class II Drug Registration Form" form must be submitted

EXCLUSIONS

- Previous treatment with **DOCEtaxel** or capecitabine. Prior adjuvant use of paclitaxel allowed if greater than or equal to 12 months disease free interval from last paclitaxel administration
- Severe hepatic dysfunction (AST/ALT greater than or equal to 5X upper limit of normal and/or bilirubin greater than 50 micromol/L)
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under **DOSE MODIFICATIONS**)
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see **PRECAUTIONS**)

TESTS

- Baseline: CBC & diff, platelets, liver enzymes*, BUN and creatinine
 - **Prior to each** cycle: CBC & diff, platelets, creatinine
 - Before Cycle 4 and anytime if clinically indicated: liver enzymes*, BUN
- *See Precaution #5 for guidelines regarding hepatic dysfunction

PREMEDICATIONS

- Dexamethasone 8 mg PO bid for 3 days, starting one day prior to each **DOCEtaxel** administration. Patient must receive minimum of 3 doses pre-treatment.
- Additional antiemetics not usually required.
- **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	BCCA Administration Guideline
DOCEtaxel	75 mg/m ² on Day 1	IV in 250 mL ** NS or D5W over 1 hour (see precaution #2) (use non-PVC equipment)
Capecitabine	1000-1250 mg/m ² BID x 14 days (Days 1-14)* (Total daily dose = 2000-2500 mg/m ² /day)	PO with food

*Capecitabine starting dose of 1000 mg/m² bid recommended for age greater than or equal to 60 years, poor performance status or extensively pretreated.

** If 75-185 mg, use 250 mL bag. If greater 185 mg, use 500 mL bag.

Repeat every 21 days x 6 cycles.

Discontinue if no response after 2 cycles.

DOSE MODIFICATIONS

Approximately 65% of patients require a dose reduction:

- 47% require a 25% dose reduction of both drugs
- 12% require a 25% dose reduction of DOCEtaxel alone
- 15% require an eventual 50% dose reduction of capecitabine

1. Hematological (DOCEtaxel only)

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (DOCEtaxel)	Dose after Neutropenic Sepsis (DOCEtaxel)
greater than or equal to 1.5	and	greater than 90	100%	55 mg/m ²
1 – 1.4	or	70-90	delay	delay
less than 1	or	less than 70	delay	delay

2. Hepatic Dysfunction (DOCEtaxel and Capecitabine)

Alkaline Phosphatase		AST +/-or ALT	Dose (both drugs)
less than 2.5 x ULN	and	less than or equal to 1.5 x ULN	100%
2.5 – 5 x ULN	and	1.6 – 5 x ULN	75%
greater than 5 x ULN	or	greater than 5 ULN	discuss with contact physician

ULN = upper limit of normal

3. Non-Hematological Toxicity

- see next table for toxicity grading criteria for hand-foot skin reaction, diarrhea, nausea and vomiting, and stomatitis
- if capecitabine treatment is interrupted due to toxicity, retain the original stop and start dates (i.e, do not make up for missed doses when treatment is resumed)

Toxicity Grade	DOCetaxel and Capecitabine Dose			
	1 st Event	2 nd Event	3 rd Event	4 th Event
0-1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	discontinue DOCetaxel and delay* then use BRAVCAP starting at 50%	discontinue
3	delay* then 75%	discontinue DOCetaxel and delay* then use BRAVCAP starting at 50%	discontinue	discontinue
4	discontinue DOCetaxel and delay* then use BRAVCAP starting at 50%	discontinue	discontinue	discontinue

*stop treatment immediately and delay until toxicity resolved to grade 0-1

Toxicity Criteria

Grade	Hand-Foot Skin Reaction*	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Skin changes with discomfort (eg, numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting normal activities	Increase of 2-3 stools/day or nocturnal stools	1 vomit per day but can eat	Painless ulcers, erythema or mild soreness
2	Skin changes with pain (eg, erythema, swelling) affecting activities of daily living	Increase of 4-6 stools/day or nocturnal stools	2-5 vomits per day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Severe skin changes with pain (eg, moist desquamation, ulceration, blistering) causing severe discomfort and inability to work or perform activities of daily living	Increase of 7-9 stools/day or incontinence, malabsorption	6-10 vomits per day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	not applicable	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

4. Renal Dysfunction (Capecitabine)

Creatinine Clearance mL/min	Capecitabine Dose
greater than 50	100%
30-50	75%
less than 30	0%

Cockcroft-Gault Equation (Female):

$$\text{Estimated creatinine clearance: (mL/min)} = \frac{1.04 (140 - \text{age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

PRECAUTIONS

- Fluid retention:** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention associated with **DOCETaxel**.
- 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 BCCA Hypersensitivity Guidelines.
- Extravasation:** **DOCETaxel** causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
- Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Hepatic Dysfunction:** **DOCETaxel** undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (eg, repeat liver enzymes prior to each treatment if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check liver enzymes after 3 cycles (i.e, at cycle 4). Capecitabine has not been studied in severe hepatic dysfunction but dose modification may be required. Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments.
- Dihydropyrimidine dehydrogenase (DPD) deficiency** can result in severe toxicity secondary to reduced capecitabine metabolism.
- Possible drug interactions with capecitabine 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 Dr. Stephen Chia or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 01 July 2002

Date revised: 1 Apr 2011 (use of pyridoxine deleted, reformatted with TALLman lettering)

References:

- O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline pre-treated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812-23.