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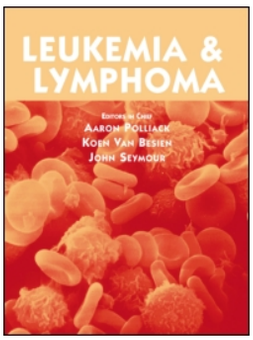

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LETTER TO THE EDITOR

Use of azacitidine and its safety and efficacy in daily clinical practice in The Netherlands: the OCEAN study

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Several clinical studies have shown superiority of azacitidine compared to conventional care regimens in frail patients with MDS and AML [1–4]. However, clinical decision making with regards to dose adjustments and interpretation of treatment responses tends to be subjective and data on this topic are scarce.

Therefore, we performed a prospective, non-interventional study from 2012 until 2016 and assessed results of azacitidine treatment in daily clinical practice in AML, MDS and CMML patients. Patients were recruited from 30 hospitals in the Netherlands and were followed until the last patient enrolled had been followed for 12 months.

At baseline and at intervals in accordance with routine clinical practice the physicians completed a case record form, containing baseline disease and patient characteristics, laboratory values, transfusion data, adverse events, dosing information and frequency and results of bone marrow evaluation (BME). Furthermore, we analyzed the occurrence of local skin reactions (LSR) after azacitidine administration and if different methods of product preparation and administration influenced its occurrence (Supplementary Table 1).

Response to treatment was measured by hematologic improvement (HI) data according to the IWG criteria for MDS [5].

Two-hundred-and-two patients were enrolled with a median follow up of 12.4 months (range 1–43). A summary of patient characteristics is shown in Table 1. Data from all patients who received at least one full cycle of azacitidine after signing informed consent and in whom at least one post baseline efficacy data point was available were included in the safety and efficacy analysis. One-hundred-and-seventy-two (86%) patients were evaluable for the achievement of HI. In 85 (49%) patients HI of one or more cell lines after a median of 2 cycles (range 1–14) was observed. This was an erythroid response in 35% of patients after a median of 4 cycles (range 2–26), platelet response in 54% after a median of 2 cycles (range 1–14), and a neutrophil response in 24% after a median of 4 cycles (range 1–10). In the transfusion dependent patients, 34% became independent of erythrocyte transfusions (TI-E) during treatment after a median of 4 (2–13) cycles, and 45% became independent of platelet transfusions (TI-P) after a median of 3.5 (2–6) cycles.

In 90 (52%) patients a BME was performed after a median of 6 cycles (range 1–20 months). This makes the results of BME difficult to interpret, since it is questionable if BME was done to seek for the best observed response or to find stable or progressive disease. In 57 (65%) of 87 patients without HI, and in 51 (81%) of the 63 patients that stopped treatment within 6 cycles, no BME was performed.

We performed an univariate logistic regression analysis (Supplementary table 3) for HI + and HI- patients. We found that HI occurred more often in patients with an ECOG score of 0–2 (OR 7.518, 95% CI not estimable, $p = .028$). Neither the age group, indication (MDS, AML, CMML), AML risk group, IPSS grade, transfusion dependency, prior intensive treatment, nor treatment schedule at start significantly differed between groups.

For the analyses of the treatment characteristics we used the subset of patients ($n = 172$) that were also evaluable for the efficacy analyses. One- hundred-forty-one patients (82%) started with 7 consecutive days

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Supplemental data for this article can be accessed here.

Table 1. Patient and disease characteristics.

n (%)	All patients *N* = 202
Subgroup	
MDS	94 (47)
AML	83 (41)
CMML	25 (12)
Age , years,	
median (range)	75.5 (51–97)
Sex,	
Male	130 (64)
MDS subgroup	*N* = 94
WHO classification 2016	
MDS with single lineage dysplasia	2 (2)
MDS with single lineage dysplasia and ringed sideroblasts	2 (2)
MDS with multi lineage dysplasia	10 (11)
MDS with excess of blasts 5–10%	24 (26)
MDS with excess of blasts 11–20%	49 (52)
MDS unclassifiable	5 (5)
Missing	2 (2)
IPSS	
Low	2 (2)
Intermediate-1	16 (17)
Intermediate-2	55 (59)
High	16 (17)
Unknown	5 (5)
cytogenetic risk score*	
Good	38 (40)
Intermediate	18 (19)
Poor	33 (35)
Missing	5 (5)
AML subgroup	*N* = 83
WHO classification 2016	
AML with recurrent genetic abnormalities	11 (13)
AML with myelodysplasia- related changes	37 (45)
Therapy-related myeloid neoplasm	6 (7)
AML, not otherwise specified	25 (30)
Unknown	4 (5)
Risk group**	
Good	10 (12)
Intermediate	33 (40)
Poor	25 (30)
Very poor	9 (11)
Missing	6 (7)
ECOG performance score	
0–2	142 (70)
>2	10 (5)
Unknown	50 (25)
Transfusion dependent patients in the last 56 days prior to treatment	
RBC	102 (51)
mean number of units (range)	4.9 (1–27)
Platelets	39 (19)
mean number of units (range)	4.1 (1–35)
Number of former lines of therapy	
0	159 (79)
1–2	41 (20)
>2	2 (1.0)

