



Efficacité de l'azacitidine dans la prise en charge des complications auto-immunes et inflammatoires des syndromes myélodysplasiques

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Université de Nice Sophia-Antipolis - Faculté de Médecine de Nice

THESE D'EXERCICE DE MEDECINE
Pour obtenir le diplôme d'état de Docteur en médecine

Présentée et soutenue le 15 septembre 2020
à la Faculté de Médecine de Nice par :

Monsieur Antoine BENICHO

Né le 20 décembre 1989 à Nanterre (92)

**Efficacité de l'azacitidine dans la prise en
charge des complications auto immunes et
inflammatoires des syndromes
myélodysplasiques**

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Résumé français du travail de thèse :

Introduction :

Les syndromes myélodysplasiques (SMD) et leucémies myélo-monocytaire chroniques (LMMC) sont des néoplasies myéloïdes du sujet âgé caractérisées par la présence de cytopénies, avec un risque variable d'évolution clonale vers des leucémies aigues myéloïdes (LAM) évalué par le biais des scores pronostic IPSS et IPSS-R.

Leur association à des manifestations auto-immunes ou inflammatoires (MAI) est connue mais reste mal définie, avec une efficacité fréquente des corticoïdes mais des taux de rechutes ou de cortico-dépendance élevés. Plusieurs travaux suggèrent l'intérêt potentiel de l'azacitidine (AZA) dans la prise en charge de ces MAI, dont l'influence pronostique reste débattue.

Patients et méthodes :

Nous avons réalisé une étude cas-témoins rétrospective mono centrique sur la cohorte de patients porteurs de SMD/LMMC traités par AZA au CHU de Nice entre 2005 et 2019 afin de comparer les caractéristiques épidémiologiques, cliniques et la survie des patients porteurs ou non de MAI associées. Nous avons par ailleurs centré notre travail sur l'influence de l'AZA dans le contrôle des MAI et sur différents facteurs pouvant influencer la survie.

Résultats :

Au sein de la cohorte, 20 patients étaient porteurs de MAI et 110 utilisés comme contrôles, soit une prévalence des MAI de 15% au sein de la cohorte. L'âge moyen était de 69 ans avec une prédominance masculine (60%). Dans la majorité des cas, le diagnostic des MAI était concomitant à celui du SMD/LMMC (55%), récent (20%) ou secondaire (20%) avec un délai moyen de 5.25 mois entre les deux diagnostics. On notait plus d'antécédents de MAI dans le groupe MAI que dans le groupe contrôle (25% vs 5% $p=0.013$). Au sein des MAI on notait des dermatoses neutrophiliques ($n=5$, 25%), des vascularites systémiques ($n=4$, 20%), des MAI spécifiques d'organe ($n=4$, 20%), des connectivites ($n=3$, 15%), des rhumatismes inflammatoires chroniques ($n=3$, 15%), une cytopénie auto-immune ($n=1$, 5%).

La classification OMS des SMD/LMMC était statistiquement différente au diagnostic ($p<0.001$) avec dans le groupe MAI, plus de LMMC1 (35% vs 9.1%) ou de SMD avec dysplasie multi-lignée (15% vs 3.6%) que dans le groupe témoin qui se présentait plus souvent sous la forme d'AREB2 (45% vs 10%).

On observait une différence statistique sur le score IPSS entre les deux groupes à l'introduction de l'AZA avec plus de patients à faible risque (Int-1 et low) dans le groupe MAI que dans le groupe témoin (48% vs 19% respectivement, $p<0.001$).

Les histoires antérieures d'évènements cardiovasculaires ou de cancers étaient comparables entre les deux groupes, ainsi que la survenue d'infections nécessitant une hospitalisation après le diagnostic de SMD/LMMC.

Concernant les MAI, avant introduction de l'AZA, 90% des patients avaient reçu une première ligne de traitement, qui comportait des corticoïdes chez 75% d'entre eux. Une seconde ligne était nécessaire dans 30% des cas, une troisième dans 10% des cas et une quatrième ligne dans 5% des cas.

A l'introduction de l'AZA, 31.5% des patients restaient cortico-dépendants avec une posologie médiane de 43.3 mg/jour de prednisone dans ce sous-groupe. Au sein des patients n'ayant pas atteint une réponse complète, on observait une amélioration de la réponse dans 81% des cas après traitement par trois à six cycles d'AZA. Sur l'ensemble des patients atteints de MAI on observait une amélioration de la réponse dans 47% des cas et une diminution globale du taux de cortico-dépendance à 5.5% après introduction de l'AZA.

