Azacitidine for MDS, CMML and AML

Indication: First line treatment for patients who are not eligible for haematopoietic stem cell transplantation with:

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia (CMML) with 10 to 29 % marrow blasts without myeloproliferative disorder
- Acute myeloid leukaemia (AML) with 20 to 30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification

Regimen details:

Azacitidine	75 mg /m^2	SC	Days 1 to 7
OR			Days 1 to 5 and 8 & 9 (5 + 2 regimen)

The 5 + 2 regimen is an unlicensed dose schedule.

Administration: Subcutaneous
If the volume is greater than 4 ml then the dose is administered over 2 sites.

Premedication: Not applicable

Frequency: Every 28 days

Treatment should be for a minimum of six cycles and continued until progression

Extravasation: Not applicable

Anti-emetics: Moderately emetogenic.

Supportive medication: Allopurinol 300 mg po od (dose adjust if renal impairment)
Movicol sachets prn for constipation
Hydrocortisone cream 1% for topical application to the injection site, if there is inflammation, rash, pruritis following the injections.
Consider PPI / H2 antagonist as per local practice.
Antifungal prophylaxis is not routinely required; however patients with baseline cytopenia or persistent neutropenia should receive antifungal prophylaxis until haematological improvement.

Regular investigations: Prior to commencing therapy:

FBC	U&E, bicarbonate, Uric acid	
LFT	LDH	
Ferritin, B12 and serum folate.	Thyroid function	
Coagulation screen	Group and Save	
HBsAg, HCV IgG, HIV 1 and 2 IgG	CXR	ECG

Urine dipstick for glucose and urine analysis if serum creatinine >177μmol/L
Bone marrow aspirate, trephine and cytogenetics as base line
Peripheral blood CD34 count (4.5ml EDTA to Stem cell lab)
During nadir: FBC weekly

Prior to each cycle (≤ 2 days): FBC LFT U&E, bicarbonate

Toxicities: Gout
Local injection site reactions are very common and usually get better with subsequent courses. Sometimes they appear as nodular lesions. 1% Hydrocortisone cream may be helpful.
Constipation/diarrhoea

Dose Modifications

Haematological Toxicity
Commence azacitidine at 100% dose in the first cycle regardless of baseline haematology values. Platelet transfusions may be needed.
Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets < 50 $x10^9$/L and / or neutrophils < 1.0 $x10^9$/L

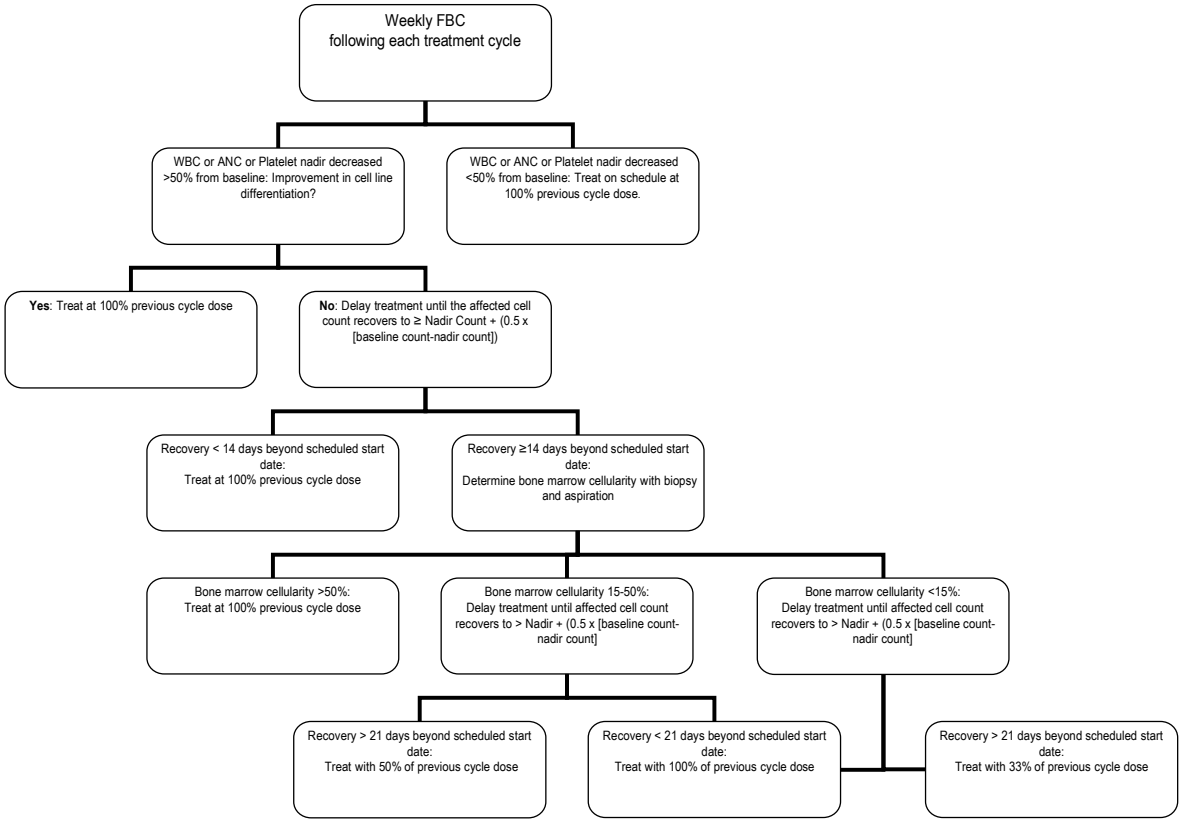
Recovery is defined as:
Blood count at recovery ≥ nadir count + (0.5 [baseline count – nadir count])