*According to IPSS; **According to HOVON-SAKK criteria, see also Supplementary Table 2.

of azacitidine administration. Nineteen (11%) patients switched to a reduced schedule, after a median of 9 cycles (range 3–21). In 5 out of 19 patients no HI was reached thus far and 2 of them underwent a BME before switching, showing a response in both of them (CRi and SD respectively). None of the 5 patients attained a HI afterwards after a median of 5 (1–16) months. In 22 (13%) patients there was a dose reduction after a median of 6 cycles (range 1–23). In 13 out of 22 patients, the dose reduction was done before HI was reached, in 3 of them a BME was done before dose reduction (1 patient had CRi, and 2 patients had SD). In 6 patients a HI was seen after dose reduction. The median number of azacitidine cycles received was 6 (range 1–41) in MDS and AML patients, and 7 in CMML patients (range 1–28). Thirteen (6%) patients stopped treatment after the 1st cycle of azacitidine and 63 (37%) patients stopped within 6 cycles. Reasons for treatment discontinuation within the first 6 cycles were adverse events (30%), patient decision (13%), non-responder (25%), disease progression (19%) and other reasons (13%). Median overall survival was 23.2 months and 1 year OS 73%.

Table 2. Mixed model analysis Local Skin Reactions: grade $\geq$ 1 vs grade 0.

	Univariate Odds ratio	95% CI	*p* value	Multi variate Odds ratio	95% CI	*p* value
Induration						
Appearance before administration			.0188			
- Colorless vs white milky	2.215	1.232–3.986		*		
- Homogeneous vs wh milky	1.169	0.915–1.493				
Needle size			.0043			.0020
- <25G vs >25G	2.085	1.301–3.340		2.460	1.354–4.470	
- = 25G vs >25 G	1.313	0.864–1.996		1.283	0.738–2.231	
Pack used			.0537			
- hot pack vs no pack	0.599	0.392–0.915				
- cold pack vs no pack	0.944	0.308–2.898				
Administration duration			.0528			
- <1 min vs > 1 min	0.780	0.606–1.003				
Vial shaken			.0103			.0212
- by hand vs shaker	4.138	1.398–12.243		3.529	1.207–10.317	
Appearance reconstituted product			.0245			.0185
- cloudy vs white milky	1.641	1.066–2.527		1.680	1.091–2.588	
Pruritus						
Needle size			.0742			
- <25 gauge vs > 25 gauge	1.787	1.028–3.108				
- = 25 G vs > 25 G	1.194	0.730–1.953				
Air trapped			.0650			
- no vs yes	1.656	0.969–2.830				
Pain						
Water (for reconstitution)			.0933			
- room temp vs refrigerated	0.643	0.384–1.077				
Tenderness						
Store (after reconstitution)			.0156			
- room temp vs refrigerated	0.530	0.343–0.819				
-in freezer vs refrigerated	0.633	0.294–1.363				
Erythema						
Needle size			.0039			.0009
- <25 G vs >25 G	1.586	0.967–2.602		1.808	0.993–3.293	
- = 25 G vs >25G	2.031	1.336–3.087		2.760	1.612–4.725	
Vial shaken			.0207			.0035
-by hand vs shaker	2.983	1.182–7.526		3.882	1.562–9.649	
Store (after reconstitution)			.0109			.0140
- room temp vs refrigerated	1.522	0.925–2.503		1.180	0.705–1.974	
- in freezer vs refrigerated	0.465	0.214–1.008		0.358	0.163–0.789	
Swelling						
Appearance before administration			.0065			
- colorless vs white milky	2.376	1.312–4.303				
- homogeneous vs wh milky	1.257	0.971–1.628				
Pack used			.0770			
- hot pack vs no pack	0.606	0.392–0.938				
- cold pack vs no pack	0.597	0.143–2.496				
Administration duration			.0866			
- < 1 minute vs > 1 minute	0.800	0.619–1.033				
Shake			.0908			
- by hand vs shaker	2.313	0.875–6.112				

*Variable not selected.

