Azacitidine 100mg/m^2 5-day Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Intermediate-1 and low risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS)[ii]	D46	00288a	**Hospital**
Treatment of adult 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)	D46	00288b	**Hospital**
Chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder	C93	00288c	**Hospital**
Acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to WHO classification	C92	00288d	**Hospital**

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Azacitidine is administered daily for 5 days, followed by a rest period of 23 days (28-day treatment cycle) for a **minimum** of 6 cycles or until unacceptable toxicity or disease progression occurs.

Day	Drug	Dose	Route and Method of Administration
1-5	Azacitidine	100mg/m^2	*SC using a 25-gauge needle into upper arm, thigh or abdomen
*Doses > 4ml should be equally divided into 2 syringes and injected into two separate sites.			
Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.			
Note: In individual cases where approved by Consultant azacitidine may be administered as IV Infusion over 30 minutes. Note that this is an unlicensed method of administration.			

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to azacitidine, or to any of the excipients.
- Advanced malignant hepatic tumours.
- Breastfeeding.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Coagulation screen
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV.

*Hepatitis B reactivation: See Adverse effects/Regimen specific complications

Regular tests:

- FBC at a minimum prior to each treatment cycle or more frequently as clinically indicated depending on level of cytopenia or haematological toxicity experienced.
- Renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Haematological:

- No dose modification with first cycle. 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 x 10^9/L and/or absolute neutrophil count (ANC) ≤ 1 x 10^9/L.

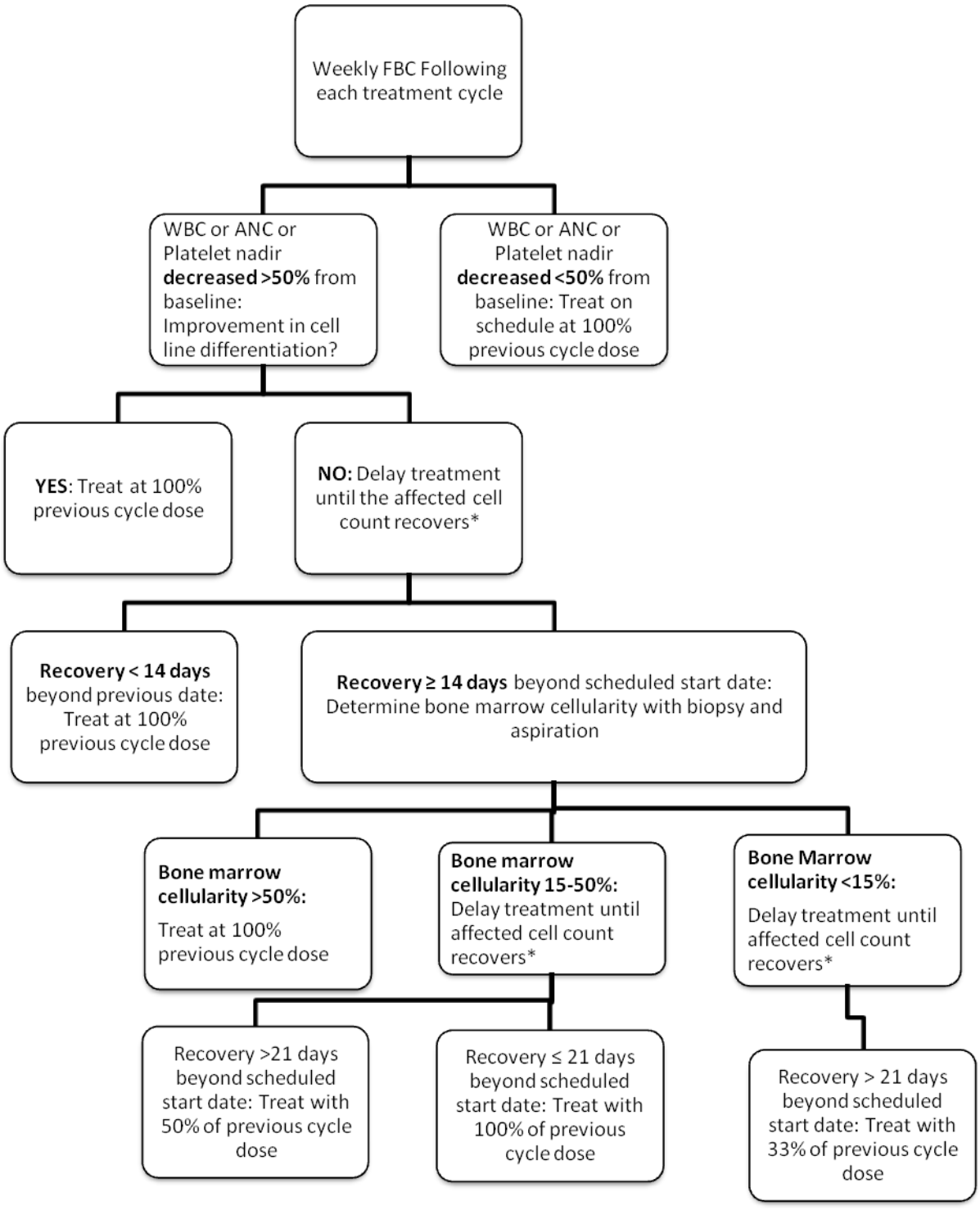
- Recovery is defined as
  blood count at recovery ≥ nadir count + (0.5 x [baseline count – nadir count]).

