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par

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TITRE

FACTEURS DE RISQUE INFECTIEUX ET IMPACT DE L'ANTIOBIOPROPHYLAXIE CHEZ LES PATIENTS TRAITES PAR 5-AZACITIDINE : UNE ETUDE RETOSPECTIVE FRANCAISE

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Infection risk factor in patient treated with 5-azacitidine and impact of antibioprophylaxis: a French multicentric retrospective study.

Background:
The hypomethylating agent, azacitidine has been approved to treat patients who suffer from acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) who or not candidate to receive intensive treatment. This population is particularly exposed to infectious episodes. The aim of our study was to identify infectious risk factor at the beginning of azacitidine treatment and impact of antibioprophylaxis.

Results:
We retrospectively included 112 patients from 4 French hospitals who started azacitidine between November 2007 and December 2018 for AML/MDS/CMML. A total of 55 infectious event were analyzed for putative risk factors, 44 (80%) of witch in the first three cycle. In univariate analysis thrombocytopenia < 50 G/L (p=0.0005) and anemia < 80 g/L (p=0.01) were significant factors associated with infection. In multivariate analysis, only thrombocytopenia < 50 G/L was significant. Median overall survival was 18 months (95%CI 12-29), 8 months (95%CI 6-NR) in thrombocytopenic < 50 G/L patients versus 24 months (95%CI 18-NR) when platelets were > 50 G/L at treatment initiation.

Conclusion:
Patients with thrombocytopenia < 50 G/L who started azacitidine for AML/MDS/CMML have a high infection risk.

Keywords: Myelodysplastic syndrome, acute myeloid leukemia, chronic myelomonocytic leukemia, 5-azacitidine, antibioprophylaxis, infection.

Facteurs de risques infectieux et impact de l'antibioprophylaxie chez les patients traités par 5-azacitidine: une étude rétrospective Française.

Introduction :

L'azacitidine en tant qu'agent hypométhylant, a été approuvée afin de traiter les patients atteints de leucémie aigue myéloblastique, de syndrome myélodysplasique ou de leucémie aigue myélomonocytaire non éligibles à un traitement intensif. Cette population est particulièrement exposée au risque infectieux. Le but de notre étude a été d'essayer d'identifier des facteurs de risque infectieux à l'initiation du traitement par azacitidine et l'impact d'une antibioprophylaxie.

Résultats :

Nous avons analysé de façon rétrospective 112 patients provenant de 4 hôpitaux de la région Centre-Val de Loire, ayant débuté un traitement par azacitidine entre Novembre 2007 et Décembre 2018. 55 patients ont présenté un événement infectieux dont 44 durant les 3 premiers cycles. En analyse univariée, la thrombopénie < 50 G/L (p= 0,0005) et l'anémie < 8 g/dl (p = 0,01) ont été identifiées comme facteurs prédictifs d'une infection. Seule la thrombopénie < 50 G/L restant significative en analyse multivariée. La médiane de survie de notre cohorte fut de 18 mois (95% IC 12-29), 8 mois (95% IC 6-NA) en cas de thrombopénie < 50 G/L et de 24 mois (95% IC 18-NA) chez les patients présentant des plaquettes > 50 G/L.

Conclusion :

Les patients avec une thrombopénie < 50 G/L à l'initiation du traitement par azacitidine sont à haut risque infectieux.

Mots-clés : Syndrome myélodysplasiques, leucémie aigue myéloblastique, leucémie myélo-monocytaire chronique, 5-azacitidine, infection, antibioprophylaxie.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples et selon la tradition d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent, et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Introduction:

5-azacitidine (AZA) was approved on Europe in 2009 on the basis of the work of Fenaux et al[1] for higher-risk myelodysplastic (MDS) patients and AML with less than 30% bone marrow blasts**.** AZA is a structural analogue of cytosine that incorporates into DNA and covalently inhibits DNA methyltransferase. This is the first treatment who increases overall survival relative to conventional care. AZA was also approved for patients with acute myeloid leukemia (AML) who are not candidate for intensive chemotherapy and chronic myelomonocytic leukemia (CMML). AZA is usually administrated within an outpatient setting for a minimum of 6 cycles before response assessment. This course can be disrupted by progressive disease and leukemic transformation or complication such as infection or bleeding[2,3] who are the major causes of resource consumption and death.

