DESCRIPTIVE ANALYSIS OF AZACITIDINE USE IN FOUR ADULT UNIVERSITY TEACHING HOSPITALS IN QUEBEC, CANADA

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BACKGROUND

Azacitidine (5-AZA; Vidaza®), a pyrimidine nucleoside analog, is used in the treatment of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and other hematological malignancies.

In November 2010, the *Institut national d'excellence en santé et service sociaux (INESSS)* recommended the use of 5-AZA for the treatment of patients with MDS who had intermediate-2 or high-risk score on the International Prognostic Scoring System (IPSS) or AML with a 20 to 30% blast count, multiple cell line dysplasia, performance status according to Eastern Cooperative Oncology Group (ECOG) equal or lower to 2 and who were not short term candidates to stem cell transplant.

Pharmacy directors gave the Therapeutic Drug Management Program (TDMP / *Programme de Gestion Thérapeutique des Médicaments (PGTM) – www.pgtm.qc.ca)* the mandate to review and evaluate 5-AZA use in our hospitals.

OBJECTIVES

Primary objectives

- Describe and review the use of 5-AZA in our hospitals
- Assess conformity rate for 5-AZA prescription based on optimal use criteria established by *INESSS*, prior TDMP publication and a review of medical literature

Secondary objectives

- Assess "real-life" use of 5-AZA compared to clinical studies:
  - Number of cycles received by patients
  - Response rate, disease-free survival and overall survival
  - Number of patients who received stem cell transplantation
  - Rate and delay of MDS transformation to AML
  - Drug safety

DESIGN

A review of pharmacy databases was performed to identify patients who received 5-AZA between January 1st 2010 and May 31st 2013. Pharmacy and medical records, laboratory results and blood bank database of every patient who received 5-AZA during the study period were reviewed retrospectively to assess diagnostic (including IPSS scores), treatment, response and non-hematological adverse events.

RESULTS

A total of 77 patients received 5-AZA during the study period

Figure 1: Indications for 5-AZA use

Table 1: Status of patients at the end of data collection (May 31st 2013)

	N = 77	%
Alive	**31**	**40.3**
- Still on active treatment	14	18.2
- Completed treatment*	3	3.9
- Treatment interrupted	14	18.2
Deceased	**35**	**45.5**
- Progressive disease	10	13
- Infection	11	14.3
- Graft versus host disease (GVHD)	1	1.3
- Other cause of death	2	2.6
- Unknown cause of death	11	14.3
Lost to follow-up / Unknown	**11**	**14.3**

**All patients who completed treatment stopped after autologous stem cell transplantation (ASCT), no patient stopped after a complete response to treatment (3 of 6 patients who received ASCT died during the study period: 1 from GVHD, 1 from post-transplantation lymphoma and 1 from pneumonia)*

MDS POPULATION

- 56 patients (33 men / 23 women)
- Mean age = 65.8 years (Interquartile range = 60-74)
- Conformity rate = 76.8 % (43 out of 56 patients) with IPSS intermediate-2 or high-risk MDS

Table 2: 5-AZA status at end of study period

	MDS		AML	
	n = 56	%	n = 15	%
Patient still on active treatment	11	19.6	2	13.3
5-AZA discontinued	43*	76.8	13**	86.7
- Autologous stem cell transplantation (ASCT)	6	10.7	0	0
- Disease progression / ineffective treatment***	27	48.2	10	66.7
- Patient withdrawal	2	3.6	1	6.7
- Adverse events	3	5.4	1	6.7
- Patient deceased during treatment	5	8.9	0	0
- Cause of discontinuation unknown / not available	0	0	1	6.7
Status unknown / Not available	2	3.6	0	0

**Twenty-five MDS patients (25) (3 ASCT patients and 22 other patients who discontinued treatment) (44.6% of total MDS population) received less than 6 cycles. **Eight AML patients (8) (53.3% of total AML population) received less than 6 cycles. ***AML transformation occurred in 16 patients (28.6% of MDS population) after a mean of 9.9 months.*

5-AZA dosage received

Forty-four MDS patients (44 of 56 patients (82.1%)) and twelve AML patients (12 of 15 patients (80%)) received a 5-AZA dose of 75mg/m²/d X 7 days every 28 days

Table 3: 5-AZA exposition time

	Mean	Median	Interquartile range
MDS population (n = 56)			
5-AZA exposition time (months)*	8.22	6.34	3.35 - 11.01
5-AZA exposition time (cycles)	7.98	6	3.5 – 10
AML population (n = 15)			
5-AZA exposition time (months)*	7.2	4.8	0.9 – 9.9
5-AZA exposition time (cycles)	6.6	5	1 – 9.5

**(Date of last dose + three weeks or date of death or lost to follow-up) – date of first dose*

The Canadian 5-AZA monograph and most guidelines and expert consensus state that patients should be treated for a minimum of 6 cycles unless unacceptable toxicities occur after dose delays / adjustments or standard supportive care have proved to be unsuccessful. In our population, excluding patients still on treatment, 32 of 63 patients (50.8%) received 6 cycles or more.

