Idelalisib (Zydelig®) +/- Rituximab

INDICATION

Licensed / NICE TA359

Idelalisib is indicated in combination with Rituximab for the treatment of adult patients

- with untreated lymphocytic leukaemia (CLL) with a 17p deletion or TP53 mutation who are not eligible for any other therapies
- OR
- relapsed within 24 months following prior anti-CD20 containing chemo-immunotherapy

Licensed / Unfunded indication

Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

TREATMENT INTENT

Induction and maintenance of remission

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine.
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and Hepatitis BsAg, hepatitis C antibody.
4. ECG.
5. Record performance status.
6. Record height and weight.
7. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
8. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
9. Treatment should be agreed in the relevant MDT.
**DRUG REGIMEN / CYCLE FREQUENCY**

Set up as a 28 day cycle

**IDELALISIB** 150 mg TWICE daily orally

Treatment should be continued until disease progression or unacceptable toxicity

**RITUXIMAB (for CLL only)**

Pre-medication (30 minutes before Rituximab):
Paracetamol 1g PO, Chlorphenamine 10 mg IV, Hydrocortisone 100 mg IV

Cycle 1 Day 1: If lymphocyte count >25 x 10^9/L:
- Give 50 mg/m² (or 100 mg flat dose) of Rituximab on day 1.
- Give the rest (i.e. 325 mg/m²) on day 2.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Rituximab Dose</th>
<th>Rituximab Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>375 mg/m²</td>
<td>IV infusion in 500 ml sodium chloride 0.9% for a total of 8 infusions</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>500 mg/m²</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>500 mg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>500 mg/m²</td>
<td></td>
</tr>
<tr>
<td>3 to 6</td>
<td>1</td>
<td>500 mg/m²</td>
<td></td>
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**RESTAGING**

Clinical response should be assessed on a monthly basis for the first 3 months, prior to CT scanning. Subsequent CT scans should be considered every 6 months

**INVESTIGATIONS**

- FBC monthly
- Creatinine
- Liver function Tests - Monitor ALT, AST, and total bilirubin every 2 weeks for the first 3 months of treatment, then as clinically indicated. If Grade 2 or higher elevations in ALT and/or AST are observed, monitor weekly until the values return to Grade 1 or below
- CMV PCR in blood (EDTA) should be monitored every 4 weeks throughout treatment. Idelalisib should be discontinued during confirmed CMV viraemia.

**Idelalisib-Associated Lymphocytosis**

Idelalisib has been shown to cause lymphocytosis when it is administered as a single agent. The addition of Rituximab to Idelalisib blunts and shortens the duration of the lymphocytosis. It is expected that the rate of lymphocytosis will peak at week 2 and resolve by week 12.
DOSE MODIFICATIONS

**Idelalisib**: Please discuss Grade 3 or 4 toxicities with consultant

**Haematological toxicity:**
If Neutrophils < 0.5 x 10^9/L withhold Idelalisib until ≥ 0.5 x 10^9/L then may resume at 100 mg twice daily.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated liver transaminases</td>
<td>Grade 3 or 4 (ALT / AST &gt; 5 x ULN)</td>
<td>Withhold Idelalisib, Resume at 100 mg TWICE a day once toxicity returns to ≤ Grade 1 (ALT/AST ≤ 3 x ULN) Dose can be re-escalated to 150 mg TWICE a day at clinician’s discretion if the toxicity does not recur</td>
</tr>
<tr>
<td></td>
<td>Recurrent Grade 3 or 4 (ALT / AST &gt; 5 x ULN)</td>
<td>Withhold Idelalisib until toxicity returns to ≤ Grade 1, after which re-initiation at 100 mg TWICE a day may be considered at clinician’s discretion</td>
</tr>
<tr>
<td>Diarrhoea /colitis</td>
<td>Grade 3 or 4</td>
<td>Withhold Idelalisib, Resume at 100 mg TWICE a day once toxicity returns to ≤ Grade 1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Suspected</td>
<td>Withhold Idelalisib until resolved, after which re-initiation at 100 mg TWICE a day may be considered at clinician’s discretion</td>
</tr>
<tr>
<td>Rash</td>
<td>Grade 3 or 4</td>
<td>Withhold Idelalisib, Resume at 100 mg TWICE a day once toxicity returns to ≤ Grade 1 Dose can be re-escalated to 150 mg TWICE a day at clinician’s discretion if the toxicity does not recur</td>
</tr>
</tbody>
</table>

**Renal/Hepatic Impairment**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose adjustment required</td>
<td>No dose adjustment mild or moderate hepatic impairment. But monitor closely. Insufficient data in severe hepatic impairment.</td>
</tr>
</tbody>
</table>