Infections are a well-known complication in MDS patients, but DATA are heterogeneous. In a retrospective work of Musto et al[4], they found 6.8% of grade 3/4 infection in lower risk MDS. They affected between 54% and 71% of high risk MDS or AML patients treated with AZA according to recent retrospective studies[5,6]. These infections caused a significant morbidity, requiring hospitalizations and intravenous treatment. Merkel et al found 75% of infected patients under AZA required hospitalization and 20% were fatal[5]. 81% required hospitalization in another retrospective study in higher risk MDS[7]. Incidence of infections were higher in the first two cycles and decreased with time. Incidence was between 20% and 30% in cycle 1 or 2 and dropped < 10% after cycle 5 in 3 retrospective work[5,7,8].

Several infection risk factors have been identified. Absolut neutrophil count (ANC) under 0.8 x 10^9/L, red blood cell transfusion dependency, platelet count < 50 G/L were found as infection risk factor in a multivariate analysis of 298 patients[9]. An expert panel recommendation published in 2018 concluded that there is a lack of randomized clinical trials testing screening and infectious prophylaxis in this setting[10]. However, they suggested an infectious risk assessment before and during MDS treatment, especially in patient with severe and prolonged neutropenia, transfusion-related iron overload or relevant co-morbidities such as diabetes or COPD[10]. Conversely in a review of literature by Radsak et al, no impact of absolut neutrophil count was seen[11]. Beside quantitative damage there is a qualitative impairment of immunity. Neutrophils from MDS patients showed attenuation in migration compared with healthy cells.[12] They also had a reduced killing activity against E.Coli and more against Candida Albicans[13]. Monocyte function and derived macrophages were impaired as well in MDS[14,15].

The role of antibiotic prophylaxis in patients treated with AZA is unclear, generally not recommended largely due to lack of evidence. The European Society of Medical Oncology (ESMO) or The National Comprehensive Cancer Network (NCCN) do not recommended antibiotic prophylaxis in routine use of AZA. In a retrospective work of Lee et al they showed 11.5% of febrile episode under Decitabine for MDS. Antibioprophylaxis was administrated in 72.5% cycles of Decitabine and were mostly fluoroquinolones. They reported significantly less incidence of febrile episode under prophylaxis than without (7.4% vs 22.2%, p=0.017)[16]. This was also demonstrated with ciprofloxacin in a retrospective study of Lorenzana et al in the subset of patients with ANC < 0.5 x 10^9 G/L[17].

AZA use is predominantly prescribed in the elderly[3]. Due to demographic change in our countries, it is expected that the prescription of AZA will progress in future years. However, recent publications have expanded the scope of use. AZA in combination with Venetoclax have shown 67% of patients with a complete remission but 45% of grade 3/4 infection resulting in 7% deaths due to infection[18].
Unpublished study by Dolleans et al was already done in our center. Neutropenia < 0.8 G/L (p= 0.023) and associated immunosuppression (p= 0.03) were predictive factors for infection in multivariate analysis. We conducted a French multicentric retrospective analysis to evaluate infection risk factors in patients treated with AZA and the potential role of antibioprophylaxis in a larger cohort.

Patients and methods

We conducted a non-interventional, multicentric study. We retrospectively analyzed data from patients who started azacitidine for MDS, AML or CMML between February 2008 and December 2018 at 4 French hematologic center (Tours, Chartres, Blois and Orleans). They were treated with azacitidine at the standard dose of 75 mg/m^2 subcutaneously for 7 days. Treatment cycles were scheduled every 4 weeks until progression or intolerance. We included patients who began azacitidine as first line, second line or after allogenic stem cell transplantation. No exclusion criteria were defined.
Diagnosis was established according to the World Health Organization 2016 classification[19] and MDS subtype on the basis of International Prognostic Scoring System revised (IPPS-R)[20]. Data were collected before start of azacitidine. For all patients we recorded age, sex, comorbidities known to promote infection (diabetes, COPD, long-term corticotherapy, hypogammaglobulinemia), complete white blood count, cytogenetic risk and therapy related or not. Those data were selected for assessment in univariate analysis. Adverse cytogenetic risk was defined according to the IPSS-R[20] for MDS and 2017 European Leukemia Network risk stratification for AML[21]**.** An infectious event was defined as Grade ≥ 2infectious complication according to the Common Terminology Criteria from Adverse Event version 5.0[22]. Additional information about microbiological sample, infection localization, treatment undertaken and clinical course were collected. Existence of antibacterial, antifungal or antiviral prophylaxis was also recorded.

