R-IDELALISIB FOR CLL

Indications
This regime has been shown to be an effective treatment choice in relapsed CLL with significant comorbidities. It has an overall response rate of 81%, with at 24 weeks, 93% progression free survival with the median duration of PFS not reached.

NICE guidance for funding in CLL (TA359):

1) For relapsed CLL patients within 24 months of treatment
2) Untreated CLL with 17p deletion or P53 deletion

Previously, the Haematology MDT were recommending accessing the drug via a compassionate usage scheme. However, following a safety alert on March 2016, Gilead has advised not starting idelalisib as front line therapy for P53 mutant CLL. The compassionate usage was previously reached on idelalisib@idispharma.com

Drugs

1) **Idelalisib**: This is given at a dosage of 150mg PO twice daily, continuous until disease progression or unacceptable toxicity. It is available as 100mg or 150mg tablets which should be swallowed whole, either with or without food. The first dosage should be taken 30 minutes prior to starting rituximab.

2) **Rituximab**: This is administered as 375mg/m² for the first dose, fractionated over 2 days if the WBC>25 x 10⁹/L, with 500mg/m² (fractionated over 2 days if the WBC>25 x 10⁹/L), given 2 weekly for 4 doses (Weeks 2, 4, 6 & 8) then 4 weekly for 3 doses (Weeks 12, 16, and 20). A total of 8 doses are given. Please ensure Hepatitis B and C serology are checked prior to prescribing.

OPMAS Regimen
This regime is available on OPMAS and is called RIDLH. The blocks for prescribing are as follows

| Cycle 1: Week 0 | Block A: Idelalisib + Rituximab 375mg/m² split over 2 days |
| Cycle 2: Week 2 | Block B: Idelalisib + Ritux 500mg/m² in split dose Block C: Idelalisib + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 3: Week 4 | Block B: Idelalisib + Ritux 500mg/m² in split dose Block C: Idelalisib + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 4: Week 6 | Block B: Idelalisib + Ritux 500mg/m² in split dose Block C: Idelalisib + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 5: Week 8 | Block B: Idelalisib + Ritux 500mg/m² in split dose Block C: Idelalisib + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 6: Week 12 | Block D: Idelalisib (4/52) + Ritux 500mg/m² in split dose Block E: Idelalisib (4/52) + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 7: Week 16 | Block D: Idelalisib (4/52) + Ritux 500mg/m² in split dose Block E: Idelalisib (4/52) + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 8: Week 20 | Block D: Idelalisib (4/52) + Ritux 500mg/m² in split dose Block E: Idelalisib (4/52) + Ritux 500mg/m² in single dose if tolerated and WCC<25 |
| Cycle 9 and subsequent | Block F: Idelalisib (4/52) |
Supportive medications
1) Allopurinol – this ideally should be started 24 hours prior to chemotherapy if WBC>100 with consideration of IV fluid hydration day 1.
2) Dexamethasone, chlorphenamine and paracetamol should be given prior to rituximab to reduce the risk of reactions.
3) Loperamide should be given if mild diarrhoea develops.
4) Routine antiemetics are not required.
5) Cotrimoxazole 480mg bd for PJP prophylaxis should be given on Monday, Wednesday and Fridays for the duration of therapy and for 3 months post.

Monitoring blood tests
1) FBC, U&Es, LFTs, LDH and hepatitis serology and CMV PCR prior to commencement.
2) Check FBC, U&Es, LFTs & LDH every 2 weeks for the first 6 months of treatment. Consideration of weekly tests should be undertaken whilst the neutrophil count is <1.
3) Check CMV PCR 4 weekly. If this becomes positive, the idelalisib should be discontinued and valgancyclovir commenced. Alternative treatment for the patient’s CLL should be considered, taking into account the various risks and benefits.

Toxicities
1) Cytokine release syndrome: This usually occurs within the first 1-2 hours of the rituximab infusion and consists of fever, headaches, rigors, flushing, transient hypotension and rash.
2) Tumor lysis syndrome: Ensure appropriate pre-medication.
3) Infections: Especially pneumocystis and CMV reactivation.
4) Abnormal Liver function tests: If the ALT rises to x3–5ULN, monitor more regularly. Idelalisib should be discontinued if ALT>5ULN until it falls to <x3ULN. Then restart at 100mg bd, considering an increase back up to 150mg bd if LFTs remain stable. If the ALT rises again to >x5ULN, withhold idelalisib until <x3ULN and consider restarting at 100mg bd at the discretion of the consultant.
5) Diarrhoea: Idelalisib must be withheld in the event of Grade 3-4 diarrhoea. It may be restarted once the diarrhoea has resolved to < or = Grade 1 at 100mg bd. If the symptom does not re-occur then the dose may be incremented back to 150mg bd.
6) Pneumonitis: Idelalisib must be withheld in the event of suspected pneumonitis and the patient treated accordingly. Once the pneumonitis has resolved and re-treatment is considered appropriate, resume at 100mg bd.
7) Rash: Withhold Idelalisib in the event of a Grade 3 or 4 rash. Once the rash has resolved to < or = to Grade 1, restart the Idelalisib at 100mg bd. Consider re-escalation to 150mg bd if the rash does not recur.

Interactions
Avoid co-administration with CYP3A inducers (e.g. rifampicin, phenytoin, St John’s Wort, carbamazepine) as this may result in reduced plasma concentrations of idelalisib.

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and so the concomitant usage of idelalisib with drugs metabolised by CYP3A4 may lead to increased serum concentrations of the other product. Further details are provided in the SPC but avoid the concomitant usage of alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, quetiapine, lovastatin, simvastatin, midazolam.

References
Idelalisib SPC – accessed July 26th 2015
Furman, R et. al., NEJM 2014; 370:997-1007
Author: Rebecca Frewin. Updated by Sue Watts & Maria Camarero
V3.2 Approved at chemo subgroup June 2016
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