For patients without reduced baseline counts (i.e WBC ≥ 3 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75 x 10^9/L prior to Cycle 1 see table 1 for dose modifications

Table 1: Dose modification of azacitidine based on nadir neutrophil and platelet count in patients without reduced baseline counts

Nadir Neutrophils (x 10^9/L)		Nadir Platelets (x 10^9/L)	Azacitidine dose
>1	and	>50	100% dose
≤ 1	or	≤50	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	or	≤50	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 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75 x 10^9/L) prior Cycle 1) dose modification are outlined in Figure 1 below



* blood count at recovery ≥ nadir count + (0.5 x [baseline count – nadir count])

Figure 1: Dose modification of azacitidine based on nadir neutrophil and platelet count in patients with reduced baseline counts

Renal and Hepatic Impairment:

Table 2: Dose modification of azactidine in renal and hepatic impairment

Renal Impairment		Hepatic Impairment
No initial dose adjustment required in patients with renal impairment		No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment Subsequent dose modifications should be based on haematology laboratory values. Patients with severe hepatic organ impairment should be carefully monitored for adverse events. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours
Dose adjustment recommended for serum bicarbonate, creatinine and BUN		
Unexplained reductions in serum bicarbonate level to < 20mmol/L	Reduce dose by 50%	
Unexplained elevation in serum creatinine or BUN to ≥ 2 above baseline and ULN	Delay next cycle until values return to normal or baseline and reduce the dose by 50% on next treatment cycle	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Tumour Lysis Syndrome prophylaxis. **(Refer to local policy).**
- Antifungal prophylaxis (if tolerated), for patients with baseline cytopenia or persistent neutropenia, continued until haematological improvement **(Refer to local policy).**
- Both diarrhoea and constipation are common side effects associated with azacitidine treatment. Patients may require either laxatives or anti-diarrhoeals.
- Women of childbearing potential and men must use effective contraception during and up to 3 months after treatment.
- Consider topical hydrocortisone 1% for treatment of local allergic skin reactions.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haematological toxicity:** Fever or other evidence of infection must be assessed promptly and treated appropriately. Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Patients and physicians are also advised to be observant for signs and symptoms of bleeding.
- **Hepatic impairment:** Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine

treatment, especially in such patients with baseline serum albumin< 30 g/l. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

- **Renal impairment:** Patients should be advised to report any oliguria and anuria to the health care provider immediately. Patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.
- **Cardiac and pulmonary disease:** Recent data from a clinical trial in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine It is therefore advised to exercise caution when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered.
- **Necrotising fasciitis:** Necrotising fasciitis, including fatal cases, have been reported in patients treated with azacitidine. Therapy with azacitidine should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely.
- No formal clinical drug interaction studies with azacitidine have been conducted.

REFERENCES:

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3. Fenaux P et al. Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia. J Clin Onc 2010;28(4):562-569
4. Pierdomenico F, Esteves S et al. Efficacy and Tolerability of 5-day azacytidine dose-intensified regimen in higher-risk MDS. Ann Hematol 2013;92:1201-1206
5. Azacitidine (VIDAZA®) Summary of Product Characteristics Accessed Feb 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/vidaza-epar-product-information_en.pdf
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	17/10/2018		Dr Kamal Fadalla
2	01/03/2021	Updated adverse effects (Hepatitis B reactivation)	Dr Kamal Fadalla

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This dosing regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this regimen and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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