Statistical analysis

Qualitative variables are described using counts and percentages and continuous quantitative variables as means ± standard deviation and also median and quartiles when necessary. Comparisons between groups were made using chi-square tests for comparing categorical variables and the Student t test or non-parametric Kruskal Wallis test where appropriate for continuous variables.
To identify independent characteristics associated with an infectious episode in this population, a proportional hazard model was used. Baseline characteristics were pooled into a multivariate Cox model. The results were expressed as hazard ratios risk (HR) and 95% confidence intervals (CI). The proportional hazard assumption was checked by plotting the log-rank Kaplan Meier curves. In all analyses, a p value <0.05 was considered statistically significant. All analyses were performed using *STATA®* and *Rstudio®*

Ethical considerations

The present study was evaluated and approved by the Regional Ethics Committee. Due to its observational nature, the need for informed consent was waived.

Results:

Description of patients:

One hundred and eighteen patients with a diagnosis of MDS, AML or CMML and who started AZA between February 2009 and December 2018 were initially included. Seven patients were excluded. One because of no bone marrow aspirate was performed, two resumption of AZA treatment and four due to lack of data. A total of 111 patients were finally included. The median age of cohort was 73 years (29-91). There were 43 diagnosis of AML, 65 of MDS and 3 of CMML, 31 were therapy-related. 3 patients were received bone marrow transplantation before azacitidine. The median percentage of bone marrow blast was 23% (0-80). 7 patients received Levofloxacin as prophylaxis, 44 Valaciclovir, 36 Trimethoprim-Sulfametaxol and 7 antifungal prophylaxis with Posaconazole. The main characteristics of the sample are detailed in Table 1.

Table 1: Main characteristics of the population at first cycle of AZA

Variable	N
Age, median, (range) in years	73 (29-91)
Sex in n (%)	
- Male	72 (65)
- Female	39 (35)
Diagnosis in n (%)	
- MDS	53 (48%)
- AML	55 (49%)
- CMML	3 (3%)
Therapy related n (%)	
- Yes	31 (28)
- No	80 (72)
Cytogenetic category n (%)	
- Favorable	58 (52)
- Unfavorable	53 (48)
Complete Blood Count median(range)	
- Hemoglobin (g/L)	94 (6.6-13.7)
- Platelets (G/L)	65 (11-287)
- Neutrophils (G/L)	1.1 (0,2-23)
- Monocytes (G/L)	0.3 (0-21)
- Lymphocytes (G/L)	1.2 (0.2-5.33)
Prophylaxis n (%)	
- Levofloxacin	7 (6)
- Posaconazole	13 (12)
- Valaciclovir	44 (40)

Description of first infectious episode:

A total of 989 AZA cycles were analyzed. 55 patients experimented an infectious event, corresponding to 50% of the cohort. Infections were more prevalent during the first three, cycles with 19 infectious event at cycle 1, 12 at cycle 2, 6 at cycle 3 and declines with the progression of therapy. Their incidence according to cycle is presented in Figure 1. Cumulative incidence of infection with a median follow up of 8 months, is represented in Figure 2. 56 days was the median between AZA first injection and infectious event.
48 patients required hospitalization and 10 were fatal. It represented 492 hospitalizations days for the entire cohort. Median duration of hospitalization was 10 days. 17 patients had to stop AZA and 19 had their next cycle shifted.
Localization of the infectious event was documented in 49 of 56 events. The lungs, with 25 diagnosis of pneumonia was the first localization. Skin was the second one with 9 cases followed by fever of unknown origin with 7 cases, urinary tract with 5 cases and 4 gastrointestinal cases. Infections were bacteriologically undocumented in 35 events. We recorded 4 episodes of *Escherichia coli,* 4 methicillin-sensible *Staphylococcus aureus*, 2 *Pseudomonas Aeruginosa*, 2 methicillin-resistant *Staphylococcus aureus* ,2 *Streptococcus* Haemolyticus, 1 *Coronavirus*, 1 *Candida Albicans*, 1 *Pneumococcus*, 1 *Serratia Marcescens*, 1 *Salmonella Typhymirium* and 1 *Enterobacter Cloacae*.

