Carfilzomib (Kyprolis®) + Dexamethasone

TA457 July 2017

INDICATION: For patients with relapsed myeloma who have only had one prior therapy which did not include bortezomib.

Prior to a course of treatment

- Carfilzomib has been associated with first dose effects including tumour lysis syndrome (TLS) and fever / chills / rigors the evening after first dose. Thus note a lower dose of 20mg/m^2 is used for day 1 & 2 of cycle 1 only, with the dose going up to 56mg/m^2 thereafter.
- 500ml of normal saline must be infused over 1 hour prior to each dose of carfilzomib and another 500ml infused over 1 hour after each dose of carfilzomib in cycle 1 only (unless raised urate or LDH at cycle 2 or other ongoing concern re risk of TLS).
- Check FBC – neutrophils should be > 1.0 and platelets > 50 unless due to marrow infiltration
- Check renal and liver function – *if abnormal discuss with consultant & see dose modification*.

Prior to each cycle

- Check FBC - *see dose modification*
- Check U&E - *see dose modification*

Days 1 & 2, **8 & 9** **15 & 16**	Carfilzomib	20 mg/m^2 (max 44mg) for day 1 & 2 of cycle 1 only 56mg/m^2 (max 120mg) thereafter	IV in 100 ml of 5% dextrose over 30 minutes Dexamethasone PO/IV given before hydration as a premed prior to carfilzomib Hydrate patient with 500ml normal saline over 1 hour before and 500ml over 1 hour after each dose of carfilzomib. (If urate or LDH raised at cycle 2 or other ongoing concern re risk of TLS then continue these measures)
Days 1 & 2, **8 & 9,** **15 & 16,** **22 & 23.**	Dexamethasone	20mg	Orally (IV cycle 1 days 1 & 2 only)

Repeat cycle every 28 days until disease progression or unacceptable toxicity.

Prophylaxis for acute emesis	Dexamethasone (if another antiemetic is required check for QT prolongation)
Other medications	Aciclovir prophylaxis 400mg o BD Consider PPI. Thromboprophylaxis with aspirin or LMW heparin (despite absence of lenalidomide) Allopurinol po daily (cycle 1 only)

Carfilzomib toxicities

Cardiac toxicities:

Cardiac failure, myocardial ischaemia and infarction, QT prolongation. Although limited to only 2 – 5% of patients and mostly reversible, use caution in patients are over 75 years old or have cardiac risk factors. See dose reduction advice and dosing steps below.

Pulmonary toxicities including ARDS, acute respiratory failure, pneumonitis, interstitial lung disease.

Hypertension	Nausea
Diarrhoea	Cough
Peripheral oedema	Acute renal failure
Tumour lysis syndrome	Infusion reactions
Thromboytopenia, GI haemorrhage	Anaemia
Venous thrombosis	Hepatic toxicity

Thromobotic microangiopathy

Posterior Reversible Encephalopathy syndrome (PRES)

Herpes zoster reactivation similar to other proteasome inhibitors.

<u>Carfilzomib dose modification for haematological toxicity, unless due to disease. (see dose reduction steps below)</u>

Neutropenia

• First fall to < 0.5	Stop carfilzomib and start GCSF
• Return to > 1.0 when neutropenia is only toxicity	Resume carfilzomib at full dose
• Return to > 1.0 and other toxicity noted	Resume carfilzomib at dose level - 1
• For each drop to < 0.5	Stop carfilzomib
• Return to > 1.0	Resume carfilzomib at next lower dose level.

Note grade 4 anaemia and thrombocytopenia without active bleeding <u>do not</u> require carfilzomib to be withheld. Supportive measures should be given as per local guidelines.

Thrombocytopenia

• First fall to < 25 with active bleeding	Stop carfilzomib, follow FBC weekly
• Return to > 25	Resume carfilzomib at full dose
• For each subsequent drop < 25 with active bleeding	Stop carfilzomib
• Return to > 25	Resume carfilzomib at 1 dose decrement.

<u>Carfilzomib Non-Haematological Toxicities</u>

Symptom	**Recommended action for carfilzomib**

Allergic reaction /hypersensitivity	
Grade 2-3	Hold until ≤ Grade 1, reinstitute full dose
Grade 4	Discontinue
Tumour lysis syndrome	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full dose.
Neuropathy	
Grade 2 with pain or grade 3	Continue to dose. If neuropathy persists for more than 2 weeks, hold carfilzomib until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement
Grade 4	Discontiue
Renal dysfunction CrCl < 15 ml/min	Hold carfilzomib until CrCl ≥ 15 ml/min. Then restart at 1 dose decrement
Congestive heart failure	Hold carfilzomib until resolution or return to baseline, after which treatment may continue at a reduced dose, or the participant may be discontinued. If no resolution after 2 weeks discontinue.
Other non-haem toxicity assessed as carfilzomib-related ≥ Grade 3	Hold carfilzomib until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

Carfilzomib dose reduction steps	
Starting dose	56 mg/m^2
Dose level - 1	45 mg/m^2
Dose level - 2	36 mg/m^2
Dose level - 3	27 mg/m^2

References:

- Carfilzomib and dexamethasone verses bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Dimopoulos et al, The Lancet Oncology, volume 17, 1, 27 – 38, Jan 2016.
- Carfilzomib SPC.
- NICE Technology Appraisal 457 July 2017