GIG CYMRU NHS WALES
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Obinutuzumab (Gazyvaro™) + Chlorambucil in Chronic Lymphocytic Leukaemia

Background:
Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic lymphocytic leukaemia who have co-morbidities that make full-dose fludarabine-based or bendamustine therapy is unsuitable for them (NICE TA 343).

Patient Group:

Adults with untreated chronic lymphocytic leukaemia who have co-morbidities that make full-dose fludarabine-based regimens unsuitable for them, only if:
- Bendamustine therapy is not suitable

Pre-treatment Assessment:
Clinical assessment
BP
Cardiac tests for patients with cardiac risk factors
Weight, Height, FBC, U&E (including uric acid), LFTs, LDH
HBV, HCV and HIV screening especially in high risk patients

Important
Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during obinutuzumab intravenous infusions. Therefore, **withholding of antihypertensive treatments** should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

Treatment Threshold
ANC 1.5 x 10^9/L (unless cytopenias caused by underlying CLL)
Platelets 75 x 10^9/L (unless cytopenias caused by underlying CLL)
Cr Cl >30mL/min
Must be adequately hydrated (prescribe IV fluid if necessary)

Pre Meds:
Tumour Lysis Syndrome (TLS) Prophylaxis: Rasburicase 0.2mg/Kg IV 12-24 prior to the first cycle of Obinutuzumab and as required if the patient is considered to be at high risk of TLS.

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Administered at least 60 minutes before Obinutuzumab:
Dexamethasone 20mg IV (can omit from cycle 1 day 8 onwards if ≤ grade 2 infusion related reactions with previous doses and lymphocytes <25x10^9/L)
Administered at least 30 minutes before Obinutuzumab:
Paracetamol 1g orally
Chlorphenamine 10mg IV (can omit from cycle 1 day 8 onwards if no infusion related reactions with previous doses)

Regimen Details:

Cycle 1

Obinutuzumab **100mg IV Day 1***
In 100mL 0.9% sodium chloride infused over 4 hours (25mg/hour)

Obinutuzumab **900mg IV Day 2***
In 250mL 0.9% sodium chloride (see table on Page 3 for rate of infusion)

**Note:* Prepare both doses together. If the 100mg bag is completed without modifications of the infusion rate or interruptions, the 900mg bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion.

Chlorambucil **0.5mg/kg** PO Days 1 & 15 only (rounded to nearest 2mg)**
Orally as a single dose or split into three divided doses (to reduce gastrointestinal irritation)

Obinutuzumab **1000mg IV Days 8 and 15**
In 250mL 0.9% sodium chloride (see table on Page 3 for rate of infusion).

Cycles 2-6

Obinutuzumab **1000mg IV Day 1**
In 250mL 0.9% sodium chloride (see table on Page 3 for rate of infusion)

Chlorambucil **0.5mg/kg** PO Days 1 & 15 only (rounded to nearest 2mg)**
Orally as a single dose or split into three divided doses (to reduce gastrointestinal irritation)

***Note:* Dose capped at weight corresponding to Body Mass Index of 35Kg/m^2

Repeated every 28 days for 6 cycles

Administration:

- Check that patients have not taken their anti- hypertensive medication the morning of treatment.
- Monitor patients closely for signs of tumour lysis syndrome and infusion related reactions (altered vital signs, nausea / vomiting, chills, flushing, dyspnoea, headache, diarrhoea)
- Full resuscitation facilities and an anaphylaxis kit must be available at all times.

Standard infusion rate in the absence of infusion reactions / hypersensitivity (including previous doses)

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued) (900 mg)	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	
Cycles 2-6	Day 1	

Management of Infusion related reactions may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Obinutuzumab:

- **Grade 4** (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- **Grade 3** (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.
- **Grade 1-2** (mild to moderate): The infusion rate must be halved and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Table 3). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

- If the previous infusion rate was not well tolerated, instructions for the Cycle 1, Day 1 and Day 2 infusion rate should be used for subsequent cycles.

- **Chlorambucil tablets** should be taken on an empty stomach (at least one hour before meals or three hours after meals).

Anti-emetics: Low emetogenicity

Additional Medication:

- Tumour Lysis Syndrome (TLS): prophylaxis is mandatory in high risk patients (high tumour burden, lymphocytes >$25x10^9$/L, and / or renal impairment). Continue TLS prophylaxis prior to each infusion until no longer deemed at risk.
- Aciclovir 400mg Twice daily (continuous throughout treatment)
- Co-trimoxazole 480mg Twice daily on Mon/Wed/Fri (continuous throughout treatment)
- Consider fluconazole 50-100mg daily and GCSF if ANC<$1.0x10^9$/L

Monitoring and Assessment:
Clinical assessment prior to each cycle
FBC - before each dose and as clinically indicated following treatment completion
U&Es & LFTs prior to Day 1 and 15 and as clinically indicated
U&E (bone profile plus uric acid) 3-4 hours after the first infusion to assess whether evidence of tumour lysis and whether further support or treatment required.

Dose Modifications:
Delay all treatment if active infection.