Figure 1: Incidence of infectious event according to cycle

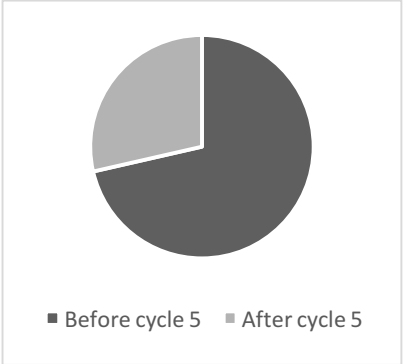
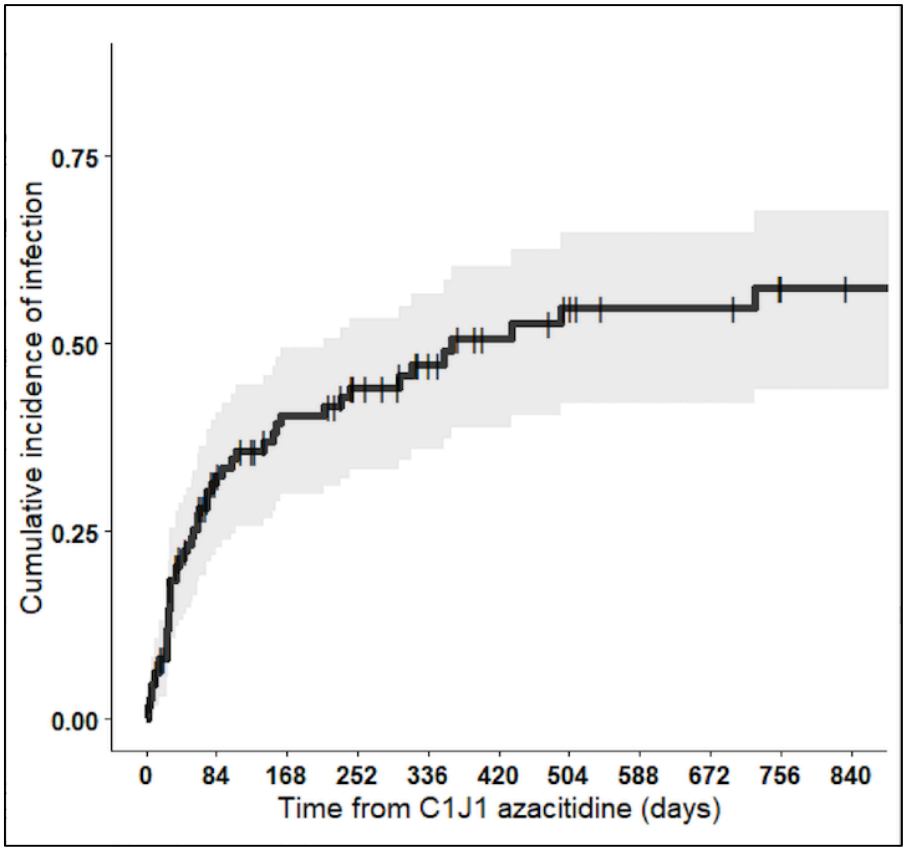


Figure 2: Cumulative incidence of infection



Factors predicting infections prior to first cycle:

Univariate analysis:

Patients with thrombocytopenia < 50 G/L had a significant higher risk of infection compared to those with platelets > 50 G/L, (hazard ratio (HR) 2.78, 95% confidence interval (CI) 1.57-4.95, p= 0.0005). Patients with platelets < 20 G/L had the same infection risk, no impact of platelets count between < 50 G/L and < 20 G/L was seen. Anemia < 100 g/L was also a significant infection risk factor (HR 2.01, 95%CI 1.09-3.71, p= 0.02). Interestingly, patients with hemoglobin level between 80 g/L and 100 g/L hadn't a significant higher risk (HR 1.78, 95% CI 0.92-3.46, p= 0.88). Only hemoglobin level < 80 g/L was a statistically significant risk factor for infection (HR 2.48, 95% CI 1.21-5.12, p= 0.01). Neutrophil count lower than 0.8 G/L or 0.5 G/L wasn't associated with a significant risk of infection but increased patient susceptibility to infection (HR 1.51, 95% CI 0.88-2.58, p= 0.13). Lymphocytes < 1G/L, Monocytes < 0.2 G/L, unfavorable karyotype or therapy related were not statistically associated with the occurrence of infection (Table2).

