Venetoclax and Azacitidine

Indication

Interim COVID-19 indication:

Newly diagnosed acute myeloid leukaemia, as an alternative to standard induction chemotherapy with DA chemotherapy.

The patient should have one of the following 3 types of AML and fulfil the criteria outlined:

- The patient does not have core binding factor AML [i.e. t(8;21) or inv(16)] and is aged > 60 years and is deemed fit for intensive chemotherapy
- The patient has mutated NPM1 or IDH1/2 AML and is either aged >50 years and deemed fit for intensive chemotherapy or has significant comorbidity (but is still deemed fit for intensive chemotherapy)
- The patient has the NPM1mutFLT3 ITDneg genotype AML of any age.

(Recommendations for the management of patients with AML during the COVID19 outbreak)

ICD-10 codes

Codes with a prefix C92

Regimen details

Cycle 1:

Day	Drug	Dose	Route
1-5 (Monday-Friday) and 8-9 (Monday and Tuesday)	Azacitidine	75mg/m^2	SC
1	Venetoclax	100mg OD	PO
2	Venetoclax	200mg OD	PO
3	Venetoclax	300mg OD	PO
4 – 28	Venetoclax	100mg OD*	PO

*Dose reduction due to recommendation to start posaconazole on day 4 – see below.

Hospitalisation is recommended for the first 5 days, during dose titration of venetoclax and for 24 hours after dose titration.

Cycle 2 onwards

Day	Drug	Dose	Route
1-5 (Monday-Friday) and 8-9 (Monday and Tuesday)	Azacitidine	75mg/m2	SC
1-28	Venetoclax	100mg OD*	PO

*If patient does not require posaconazole (e.g. in remission after the first two cycles and is not neutropenic; or cannot tolerate), the venetoclax dose should be increased to 400mg once daily, starting 2 to 3 days after stopping the posaconazole.

NOTE: 7-day washout needed for any strong CYP3A4 inhibitors prior to starting venetoclax.

Cycle frequency

28 days

Number of cycles

Patient may proceed to allograft as soon as in remission and a donor is available (following a minimum of two cycles).
When used as a bridging therapy, continue until transplantation, or disease progression or unacceptable toxicity.

Administration

Azacitidine is administered by SC injection over 1 minute. Before administration the contents of the syringe must be re-suspended by inverting the syringe 2-3 times and vigorously rolling the syringe between the palms for 30 seconds. A uniform cloudy suspension should be achieved. The needle should not be purged prior to injection in order to reduce the incidence of local injection site reactions. Azacitidine should be injected subcutaneously using a 25-gauge needle into the upper arm, thigh or abdomen. Sites of injection should be rotated. New injections should be given at least 2.5cm from the previous site and never into areas where the site is tender, bruised, red or hardened. It is recommended that the injected region is gently massaged after the injection has been delivered. Doses greater than 4mL (i.e. >100mg) should be divided and injected into two separate sites. The drug should be administered over approximately one minute and then the injection site covered with sterile gauze.

Azacitidine has a very short expiry: up to 8 hours if stored between 2-8°C immediately after reconstitution. If stored at room temperature, it only has 45 minutes expiry. If refrigerated, allow up to 30 minutes prior to administration to reach room temperature. The shelf life of azacitidine can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. When azacitidine is reconstituted using refrigerated water for injections, the chemical and physical in-use stability of the reconstituted medicinal product is 22 hours if stored between 2°C to 8°C.

Venetoclax is available as 10mg, 50mg and 100mg tablets. The tablets should be swallowed whole with water at approximately the same time each day. It is preferable that the dose is taken in the morning to allow for laboratory monitoring. Tablets should be taken with a meal, ideally breakfast.

Grapefruit products, Seville oranges and starfruit should be avoided during treatment with venetoclax.

If a patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

If a patient vomits following a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time on the following day.

Some patients especially those at greater risk of TLS, may require hospitalisation for more intensive prophylaxis and monitoring.

Pre-medication

Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should drink at least 1.5 to 2.0 L of water daily starting 2 days before the first dose and throughout the dose-titration phase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and may be continued through the titration phase.

Emetogenicity

This regimen has high emetic potential on days of azacitidine. Low emetic potential with venetoclax alone.