Non-Haematological Toxicity
Defer until resolved to ≤Grade 1 (or baseline) and discontinue treatment if delayed more than 4 weeks.

Haematological Toxicity
Day 1 - defer until cytopenia(s) resolved to ≤Grade 2 (or baseline if pre-treatment cytopenia) and permanently reduce dose of chlorambucil to 75% after first episode, 50% after second episode, and discontinue after third episode. Give GCSF / transfuse as required. Discontinue treatment if delayed more than 4 weeks. No dose reductions of Obinutuzumab are recommended.
Day 15 chlorambucil - omit if grade 3 or 4 cytopenia(s) and reduce dose on day 1 of next cycle onwards to 75% after first episode, 50% after second episode, and discontinue after third episode.

Infusion Related Reactions (IRRs)
The most frequently observed adverse drug reactions (ADRs) in patients receiving Obinutuzumab were IRRs, which occurred predominantly during infusion of the first 1,000 mg. In patients who received the combined measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) a decreased incidence of all Grade IRRs was observed. The rates of Grade 3-4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. Mitigation measures to reduce IRRs should be followed The incidence and severity of infusion-related symptoms decreased substantially after the first 1,000 mg was infused, with most patients having no IRRs during subsequent administrations of Obinutuzumab.

If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction (see section on administration).

Hypersensitivity reactions including anaphylaxis
Anaphylaxis has been reported in patients treated with obinutuzumab. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated.

Tumour Lysis Syndrome (TLS)
TLS has been reported with Obinutuzumab. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count [> 25 x 10^9/L] and/or renal impairment [CrCl <70 mL/min]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidate (e.g. rasburicase) starting 12-24 hours prior to the infusion of obinutuzumab as per standard practice. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Neutropenia and Thrombocytopenia
Severe and life-threatening neutropenia and thrombocytopenia including febrile neutropenia has been reported during treatment with obinutuzumab. Patients who experience neutropenia or thrombocytopenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary it should be administered in accordance with local guidelines and the administration of granulocyte-colony stimulating factors should be considered. Any signs of concomitant infection should be treated as

Neutropenia and Thrombocytopenia continued:
appropriate. Dose delays should be considered in case of severe or life-threatening neutropenia. It is strongly recommended that patients with severe and long lasting (>1 week) neutropenia receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia.

Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies which could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Worsening of pre-existing cardiac conditions
In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Hepatitis B reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including obinutuzumab. Hepatitis B virus screening should be performed in all patients before initiation of treatment. Patients with active hepatitis B disease should not be treated with obinutuzumab. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation.

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Progressive multifocal leukoencephalopathy (PML)
Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations.

Renal Impairment
Obinutuzumab - No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min). Use with caution if CrCl 30-49 mL/min. The safety and efficacy has not been established in patients with severe renal impairment (CrCl < 30 mL/min).
Chlorambucil – No dose adjustment required. Monitor patients closely.

Hepatic Impairment:
Obinutuzumab - The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.
Chlorambucil - Consider dose reduction in patients with gross hepatic dysfunction.

Pharmaceutical Care:

- *Delayed or missed doses*- If a planned dose of Obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for Obinutuzumab should be maintained between doses.

- Vaccination with live virus vaccines is not recommended during treatment and until B cell recovery because of the immunosuppressive effect of obinutuzumab.

Most Common Toxicities:

- Infusion-related reactions (dyspnoea, often accompanied by bronchospasm and hypoxia, fever, chills, rigors, urticaria, and angioedema etc)
- Hypersensitivity
- Tumour lysis syndrome, hyperuricaemia
- Neutropenia, thrombocytopenia, anaemia
- Infections
- Acute secondary haematological malignancies
- Squamous cell carcinoma of the skin
- Nausea and vomiting
- Mouth ulceration
- Atrial Fibrillation
- Hypertension
- Cough
- Diarrhoea
- Constipation
- Alopecia
- Pyrexia
- Arthralgia , myalgia, pain
- Rash

References:

1. SPC Gazyvaro 1000mg ® Roche Products Limited. www.medicines.org.uk [Accessed 25th May 2016]

2. SPC Chlorambucil 2mg tablets ® www.medicines.org.uk [Accessed 25th May 2016]

3. NICE Technology Appraisal 343 www.nice.org.uk [Accessed 25th May 2016]

4. CLL11 Study (EudraCT NO 2009-012476-28) Protocol Version J (Approved 08 Jun 13)

ChemoCare Only

- Decision points – None
- Critical tests:

Day 1 Cycle 1;	Hb, Plat 75, ANC 1.5, Creatinine
Day 1 Cycles 2-6;	Hb, Plat 50, ANC 1.0, Creatinine
Day 15 Cycle 1;	Hb, Plat 50, ANC 1.0, Creatinine
Day 15 Cycles 2-6;	Hb, Plat 50, ANC 1.0

- Nursing units – Cycle 1 32 units on Day 1,2,8 &15, Cycle 2 32 units on Day 1 and 2 units on Day 15
- Max. chlorambucil dose 70mg