For patients without reduced baseline counts (i.e. WBC ≥ 3.0 $x10^9$/L, neutrophils ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L) prior to first treatment:

- Azacitidine therapy should be delayed until the platelet count and the neutrophil count have recovered (see recovery definition above).
- If recovery is achieved within 14 days (i.e. maximum of 6 weeks between cycles) no dose adjustment is necessary.
- If recovery is not achieved within 14 days (i.e. > 6 weeks between cycles), the dose should be reduced according to the following table:

Nadir Neutrophils (x 10^9/L)		**Nadir Platelets** (x 10^9/L)	**Azacitidine dose**
> 1.0 x 10^9/L	&	> 50 x 10^9/L	100% dose
≤ 1.0 x 10^9/L	or	≤ 50x 10^9/L	Delay treatment until cell counts recover. If recovery < 14 days beyond scheduled start date (i.e. < 6 weeks from previous course) treat with 100% dose
≤ 1.0 x 10^9/L	or	≤ 50x 10^9/L	If recovery > 14 days beyond scheduled start date (i.e. >6 weeks from previous course) treat with 50% of previous cycle dose

For patients with reduced baseline counts (i.e. WBC < 3.0 x10^9/L, neutrophils < 1.5 x10^9/L and platelets < 75 x10^9/L) prior to first treatment:



(Diagram modified from the Vidaza Dosing Guide , SPC 2008)

Renal Impairment — If the serum creatinine increases by 2-fold or more from baseline and exceeds normal values, exclude other causes.
If attributed to azacitidine, delay the next cycle until the results are in the normal range and reduce the dose by 50% in the next cycle.
Severe renal tubular dysfunction manifesting as hypophosphatemia, hypokalemia or hyponatremia with or without increases in serum creatinine occurs infrequently. Monitor serum bicarbonate, BUN and creatinine. If serum bicarbonate is less than 19mmol/L due to azacitidine then replace with oral sodium bicarbonate. Reduce the dose of azacitidine by 50% at the next cycle

Hepatic Impairment — Azacitidine should be avoided if the AST/ALT or bilirubin is > 2 x ULN unless this is due to haemolysis

Drug interactions: None known.

References: Silverman, L.R., et al., Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol, 2002. **20**(10): p. 2429-40.

Silverman, L.R., et al., Further Analysis of Trials With Azacitidine in Patients With Myelodysplastic Syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B J Clin Oncol, 2006. **24**(24): p. 3895-3903.
Kaminskas, E., et al., FDA Drug Approval Summary: Azacitidine (5-azacytidine, VidazaTM) for Injectable Suspension. Oncologist, 2005. **10**(3): p. 176-182.