La réponse des SMD/LMMC à l'AZA était comparable entre les deux groupes et n'était pas corrélée à la réponse des MAI.

Aucune différence de survie globale n'était observée entre les deux groupes (survie médiane de 20.6 mois). La survie était statistiquement modifiée par la catégorie de risque IPSS-R et par la survenue d'une transformation en LAM. L'existence d'un antécédent de cancer était également associée à une survie altérée (17.4 vs 28.5 mois, $p=0.029$). La survenue d'infection nécessitant une hospitalisation après le diagnostic de SMD/LMMC ne semblait pas influencer la survie globale.

Conclusion :

L'AZA semble apporter un bénéfice en termes de contrôle des MAI et de cortico-dépendance chez des patients porteurs de SMD/LMMC majoritairement à risque élevés. L'association d'une MAI ne semble pas influencer la survie globale. Le pronostic apparaît principalement relié aux caractéristiques intrinsèques des maladies hématologiques sous-jacentes et aux fragilités des patients.

Version anglaise au format article :

Title: Efficacy of azacitidine in management of auto-immune or inflammatory manifestations associated to high risk myelodysplasia and chronic myelomonocytic leukemia.

Introduction:

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML) are chronic myeloid stem cell neoplasms characterized by an impairment of hematopoiesis with a variable risk of clonal progression into acute myeloid leukemia (AML) (1). The frequency of auto-immune or inflammatory manifestations (AIMs) is higher in MDS/CMML patients in comparison with the general population or with lymphoid malignancies (2,3) ranging from 10 to 30% of patients (4). Accumulation of genetic abnormalities within bone marrow progenitors is known to be responsible for local immune dysregulation that could be linked by many pathways to AIMs (5)(6). Yet, the pathophysiological link between these conditions is not univocal as illustrated by the wide spectrum of observed AIMs and the frequency of undefined or atypical manifestations, compared to traditional AIMs.

Furthermore, therapeutic management of MDS/CMML related AIMs is challenging. Despite an important response rate with steroids, most patients require the use of a second line therapy. Treatment strategies in steroid-dependent or refractory patients remain uncoded. Efficacy of azacitidine (AZA) in these patients is suggested in various case reports and small retrospective series (7).

Moreover, patient outcome with MDS/CMML related AIMs remains controversial (8).

We conducted a single-center retrospective case control study in order to describe the clinical features, outcomes and treatment strategies in our cohort of AZA treated high risk MDS/CMML patients with or without AIMs. We focused our work on AIMs response to AZA and potential factors that could influence outcomes in each group such as infections, past cardiovascular events, or history of cancer.

Patients and methods:

Medical records of patients treated with AZA for myeloid neoplasms according to international recommendations in the Nice University Hospital between 2005 and 2019 were evaluated. Patients were included if age ≥ 18 years with a diagnosis of MDS or CMML confirmed by a bone marrow aspiration. Patients with an initial diagnosis other than MDS or CMML, or those referred by other medical centers that had subsequently too much missing data were excluded. MDS and CMML diagnosis were classified according to WHO 2016 criteria (1) at diagnosis

and at AZA onset. MDS and CMML were stratified by IPSS (9) and IPSS-R (10) prognosis scoring systems at AZA onset. The time of MDS diagnosis retained was the date of bone marrow aspiration. We also collected laboratory data and karyotypes when available, number of prior hematologic treatments to AZA and use of bone marrow transplantation. AZA response was assessed for MDS and CMML using the International Working Group 2006 criteria (11). Autoimmune and inflammatory manifestations (AIMs) were recorded based on the medical records and classified according to expert review and usual international classification criteria such as the Chapel Hill classification for systemic vasculitis (12), Michet criteria for relapsing polychondritis (13), or Von den Driesch criteria for Sweet syndrome (14). Hypothyroidism or isolated biological anomalies were not considered as clinical AIMs. When complete classification criteria were not met, AIMs diagnosis had to be confirmed by an expert and was considered incomplete.

AIMs were grouped as follows: systemic vasculitis, connective tissue diseases (CTD), inflammatory arthritis, neutrophilic dermatosis, immune cytopenia or organ limited immunologic disease. We recorded clinical manifestations, organ involvement, immunological abnormalities at AIMs diagnosis and each specific AIMs treatment received before MDS/CMML diagnosis and during follow up.

