AZACITIDINE (Vidaza)

For treatment MDS (IPSS int-2 and high risk) and AML

See Practical use of azacitidine in higher risk myelodysplastic syndromes: An expert Panel opinion - PierreFenaux, David Bowen et al – *Leukemia Research 34 (2010) 1410–1416*

Prior to a course of treatment

- Check FBC, U&Es, creat, LFTs
- Perform FBC weekly in the first 3 cycles or more frequently if clinically indicated –subsequent cycles check FBC every 2 weeks
- Written consent for course

Prior to each prescription

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC, electrolytes and LFTs

AZACITIDINE *	**75 mg/m2 daily s.c for 7 days** (If day case or OP therapy then give daily injection Mon- Friday then 2 day break for weekend followed by final two injections on the Mon and Tuesday	**Number of cycles** Patients should receive at least 6 cycles of azacitidine before any treatment decisions are made as to continuing therapy unless frank progression is observed before completion of those six cycles Treatment should be maintained until disease progression occurs

- Dose reductions are not recommended for the first three treatment cycles irrespective of the presence of severe cytopenias at baseline
- * available as 100 mg single vials each re-constituted with 4 ml of water for injection
- * Volume per injection site should not exceed 4 ml and injection sites should be at least 2 cm apart. Do not purge air from the syringe prior to injection and do not administer to sites of any previous reactions. Gently massage the injected region after the injection has been delivered. If local reactions persist then a local non-steroidal cream or lotion can be applied.
- Consider quinolones and anti-fungal as secondary prophylaxis following an infectious episode
- Consider use of GCSF for patients developing febrile neutropenia or as secondary prophylaxis after a severe infectious episode

Prophylaxis for acute & delayed emesis	Give ondansetron or similar before each injection Laxatives may be required with regular use of 5HT3 anti-emetics

DOSE MODIFICATIONS FOR HAEMATOLOGICAL TOXICITY

- **Treatment delays and dose reductions should be avoided as much as possible in the first three cycles**

Dose adjustment due to haematological toxicity

Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets fall below 50.0 x 10^9/l and/or absolute neutrophil count (ANC) below 1 x 10^9/l.
Recovery is defined as an increase of cell line(s) where haematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e. blood count at recovery ≥ Nadir Count + (0.5 x [Baseline count – Nadir count]).

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) > 3.0 x 10^9/l and ANC >1.5 x 10^9/l, and platelets > 75.0 x 10^9/l) prior to the first treatment
If haematological toxicity is observed following Azacitidine treatment, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Nadir counts		% Dose in the next cycle, if recovery* is not achieved within 14 days
ANC (x 1 0^9/l)	Platelets (x 1 09/l)	
≤ 1.0	≤ 50.0	50 %
> 1.0	> 50.0	100 %

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

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/l or ANC < 1.5 x 10^9/l or platelets < 75.0 x 10^9/l) prior to the first treatment
Following Azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is less than 50 %, or greater than 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 or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Azacitidine therapy should be delayed until the platelet count and the ANC 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 the 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 modifications, the cycle duration should return to 28 days.

DOSE MODIFICATIONS FOR RENAL FAILURE

- Limited information to make specific recommendations – several dialyzed patients have been successfully treated with no major cytopenias by reducing the dose of azacitidine by about one third

Dose modification for liver dysfunction

- Limited information – clinical decision. Liver function abnormalities occurred in 16% of patients with intercurrent hepatobiliary disorders and in two patients with previously diagnosed liver cirrhosis.

AZACITIDINE TOXICITIES

Common adverse events associated with azacitidine treatment were **gastrointestinal** (nausea, vomiting, diarrhea, constipation, and anorexia**), hematologic** (neutropenia, thrombocytopenia), fevers, rigors, ecchymoses, petechiae**, injection site events**, arthralgia, headache, and dizziness. Renal failure occurred in patients during sepsis and hypotension. **Contra-indicated in mannitol hypersensitivity**

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