There were differences in azacitidine product reconstitution and administration within different hospitals. For product reconstitution water was added and the vial was shaken by hand (94%) or by use the of a shaker (6%). Afterwards the product was stored at room temp (16%), refrigerated (78%) or in a freezer (6%). A 25 G needle was used for administration in 73%.

In total, 5567 injections were given. Approximately 70% of administrations could be assessed for the occurrence of LSR. Most observed LSR were erythema (grade 1–2: 76%; grade 3–4: 4%) and tenderness (grade 1–2: 38%, grade 3–4: 1%). All other LSR (induration, pruritus, pain, swelling) grade 2 and grade 3–4 occurred in respectively less than 5% and 1% of patients.

A uni- and multivariate mixed model analysis for the product reconstitution methods and variables of administration methods was performed, to assess its impact on the occurrence of LSR (Table 2). Smaller needle size (>25 Gauge, $p = .0020$), use of a vial shaker ($p = .0212$) and a milky instead of a cloudy appearance of the reconstituted product was associated with less induration ($p = .0185$). Erythema was also seen less often if a smaller needle was used ($p = .0009$), the vial was shaken with a shaker instead of by hand ($p = .0035$) and if the product was stored in the freezer instead of refrigerated or at room temperature ($p = .0140$).

To conclude, we came across several interesting findings that could be used to formulate clinical guidelines

in order to improve azacitidine management. First of all, the treatment schedule adherence was quite high: 82% started with a 7 day schedule and dose reductions and/or switch to 5 day schedule were seen in 13% and 11%, respectively, although sometimes even before a (HI) response was seen or BME was performed. Nevertheless, we observed a HI of 49% and a TI-E and TI-P of 34% and 45% respectively, which is comparable to former studies [1–4,6], and a median OS of 23.2 months. Especially the latter in this real life population is remarkable, while it is almost equivalent to the AZA-001 study, and former studies showed a median OS that never approached the AZA-001 results, as summarized in the paper of Zeidan et al. [7]. They pooled analyses of 4 studies and found a median OS of 19.2 months (95% CI 16.9–21.8 months). There might be several possible explanations for our good OS. First, in our cohort 19% of the MDS subgroup had low risk disease (IPSS low or intermediate-1) and 4% of patients proceeded to allo HCT. This might in part explain the difference compared to the Dutch Pharos registry[4] and the population-based cohort study [8] in the US, with a median OS of 16.9 and 15 months respectively, with a lower amount of low risk patients and less/no patients proceeding to allo HCT. Secondly, our study was performed within a later time frame (2012–2016) compared the the Pharos registry (2008–2011), and also compared to other population-based studies like the US AVIDA registry [9] (2006–2010). Could there be a learning effect? As Grinblatt et al. wrote in this Journal, in the AVIDA registry only 15% of patients received azacitidine treatment for 7 consecutive days.

The reasons for changing the dose or schedule in our cohort were not well defined. Physicians might tend to reduce the dose in case of emerging cytopenias. Although based on the kinetics of HMA, of which we know that several cycles are often needed to achieve a response [1], adherence to the schedule and tolerance of cytopenias in the early phase of HMA treatment might result in higher efficacy. Furthermore, the importance of achieving SD with or without HI on survival [10] might not be known in all physicians, since 51 (81%) patients without HI stopped treatment within 6 cycles without BME.

So we question if treatment outcomes are perhaps underestimated by subjective physician decisions and be different if we adhere more to registered doses/schedules and do more BME in case of doubt before treatment adaptations?.

We also showed that there are quite some differences in drug handling and that these differences are related to the occurrence of LSR. Since the reason to stop treatment within 6 cycles due to AEs in this Dutch cohort was 30%, it seems noteworthy to focus more on attempts to prevent the occurrence of infections by prophylactic antibiotics, and lower the incidence of LSR by use of a smaller needle size, a vial shaker for product preparation and freezer storage of the reconstituted product as shown in our analyses.

Disclosure statement

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