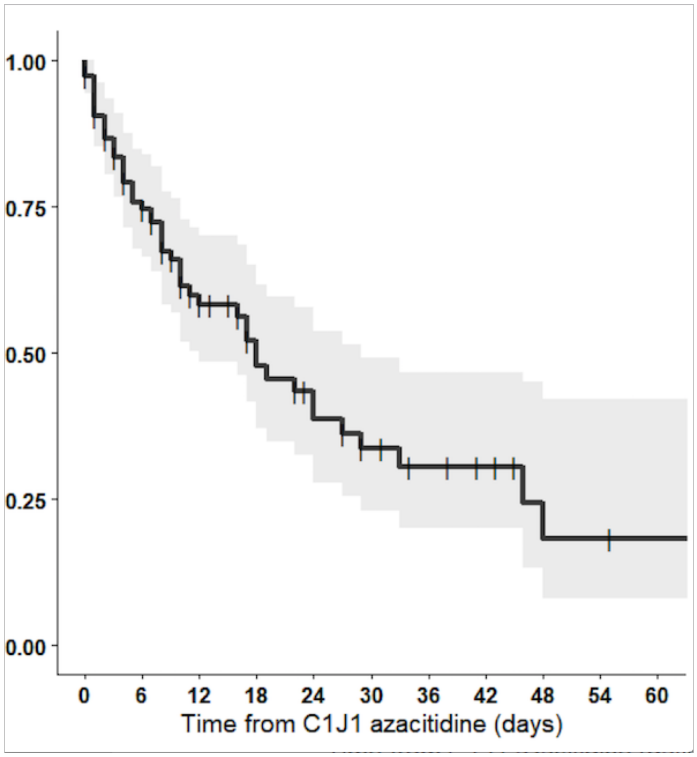
Table 2: Univariate analysis of infection risk factor at azacitidine initiation.

	Hazard Ratio	95% CI low	95% high	p-value
Neutrophils				
< 0.8 G/L	1.51	0.88	2.58	0.13
0.5-0.8 G/L	1.45	0.70	3.01	0.31
< 0.5 G/L	1.42	0.79	2.55	0.24
Platelets				
< 50 G/L	2.78	1.56	4.95	0.0005
20-50 G/L	2.79	1.51	5.16	0.001
< 20 G/L	2.75	1.11	9.82	0.02
Hemoglobin				
< 10 g/dl	2.01	1.09	3.72	0.0252
8-10 g/dl	1.78	0.91	3.46	0.88
< 8 g/dl	1.80	0.99	3.25	0.05
Lymphocytes < 1G/L	2.25	0.73	2.15	0.41
Monocytes < 0.2 G.L	1.27	0.74	2.18	0.38
Unfavorable Karyotype	1.02	0.60	1.74	0.95
Therapy-related	0.80	0.45	1.44	0.47

Multivariate analysis:

We took into account the influencing factors of univariate analysis with p=20%. We added them sequentially according a Cox model from most significant to least significant. Finally, no matter what model we chose, only thrombocytopenia < 50 G/L was independently associated with a higher risk of infection. Hemoglobin level and neutrophil count weren't associated independently with infection risk.

Figure 3: Overall survival of the entire cohort using Kaplan Meyer survival analysis.



Overall survival:

Median overall survival of the entire cohort was 18 months (95% CI 12-29) with a median follow-up of 8 months, Figure 3. Patients who presented an infectious episode had a shorter median overall survival compared to those who hadn't, 10 months (95% 7-22) vs 29 months (95% CI 17-NR), Figure 4. Likewise, patient who presented thrombocytopenia < 50 G/L at azacitidine initiation had a shorter median overall survival, 8 months (95% 6-NR) vs 24 months (95% 18-NR), Figure 5.

Figure 4: Overall survival between infected vs non infected patient, using Kaplan Meyer survival analysis.

