AZACITIDINE

An option for patients who are not eligible for haematopoietic stem cell transplantation, with the following conditions:
1. Intermediate-2 or high risk myelodysplastic syndrome
2. Chronic myelomonocytic leukaemia with 10-29% marrow blasts without myeloproliferative disorder
3. AML with 20-30% blasts and multilineage dysplasia
NICE approved March 2011

Drugs/Dosage: The licensed azacitidine scheduling of daily administration for 7 consecutive days cannot be followed locally due to the logistical issues of preparing and administering the weekend doses. In the absence of any proven superior alternative dosing or scheduling, the 2 unlicensed options given below allow for clinician preference across the region:

Schedule 1:	**Azacitidine** (25mg/ml)	100mg/m^2	s/c bolus	once daily on Days 1 to 5 (5 doses in total)
or				
Schedule 2:	**Azacitidine** (25mg/ml)	75mg/m^2	s/c bolus	once daily on Days 1 to 5, and Day 8 and Day 9 (i.e. 2 day break over weekend, with 7 doses in total – sometimes referred to as 5+2 schedule)

Administration: The azacitidine suspension should be prepared immediately before use and administered within 45 minutes. Alternatively, if it is reconstituted in advance of administration, it should be stored in a refrigerator for a maximum of 8 hours. The syringe(s) filled with reconstituted suspension should then be allowed up to a maximum of 30 minutes prior to administration to reach a temperature of approximately 20°C – 25°C.

The contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. **The product should be discarded if it contains large particles or agglomerates.**

Inject subcutaneously using a 25 gauge needle into the upper arm, thigh or abdomen. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.

Doses greater than 4 ml (100mg) should be divided equally between 2 separate 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.

Other Drugs: Allopurinol 300mg po od (review after 4 weeks)

Itraconazole liquid 200mg bd as antifungal prophylaxis (if tolerated), for patients with baseline cytopenia or persistent neutropenia, continued until haematological improvement

Hydrocortisone cream 1%, for topical application to injection site if there is inflammation, rash or pruritis following the injections

Reason for Update: antiemetics updated ; general review	Approved by Chair of Network TSSG: Dr A Laurie
Version: 2	Date: 28.4.14
Supersedes: Version 1	Review date: May 2016
Prepared by: S Taylor	Checked by: C Tucker

Frequency:	Every 28 days treat for a minimum of 6 cycles; continue as long as there is patient benefit, or until disease progression	
Main Toxicities:	myelosuppression; injection site reactions; ovarian failure; infertility	
Anti- emetics:	highly emetic: ondansetron 8mg po to be taken 1 – 2 hours before each azacitidine injection, plus oral domperidone or metoclopramide as required	
Regular Investigations:	FBC	Day 1, weekly during nadir, and as indicated
	U&Es	Day 1
	LFTs	Day 1
	Serum bicarbonate	Day 1

Dose Modifications

Haematological Toxicity:

Cycle 1: There are no dose modifications for myelosuppression

Cycle 2 onwards:

Patients without reduced baseline blood counts (i.e. WBC > 3.0 x 10^9/l, neutrophils > 1.5 x 10^9/l, and platelets > 75 x 10^9/l prior to the first treatment)

If haematological toxicity – neutrophils < 1.0 x 10^9/L or platelets < 50 x 10^9/L at any time - is observed following azacitidine, the next cycle should be delayed until the platelet and neutrophil counts have recovered*. If recovery* is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, give 50% azacitidine dose once recovery has occurred. Following dose modification, the cycle duration should return to 28 days.

*Recovery = current counts $\geq$ nadir count + (0.5 x [Baseline count – Nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/l, neutrophils < 1.5 x 10^9/l or platelets < 75 x 10^9/l prior to the first treatment)

Following azacitidine treatment, if the decrease in WBC, neutrophils or platelets from that prior to treatment is < 50 %, or > 50 % but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC, neutrophils or platelets is > 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle should be delayed until the platelet and neutrophil counts have recovered. If recovery* is achieved within 14 days, no dose adjustment is necessary.

However, if recovery* has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50 %, no dose adjustments should be made.

If bone marrow cellularity is ≤ 50 %, treatment should be delayed and the dose reduced according to the following table:

Bone marrow cellularity	% dose in next cycle if recovery is not achieved within 14 days	
	Recovery* ≤ 21 days	Recovery* > 21 days
15 – 50 %	100 %	50 %
< 15 %	100 %	33 %

*Recovery = counts ≥ nadir count + (0.5 x [Baseline count – Nadir count])

Following dose modification, the cycle duration should return to 28 days.

Renal Impairment: Patients with renal impairment should be closely monitored for toxicity as azacitidine and its metabolites are primarily renally excreted. However, no formal studies have been carried out in patients with impaired renal function, and no specific starting dose modifications are recommended.
If unexplained fall in serum bicarbonate to < 20mmol/l, give 50% azacitidine dose on next cycle.
If serum creatinine becomes elevated to ≥ 2 times baseline value, the next cycles should be delayed until serum creatinine returns to normal, then give 50% azacitidine dose on the next cycle.

Hepatic Impairment: No formal studies have been carried out in patients with hepatic impairment. Monitor carefully if azacitidine is used in patients with severe liver impairment, and adjust doses according to haematological values.

Patient Information: Macmillan leaflet for Azacitidine

References:
Silverman, LR et al; JCO 2002; 20 (10): 2429 -2440
Silverman, LR et al; JCO 2006; 24 (24): 3895-3903
Garcia, R et al; Spanish Azacitidine Compassionate Use Registry; Proceedings from ASH 2009; Abstract 2773 and poster
Haq, B; JCO; ASCO Proceedings 2006; 24 (18S): Abstract #16532 (5 day schedule)
Pierdomenico, F; Proceedings of the 15th Congress of the European Hematology Association 2010; Abstract #1402 (5 day schedule)