Additional supportive medication

8mg PO ondansetron (or equivalent) is recommended 30 minutes prior to each dose of azacitidine.
Aciclovir 400mg PO BD days 4-28
Posaconazole tablets 300mg PO BD on day 4, then 300mg OD from days 5-28
Anti-hyperuricaemic agents – see below. Allopurinol should be started at least 3 days before starting venetoclax.
Loperamide if required.
Hydrocortisone cream 1%, for topical application to azacitidine injection site if there is inflammation, rash or pruritis.

Extravasation

N/A

Investigations – baseline

Investigation	Validity period
FBC*	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
U+Es (including creatinine)	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
Urate	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
LFTs	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
Serum Bicarbonate	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
LDH	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
Calcium	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
Magnesium	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.
Phosphate	Within 4 hours of dose and 6-8 hour post dose for first 5 days and then as clinically indicated.

* If WBC ≥ 25 x 10^9/L, treat with hydroxycarbamide to achieve a WBC of < 25 x 10^9/L.

Any electrolyte abnormalities should be corrected prior to commencing treatment.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly or as clinically indicated
U+Es (including creatinine)	Monthly or as clinically indicated
Urate	Monthly or as clinically indicated
LFTs	Monthly or as clinically indicated
Serum Bicarbonate	Monthly or as clinically indicated
Calcium	Monthly or as clinically indicated
Magnesium	Monthly or as clinically indicated
Phosphate	Monthly or as clinically indicated

Standard limits for go ahead at the start of a cycle.

Treatment shouldn't be interrupted for haematological toxicity during a cycle.
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	> 75 x 10^9/L
CrCl	> 80 mL/min
Potassium	Within normal limits
Calcium	Within normal limits
Phosphate	Within normal limits
Bilirubin	See below
AST/ALT	See below

Dose modifications

Any venetoclax dose reductions should be as follows:

Dose at interruption	Dose to restart
400mg	300mg
300mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	10mg

Once a dose has been reduced it should be continued for 1 week before increasing.

- **Haematological toxicity**

Venetoclax should not be interrupted for haematological toxicity prior to documentation of marrow response on Cycle 1 day 21 – 28:

- If blast clearance confirmed and the patient has Grade 4 neutropenia (neutrophils < 0.5 x 10^9/L) G-CSF may be commenced until neutrophil recovery.
- Commence next cycle when neutrophil count > 1.0 x 10^9/L and platelet count > 75 x 10^9/L.
- If counts have not recovered above these levels by day 42, consider bone marrow aspirate.
- Once in complete remission, if Grade 4 neutropenia (neutrophils < 0.5 x 10^9/L) or thrombocytopenia (platelets < 25 x 10^9/L) develops, cease venetoclax and commence G-CSF until resolution of grade 4 neutropenia.
- If grade 4 toxicity persists beyond day 42 of the previous cycle, the duration of venetoclax may be reduced to 14 - 21 days.
- If prolonged treatment-related Grade 4 neutropenia or thrombocytopenia occurs in subsequent cycles, azacitidine treatment may also be reduced to < 7 days.

In patients who have not yet been confirmed to be in CR, the length of treatment cycles should not be altered. Patients who do not achieve CR after cycle 2 should be discussed at MDT.

- **Renal impairment**

Renal function should be evaluated prior to commencing treatment.

Patients with CrCl <80 mL/min are at increased risk of TLS and may require more intensive prophylaxis and monitoring to reduce the risk of TLS during the initiation and titration phase.

CrCl ≥30 mL/min- No venetoclax dose modification required.

CrCl <30 mL/min or dialysis- No information for venetoclax available. Administer only if the benefit outweighs the risk. Patients should be monitored closely for signs of toxicity.

Azacitidine may be administered in renal impairment without initial dose adjustment. As azacitidine and its metabolites are excreted via the kidneys close monitoring is required. If serum bicarbonate levels < 20mmol/L (without explanation) reduce subsequent cycle doses to 50%. If serum creatinine or blood urea nitrogen ≥ 2 x ULN (without explanation) reduce subsequent cycle doses to 50%.

- **Hepatic impairment**

No dose adjustment required for venetoclax in mild or moderate hepatic impairment.

Severe hepatic impairment- No information available. It is not recommended to administer venetoclax to patients with severe hepatic impairment.

No formal studies have been carried out in patients with hepatic impairment. Patients with severe hepatic impairment should be closely monitored for adverse events. No starting dose modification is required. Doses should be adjusted according to haematological values. Azacitidine is contraindicated in patients with malignant hepatic tumours.