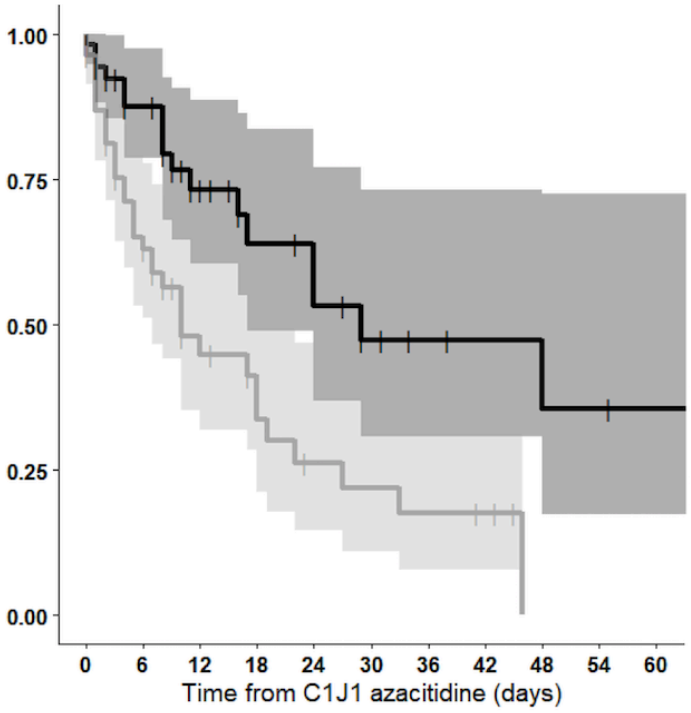
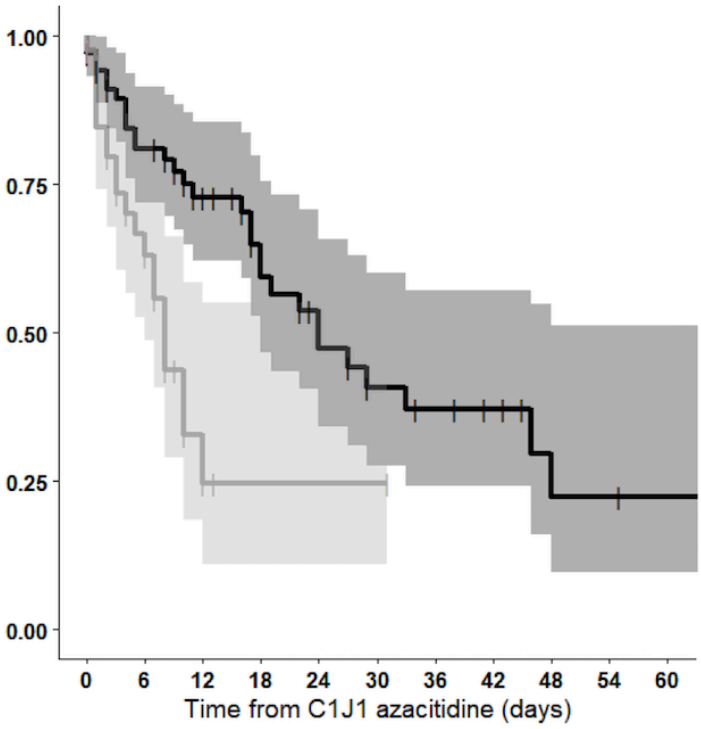


Figure 5: Overall survival between thrombocytopenic vs non thrombocytopenic patients, using Kaplan Meyer survival analysis.



Discussion:

