Chemotherapy Protocol

SARCOMA

DOCETAXEL-GEMCITABINE

Regimen

- Sarcoma-Docetaxel-Gemcitabine

Indication

- Relapsed metastatic osteosarcoma
- Selected metastatic soft tissue sarcomas (third line) / uterine leiomyosarcoma
- Relapsed Ewings (if other second line therapy is not suitable)

Toxicity

Drug	Adverse Effect
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Gemcitabine	Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza-like symptoms, radiosensitising

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC prior to day one and eight of treatment
- LFTs and U&Es prior to day one of treatment

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be

dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Day 1

Neutrophils ($x10^9$/L)	**Dose Modifications (gemcitabine)**
Less than 1	Delay for one week. If the neutrophils recover continue with full dose. If there is no recovery after two weeks, review treatment
Platelets ($x10^9$/L)	**Dose Modifications (gemcitabine)**
Less than 100	Delay for one week. If the platelets recover continue with full dose. If there is no recovery after two weeks, review treatment

Day 8

Neutrophils ($x10^9$/L)	**Dose Modifications (docetaxel and gemcitabine)**
greater than or equal to 1	100%
0.5 - 0.9	Administer 75% of the original dose of gemcitabine and docetaxel
less than 0.5	Omit
Platelets ($x10^9$/L)	**Dose Modifications (docetaxel and gemcitabine)**
Greater than or equal to 100	100%
50–99 with no evidence of bleeding	Administer 75% of the original dose of gemcitabine and docetaxel
Less than 50 or bleeding	Omit

If a patient has febrile neutropenia or platelets less than 25 x 10^9/L for more than 5 days, use a 25% dose reduction of docetaxel and gemcitabine for further cycles. If there is a reoccurrence at the lower dose then treatment should be discontinued

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin µmol/L		AST/ALT units		Alk Phos units	Dose (% of original dose)
Docetaxel	N/A		1.5xULN or greater	and	2.5xULN or greater	75%
	22 or greater	and/or	3.5xULN or greater	and	6.0xULN or greater	Not recommended
Gemcitabine	greater than 27		N/A			Initiate treatment with a dose of 800mg/m^2

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Docetaxel	n/a	No dosage adjustment necessary
Gemcitabine	greater than or equal to 30	100%
	less than 30	Consider dose reduction

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Gemcitabine

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose should then be reduced to 75% of the original dose or discontinued as appropriate.

Docetaxel

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of docetaxel should then be reduced to 60mg/m^2 or discontinued as appropriate.

Peripheral Neuropathy

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 75mg/m^2 to 60mg/m^2 once the neuropathy has resolved to NCI-CTC grade 2 or below. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m^2 or a NCI-CTC grade 4 toxicity develops consider stopping treatment.

Lacrimation

Excessive lacrimation is related to cumulative docetaxel doses and occurs after a median of 400mg/m^2. Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 60mg/m^2.

Skin

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m^2 or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Stomatitis

A NCI-CTC grade 2 stomatitis should result in a delay in treatment until it has become NCICTC grade 1 or below. Treatment may then be re-started at the previous dose. For a NCICTC grade 3 stomatitis delay treatment until it has recovered to NCI-CTC grade 1 or below then reduce the dose to 60mg/m^2. Treatment should be stopped in relation to a NCI-CTC grade 4 stomatitis.

Regimen

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	8	Intravenous infusion in 250ml sodium chloride over 60 minutes
Gemcitabine	675mg/m^2	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

In patients who tolerate this or who have had no previous treatment and / or a PS of 0 consider increasing the doses as follows;

Drug	Dose	Days	Administration
Docetaxel	100mg/m^2	8	Intravenous infusion in 250ml sodium chloride over 60 minutes
Gemcitabine	900mg/m^2	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Dose Information

- Docetaxel will be dose banded according to the agreed bands
- Gemcitabine will be dose banded according to the agreed bands

Administration Information

- Docetaxel hypersensitivity reactions tend to occur with the first or second infusion. For minor symptoms such as flushing or localised rashes the infusion should not be interrupted. For severe reactions including profound hypotension, bronchospasm and generalised erythema discontinue the infusion immediately.
- In this regimen the gemcitabine is administered over 90 minutes.

Extravasation

- Docetaxel – exfoliant
- Gemcitabine - neutral

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on **day 1 and day 8**

  - metoclopramide 10mg oral or intravenous

  As take home medication on day 1

  - metoclopramide 10mg three times a day oral as necessary

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day oral for three days starting 24 hours before docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg intravenous.

- Growth factor according to local formulary choice. For example;

  - filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day 9 of the cycle
  - lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day 9 of the cycle
  - pegfilgrastim or bioequivalent 6mg subcutaneous on day 9 of the cycle

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines.

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding

- Procurement – X71.5
- Delivery – X72.1 Day 1, X72.4 Day 8

References

1. Pautier P, Floquet A, Penel N et al. Randomised multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcoma: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist 2012; 17 (9): 1213-1220.
2. Fox E, Patel S, Wathen JK et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma or unresectable or locally recurrent chondrosarcoma: results of Sarcoma Alliance for Research through Collaboration Study 003. Oncologist 2012; 17 (3): 321
3. Hensley ML, Ishill N, Soslow R et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: results of a prospective study. Gynecol Oncol 2009; 112 (3): 563-567.
4. Hensley ML, Blessing JA, Mannel R et al. Fixed dose rate gemcitabine plus docetaxel as first line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group Phase II trial. Gynecol Oncol 2008; 109 (3): 329-334.

5. Maki RG, Wathen JK, Patel SR et al. Randomised phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. J Clin Oncol 2007; 25 (19): 2755-63.

REGIMEN SUMMARY

Docetaxel-Gemcitabine

Day 1

1. Metoclopramide 10mg oral or intravenous

2. Gemcitabine 675mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Take home medicines (day 1 only)

3. Dexamethasone 8mg twice a day for three days starting the day before docetaxel (days 7, 8, 9 of the cycle)

4. Metoclopramide 10mg three times a day when necessary for the relief of nausea
   Administration Instructions
   Please supply 28 tablets or nearest equivalent pack size

Day 8

5. Metoclopramide 10mg oral or intravenous

6. Gemcitabine 675mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

7. Docetaxel 75mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat 15-30 minutes before chemotherapy.

Take Home Medicines (day 8 only)

8. Growth Factor
   Administration Information
   Please supply according to local formulary choice. For example;

   - filgrastim or bioequivalent 30million units once a day subcutaneous for seven days starting on day 9 of the cycle
   - lenograstim or bioequivalent 33.6million units once a day subcutaneous for seven days starting on day 9 of the cycle
   - pegfilgrastim, lipegfilgrastim or bioequivalent 6mg once subcutaneous on day 9 of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	January 2016	Gemcitabine administration changed to over 90 minutes Administration instructions altered for metoclopramide and growth factors	Dr Deborah Wright	Donna Kimber Pharmacy Technician
1.1	December 2015	OPCS codes updated	Rebecca Wills Pharmacist	Dr Deborah Wright Pharmacist
1	September 2015	None	Dr Deborah Wright Pharmacist	Dr Nicola Keay Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.