OBINUTUZUMAB-CHLORAMBUCIL

INDICATION: CLL

Prior to a course of treatment

- Check FBC. Patient should have adequate bone marrow reserve, i.e neutrophils > 1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly - *if not discuss with consultant*
- Check U&Es, creat and LFTs – *see dose modification.*
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss risk of infertility - offer semen cryopreservation to male patients
- Written consent for course
- Advise patient to omit any antihypertensive medicines on the morning of treatment, particularly on the first cycle
- Check hepatitis B status

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC, U&Es, creat, LFTs - neutrophils should be >1.0 and platelets >75 *(see dose modification)*

Cycle 1

Chlorambucil *	10mg/m^2 od PO	days 1-7
Obinutuzumab	100mg IV	day 1
Obinutuzumab	900mg IV	day 2
Obinutuzumab	1000mg IV	days 8 & 15

Cycle 2 onwards

Chlorambucil *	10mg/m^2 od PO	days 1-7
Obinutuzumab	1000mg IV	day 1

Repeat every 28 days for up to 6 cycles

Obinutuzumab premed:

Dexamethasone 20mg IV (>60 minutes before treatment)

Paracetamol 1g orally, chlorphenamine 10mg IV (>30 minutes before treatment)

Once WBC <25 **and** if previous infusions are tolerated then steroid dose may be reduced or omitted at clinician's discretion

In patients with high initial counts (WBC >100) or bulky disease, it is suggested that at least 1 litre of 0.9% sodium chloride is administered before starting treatment

Patients with severe and long lasting (> 1 week) neutropenia should also receive antimicrobial prophylaxis throughout the treatment period

* 2mg tablets

Prophylaxis for emesis Not usually needed – but if nausea a problem consider metoclopramide *or* divide daily dose into three

Other medications

Allopurinol 300mg od days 1-7 with cycle 1-3

Administration

Obinutuzumab is administered intravenously in 250ml (100ml on day 1) sodium chloride 0.9% via a PVC-free giving set with a 0.2 micron in-line filter, as follows:

First infusion

Initiate the infusion at 12ml/hour for 30 minutes then increase the infusion rate as follows every 30 minutes to a maximum of 400ml/hour

Cycle/day	Infusion Rate
Cycle 1, day 1 (100mg in 100ml)	Administer 100ml infusion at 25ml/hour over 4 hours. Do not increase the infusion rate Monitor vital signs at baseline and every 15 minutes
Cycle 1, day 2 (900mg in 250ml)	Administer at 50mg/hr (14ml/hr) and increase in increments of 50mg/hr (14ml/hr) every 30 minutes to a maximum rate of 400mg/hr (~100ml/hr) Monitor vital signs at baseline and every 15 minutes
Subsequent doses (1000mg in 250ml)	Administer at 100mg/hr (25ml/hr) and increase by 100mg/hr (25ml/hr) increments every 30 minutes to a maximum of 400mg/hr (100ml/hour) Monitor vital signs at baseline and every 30 minutes

Infusion reactions

In the event of a Grade 1-2 (mild or moderate) infusion-related reaction, the infusion rate must be slowed down and symptoms treated. Once the symptoms have resolved, the infusion rate can be escalated according to standard procedure for the dose.
(For the Cycle 1, Day 1 dose, increase up to 25ml/hr only after 60 minutes at a slower rate)

In the event of a Grade 3 (severe) infusion-related reaction, the infusion should be interrupted and, when the patient is stable, re-started at no more than half the previous rate at the time the reaction occurred. The infusion rate can then be increased according to standard procedure for that dose.
(For the Cycle 1, Day 1 dose, re-start at 12.5ml/hour for 60 minutes, then increase up to 25ml/hour)

In the event of a Grade 4 (life-threatening) infusion-related reaction, or a second occurrence of a Grade 3 (severe) infusion-related reaction, the infusion must be stopped and obinutuzumab permanently discontinued.

Dose modification for haematological toxicity (unless due to disease)

Neuts <1.0 or plats < 75	Defer until neuts>1.0 and plats >75	When counts have recovered reduce dose of chlorambucil to 7.5mg/m^2/day

Chlorambucil dose may be further reduced to 5mg/m^2/day but if counts continue to fall then both chlorambucil and obinutuzumab should be discontinued

Dose modification for renal dysfunction — No initial reduction indicated but monitor carefully for haematological toxicity and adjust as necessary

Chlorambucil Toxicities

Neutropenic sepsis & thrombocytopenia	Nausea & vomiting (none-mild)
Rash	Amenorrhoea & infertility (offer semen cryopreservation)
Mucositis	Potentially alopecia (mild)

Hepatotoxicity	Pulmonary fibrosis (late)
Second malignancies (late)	

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