ADVERSE EVENTS - GLOBAL POPULATION

Table 4: Non-hematological adverse events related to treatment

	N = 77	%
Constipation	39	50.6
Nausea	30	39
Vomiting	18	23.4
Diarrhea	16	20.8
Fatigue	44	57.1
Skin rash	20	26
Injection site reaction	16	20.8
Fever / infection	22	28.6
Other*	57	74

**Other reported adverse events: loss of appetite, numbness in arm, gastric reflux, mouth ulcers, anorexia, skin discoloration, cramps, ecchymosis and pain at injection site, dyspnea to effort, stomach cramps, insomnia, blurred vision, muscle pain, bone pain, elevation of hepatic enzymes, change in taste, headache, peripheral neuropathy, tremors*

Non-hematological adverse events were seen in 67 patients (87%) but were mostly mild and most did not lead to delays or dose reduction, which occured in only 11 patients. Treatment intensity was very high at 96% across all populations.

AML POPULATION

- 15 patients (10 men / 5 women)
- Mean age = 71.0 (Interquartile range = 68.5 – 75.5)
- Conformity rate = 33.3 % (5 out of 15 patients*) had a 20 to 30 % blast count in bone marrow biopsy, multiple cell line dysplasia, ECOG performance status score ≤ 2 and were not candidates to short term stem cell transplant

**Missing information (ECOG score (missing in 8 patients) or eligibility to stem cell transplantation (missing in 3 patients)) that could not be found retrospectively in the medical records can explain the low conformity score in the AML population.*

CLINICAL BENEFIT

Table 5: Best response obtained

	MDS		AML	
	n= 56	%	n= 15	%
Complete remission	1	1.8	0	0
Partial remission	14	25.0	1	6.7
Complete bone marrow remission	1	1.8	1	6.7
Hematological improvement	7	12.5	1	6.7
Stable disease	4	7.1	1	6.7
Progressive disease	8	14.2	6	40
Not known*	3	5.4	0	0
Not available** / Other	18	32.1	5	33.3

** Not known: Patients received at least 6 cycles but unable to assess response*
*** Not available: Patients received less than 6 cycles and response has not been evaluated*

- Overall benefit rate (complete or partial remission, complete bone marrow remission, hematological improvement or stable disease)
  - MDS population= 48.2 %
  - AML population = 26.7 %

Figure 2. Kaplan-Meier curves for disease-free survival in MDS population (N = 56)

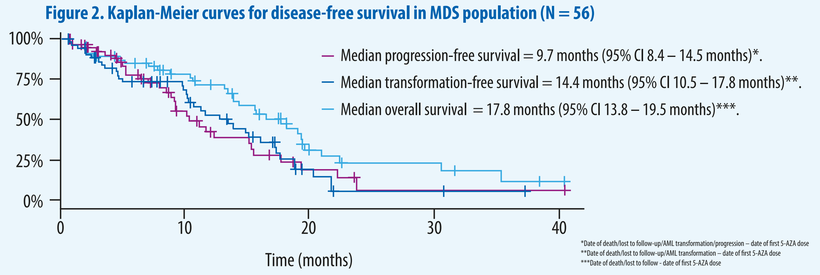
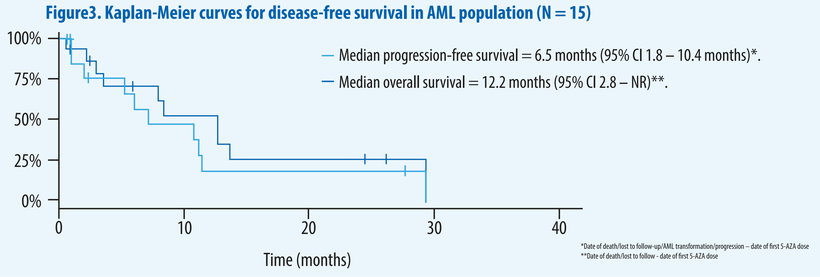


Figure3. Kaplan-Meier curves for disease-free survival in AML population (N = 15)



CONCLUSION

At the end of our study period, 14 patients were still receiving active treatment and 35 patients had died (11 patients were also lost to follow-up and probably deceased). As seen in table 6, our results show that 5-AZA had a limited effect in our real-life population when compared to those in published clinical trials

Table 6: Overall benefit rate compared to pivotal clinical trials

	AZA-001	CALGB 9221	TDMP
% of MDS patients with IPSS int-2 or high risk	89%	41%	**55.8%**
% of AML patients	1%	11%	**19.4%**
Overall Benefit Rate	61%	60%	**44.2%**
Mean 5-AZA exposition (months)	10.3	11.4	**8.1**

Considering that 5-AZA is often the only treatment we can offer these patients and considering its high cost, it would be of highest importance to cautiously choose patients to whom we offer this treatment and to periodically re-evaluate its use (with periodical bone marrow biopsies (ex: every 6 months) in patients with stable or slowly declining cell counts) to confirm the patient is still benefiting from treatment.

Le pGTm est une initiative des cinq centres hospitaliers universitaires du Québec

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