**ANTI-EMETICS**

Low emetic risk.
CONCURRENT MEDICATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and duration</th>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>300 mg daily for 7 days starting 24-48 hours prior to chemotherapy (first course/cycle only)</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>200 mg 3 times daily for duration of chemotherapy and for 3 months after completion.</td>
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<tr>
<td>Co-trimoxazole</td>
<td>480 mg daily on Mon/ Wed/ Fri for duration of treatment and for 3 months afterwards (Consider reducing the dose to 480 mg twice weekly during neutropenic periods)</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS (Refer to the SmPC for further full details)

**Idelalisib:**
Hypersensitivity to Idelalisib or to any of the excipients
Active liver disease of a certain level/history of severe colitis

**Rituximab:**
Hypersensitivity to Rituximab or to murine proteins, or to any of the excipients.
Active, severe infections.
Patients in a severely immunocompromised state.

SPECIAL WARNINGS / PRECAUTIONS (Refer to the SmPC for further full details)

**Idelalisib:**
**Serious infections:**
Increased rates of serious adverse effects including deaths were seen in 3 clinical trials in first-line CLL and relapsed indolent non-Hodgkin lymphoma. Most deaths related to infections such as Pneumocystis jirovecii pneumonia and cytomegalovirus infections and were seen in combination with chemo-immunotherapy. Other excess deaths related mainly to respiratory events. Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new respiratory symptoms promptly. Regular clinical and laboratory screening for CMV infection should be conducted.

**Diarrhea /colitis:**
Cases of severe drug-related colitis can occurred relatively late (months) after the start of therapy, sometimes with rapid aggravation, but resolved within a few weeks with dose interruption and additional symptomatic treatment.

**Pneumonitis:**
Cases of pneumonitis have been reported in clinical studies with Idelalisib. Patients presenting with serious lung events that do not respond to conventional antimicrobial therapy should be assessed.
for drug-induced pneumonitis. If pneumonitis is suspected, Idelalisib should be interrupted and the patient treated accordingly. Treatment must be discontinued for moderate or severe symptomatic pneumonitis.

**Hepatic impairment**

Closely monitor adverse reactions in patients with impaired hepatic function as exposure is expected to be increased, particularly in severe hepatic impairment. No patients with severe hepatic impairment were included in clinical studies of Idelalisib. Caution is recommended when administering Idelalisib in this population.

**Chronic hepatitis**

Idelalisib has not been studied in patients with chronic active hepatitis including viral hepatitis. Caution should be exercised when administering Idelalisib in patients with active hepatitis.

**Women of childbearing potential**

Women of childbearing potential must use highly effective contraception while taking Idelalisib and for 1 month after stopping treatment. Women using hormonal contraceptives should add a barrier method as a second form of contraception since it is currently unknown whether Idelalisib may reduce the effectiveness of hormonal contraceptives.

**Rituximab:**

Patients with high tumour burden or with a high number of circulating malignant cells are at risk of cytokine release syndrome. This may manifest as severe dyspnoea, bronchospasm and hypoxia in addition to fever, chills, rigors, urticaria and angio-oedema (usually presents after 1 - 2 hours of infusion). For patients who are at risk of tumour lysis syndrome, refer to the tumour lysis protocol. Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with rituximab. Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

10% of patients experience hypotension with the first dose of rituximab, therefore consideration should be given to withholding anti-hypertensive medications 12 hours prior to the Rituximab infusion.

**INTERACTIONS**

(Consult with pharmacist and Refer to the SmPC for further full details)

**Idelalisib:**

Idelalisib is metabolised primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117, which is not pharmacologically active. Idelalisib and GS-563117 are substrates of P-gp and BCRP.

**Effect of other medicinal products on Idelalisib pharmacokinetics**

**CYP3A inducers**

Co-administration of Idelalisib with moderate or strong CYP3A inducers e.g. Rifampicin, Phenytoin, St. John's Wort (*Hypericum perforatum*), or Carbamazepine should be avoided as this may result in decreased efficacy.
CYP3A/P-gp inhibitors
No initial dose adjustment of Idelalisib is considered necessary when administered with CYP3A/P-gp inhibitors, but an intensified monitoring of adverse reactions is recommended.

Further drug interactions available via:

http://www.medicines.org.uk/emc/medicine/29201
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

REFERENCES

1. NICETA 359. Idelalisib for treating chronic lymphocytic leukaemia. 28 October 2015
   https://www.nice.org.uk/guidance/TA359/chapter/2-The-technology
3. SmPC Idelalisib (Zydelig®) last updated 01/04/2016 via
   http://www.medicines.org.uk/emc/medicine
4. SmPC Rituximab (MabThera®) last updated 06-Jun-2014 via
   http://www.medicines.org.uk/emc/medicine/2570