Here we reported a retrospective multicentric study of 111 patients who started azacitidine. 55 patients experimented an infectious event. In the univariate analysis we identifying thrombocytopenia < 50 G/L (p=0.0005) and anemia < 8 g/dl (p=0.01) as infection risk factors at the beginning of azacitidine treatment. Thrombocytopenia < 50 G/L remained the only predictive infection factor in multivariate analysis. Platelets count < 50 G/L increased risk of infection around 3 times. This result, was also find in others retrospectives studies[4,9].
Platelets function in immunity against bacteria has been studied. Their role in innate and adaptive immunity was already described[23,24]. Thrombocytopenia may impair immune response to invading pathogens. Focusing on thrombocytopenic patient is probably determinant to prevent infection.
Anemia < 10 g/dl was also statistically significant in univariate analysis (p=0.02) but when we separated cohort in 2 groups (8-10 g/dl or < 8 g/dl) only patients with anemia < 8 g/dl had a significant higher risk of infection. This correlated with red blood cell transfusion (RBC) dependency as infection risk factor reported in few studies[5,9,17]. Madry et al developed an infection risk model where RBC transfusion dependency was an independent infection risk factor whereas anemia wasn't[9]. Transfusion recommendations and practices might be different between France and Poland and can explain this difference. However, anemia < 8g/dl or RBC transfusion dependency reflect a more active underlying disease with hospitalized patients and a higher infection risk.
Surprisingly, a neutrophil count < 0.8 G/L or < 0.5 G/L wasn't an independent infection risk factor in our cohort. Because of their role in immunity against bacteria, neutropenia was commonly accepted as infection risk factor. Some authors reported neutropenia as infection risk factor in this setting, but only in univariate analysis[5,7]. Neutropenia wasn't a predictive factor in multivariate analysis. Madry et al found a statistic association between neutropenia and infection in univariate and multivariate analysis. It increased infection episode approximately 3 times and they incorporated neutropenia < 0.8 G/L in their predictive infection risk model[9]. Neutrophil function is also altered in myelodysplastic syndrome[25]. Response to infection can be impaired not only due to neutropenia but also due to altered function. In our cohort, a large proportion of patient had therapy related disease and had already receive chemotherapy. A higher proportion of neutropenic patient in our cohort could explain that neutropenia wasn't found as infection risk factor.
Importantly, as reported in others retrospectives studies, 80% of reported infection in our study occurred before the fourth azacitidine cycle. Patients appear more likely to develop infection within first 3 cycles. Response to azacitidine is usually retarded and assessed after 6 cycles. Prolonged treatment can improve response to azacitidine and probably decrease infection susceptibility.
Only seven patients received antibioprophylaxis with levofloxacin on our cohort, since there is no clear recommendation for its use. We were not able to show a benefice for antibioprophylaxis in this setting. However, two retrospective studies were in favor of the use of antimicrobial prophylaxis. On another side antibioprophylaxis might increase bacterial resistance[16,17].
Our study has several strengths. First, this is a large cohort who represented real-life clinical data of patients treated with azacitidine. Second, its multicentric nature limited recruitment bias and presence of center effect. We must keep in mind that our study was based on retrospective data and could include selection bias and missing data.

Conclusion:

Our large multicentric cohort confirmed existence of a subgroup of patients who were particularly prone to develop infection within first three cycle of azacitidine. Thrombocytopenic patients might benefit from an early intervention such as antibioprophylaxis in this setting. To validate our hypothesis, we propose prospective study with levofloxacin prophylaxis in thrombocytopenic patients < 50 G/L during the first three cycle of azacitidine.

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PONARD Antoine Jean-Pascal Daniel
12 pages – 5 figures – 2 tableaux

Résumé :
Introduction :
L'azacitidine en tant qu'agent hypométhylant, a été approuvée afin de traiter les patients atteints de leucémie aigue myéloblastique, de syndrome myélodysplasique ou de leucémie aigue myélomonocytaire non éligibles à un traitement intensif. Cette population est particulièrement exposée au risque infectieux. Le but de notre étude a été d'essayer d'identifier des facteurs de risque infectieux à l'initiation du traitement par azacitidine et l'impact d'une antibioprophylaxie.
Résultats : Nous avons analysé de façon rétrospective 112 patients provenant de 4 hôpitaux de la région Centre-Val de Loire, ayant débuté un traitement par azacitidine entre Novembre 2007 et Décembre 2018. 55 patients ont présenté un événement infectieux dont 44 durant les 3 premiers cycles. En analyse univariée, la thrombopénie < 50 G/L (p= 0,0005) et l'anémie < 8 g/dl (p = 0,01) ont été identifiées comme facteurs prédictifs d'une infection. Seule la thrombopénie < 50 G/L restant significative en analyse multivariée. La médiane de survie de notre cohorte fut de 18 mois (95% IC 12-29), 8 mois (95% IC 6-NA) en cas de thrombopénie < 50 G/L et de 24 mois (95% IC 18-NA) chez les patients présentant des plaquettes > 50 G/L.
Conclusion : Les patients avec une thrombopénie < 50 G/L à l'initiation du traitement par azacitidine sont à haut risque infectieux.

Mots-clés : Syndrome myélodysplasiques, leucémie aigue myéloblastique, leucémie myélo-monocytaire chronique, 5-azacitidine, infection, antibioprophylaxie.

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