- **Other toxicities**

In patients with Grade 3 - 4 abnormal ALT, AST and/or bilirubin, venetoclax and any potentially hepatotoxic drugs (including azole antifungals) should be withheld until these have resolved to ≤ Grade 2. Then venetoclax (and the azole antifungal if applicable) should be restarted at the original dose.

- Venetoclax should not be interrupted for any other non-haematological toxicity for patients who are not in CR.
- In patients in CR and with Grade 3 or 4 non-haematological toxicity thought to be related to venetoclax, then venetoclax should be withheld until the toxicity has resolved to ≤ Grade 2, and then restarted at the original dose.

Tumour Lysis Syndrome (TLS):

Changes in electrolytes consistent with TLS (hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalcaemia) can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase. Prompt management is required.

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors is contraindicated as this may increase venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities.

Biochemistry results:

If any of the following occur withhold venetoclax until resolved:
Potassium > 0.5mmol/L increase from prior value or >ULN
Urate > 476 umol/l (8.0mg/dL)
Corrected Calcium <1.75 mmol/L
Phosphate > 1.615 mmol/l
Creatinine >25% increase from baseline

Risk Assessment for TLS:
There is a potential risk for TLS in patients with AML, especially in those with elevated leukocyte count, circulating blasts, elevated pre-treatment LDH levels, renal dysfunction, and dehydration.

Blood chemistry (creatinine, uric acid, potassium, phosphate, magnesium and calcium) should be carried out for all patients prior to starting treatment and pre-existing abnormalities should be corrected.

Prevention of TLS:
Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment and patients should be adequately hydrated (see above).

Treatment of TLS:
The following changes on biochemistry require action and indicate TLS:

Potassium > 0.5mmol/L increase from prior value or >ULN
Urate > 476 umol/l (8.0mg/dL)
Corrected Calcium <1.75 mmol/L
Phosphate > 0.16 mmol/l rise from baseline or >ULN
Creatinine >25% increase from baseline (even if in normal range)

- If one electrolyte abnormality with stable creatinine repeat TLS bloods within 1-2 hours. If resolves no need for further bloods or additional management
- If two or more electrolyte abnormalities or rise in creatinine initiate TLS treatment and withhold venetoclax.
- If TLS resolved within 24-48 hours of last dose continue with same dose on resolution.
- If takes more than 48 hours continue with reduced dose on resolution. Discuss with consultant. If rapid dose escalation required due to progressive disease consider admission for IV hydration.

Other toxicities:
Azacitidine should be used with caution in patients with cardiac and pulmonary disease.

For any other grade 3-4 toxicity:
- Withhold treatment.
- Once resolved to grade 1 or baseline resume with same dose.
- If recurs once resolved continue with dose reduction.

Adverse effects

Myelosuppression
Hepatic failure
Renal failure
Interstitial lung disease
Haemorrhage
Tumour lysis syndrome
Diarrhoea, constipation
Nausea and vomiting
Upper respiratory tract infection
Fatigue
Electrolyte abnormalities
Hypotension and bronchospasm (infusion related and usually transient)
Cardiac disorders
Angioedema
Pruritus, rash
Headache

Significant drug interactions

Note this list is not exhaustive. Always refer to the product SPC and consult with a pharmacist.

Venetoclax:

Strong CYP3A inhibitors: (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) Concomitant use is contraindicated during initiation and the dose-titration phase. If the patient requires use of these medications after titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Patients must not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Moderate CYP3A inhibitors and P-gp and BCRP inhibitors:
Avoid concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) and P-gp and BCRP inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor or P-gp inhibitor must be used, reduce the initiation and titration doses of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

CYP3A inducers:
Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

Bile acid sequestrants:
Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the summary of product characteristics for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

Warfain:
If concomitant use is necessary the INR should be closely monitored.

Substrates of P-gp, BCRP, and OATP1B1:
Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g. digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

Additional comments

References

- Summary of Product Characteristics Venetoclax (AbbVie) accessed 21 May 2020 via www.medicines.org.uk
- Summary of Product Characteristics Azacitidine (Celgene) accessed 21 May 2020 via www.medicines.org.uk
- DiNardo, C et al; Venetoclax combined with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid. Leukemia. Blood 2019; 133 (1): 7 – 17
- Recommendations for the management of patients with AML during the COVID19 outbreak: a statement from the NCRI AML Working Party. Version 3.4 dated 05.05.2020.

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