Patients with AIMs diagnosed more than 5 years before MDS/CMML and who had no clinical nor biological activity for years and during follow-up were not considered as MDS/CMML associated AIMs. Temporal association between active AIMs and MDS/CMML diagnosis were classified as : 1) old (AIMs diagnosed > 5 years before and still active at the diagnosis of MDS/CMML), 2) recent (AIMs diagnosed < 5 years before MDS/CMML), 3) concomitant (AIMs diagnosed 3 months before or after MDS/CMML) or 4) secondary (AIMs diagnosed > 3 months after MDS/CMML).

AIMs response to both specific treatments and AZA was assessed based on clinical, biological and radiological evaluations and submitted to expert review. Complete response was defined as the disappearance of clinical features and normalization of biological and immunological parameters present at baseline. Partial response was defined as a $\geq 50\%$ improvement of clinical, biological and immunological parameters. Failure was defined either as an < 50% improvement, a worsening of clinical, biological, immunological and imagery features under treatment or a flare with a need for intensification in AIMs treatment. Steroid dependence was defined as a prednisone equivalent amount > 20 mg/day during at least 2 months without worsening. Patients with no AIMs were used as a control group.

In addition, we collected information about prior medical history of all patients before MDS/CMML diagnosis. We recorded cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity, tobacco use), occurrence of major cardiovascular events (peripheral artery

disease, coronary artery disease, vascular chronic kidney disease or strokes). Was also recorded history of cancer and use of chemotherapy, radiotherapy or surgery.

Finally, we compared the propensity of patients to develop infections after MDS/CMML diagnosis and their potential influence on overall survival. Every infection related hospitalization in the Nice University hospital was recorded as well as its duration. When available, infectious cause of death was recorded.

Descriptive statistics included the mean, median and standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables. A chi-square test or Fisher's exact test was used to compare categorical variables, and if normality was verified, Student's t-test was used to compare continuous variables. Survival was calculated from the time of MDS/CMML diagnosis and compared in MDS/CMML patients with and without AIMs. To account for missing data, results were expressed as observed data (missing data were not replaced). Survivals were estimated according to Kaplan-Meier method and compared by the log-rank test (at the 5% level). A P-value <5% was considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results:

Between 2005 and 2019, 385 patients were treated by AZA in Nice University Hospital. One-hundred and ninety-seven had an initial diagnosis other than MDS or CMML and were excluded. Among the remaining patients, 58 had been referred by other centers and were excluded due to missing clinical data. One-hundred and thirty patients were included in the analysis. Seven patients had a past medical history of inflammatory or auto-immune disease with no clinical nor biological activity in the previous years and were not considered as active MDS/CMML related AIMs, thus excluded of AIMs group (Figure 1). These seven patients had presented psoriasis n=1, Behcet's disease n=1, psoriatic rheumatism n=1, rheumatoid arthritis n=2, vitiligo n=1, and polymyalgia rheumatica n=1.

AIMs characteristics:

Out of the 130 patients with MDS/CMML, 20 presented an active AIM (15%).

Baseline demographic characteristics were comparable between AIMs and control groups (Table 1) with a mean age at diagnosis of 68.0 years in AIMs group and 69.1 years in the control group (SD 9.25 and 9.79 respectively, p=0.53). Male to female ratio was strictly identical in the two groups with 60% males (p=1).

Mean delay between AIMs and MDS/CMML diagnosis was 5.25 months (SD 29.9). Four patients had recent AIM diagnosis (20%), 11 a concomitant diagnosis (55%), 4 a secondary

diagnosis (20%) and one patient had an old diagnosis of AIM (still active psoriasis, with a severe relapse at MDS diagnosis). No association was found between diagnosis temporal association and AIMs subtype ($p=0.43$).

Among AIMs patients, five (25%) had a prior history of AIM (Sweet dermatosis $n=1$, Kikuchi disease $n=1$, rheumatoid arthritis $n=1$, auto-immune thyroiditis $n=1$, severe psoriasis $n=1$,). Among them, one patient experienced a relapse of AIM concomitant to MDS onset (severe psoriasis). Past history of AIM was significantly lower in the control group ($n=7$, 6,4%, $p=0.013$). In the AIMs group, five patients had received a prior disease modifying anti-rheumatic drug (DMARD) treatment (Methotrexate $n=4$, Leflunomide $n=1$). No immunosuppressive therapy or biologics was recorded.

AIMs subtypes were classified as neutrophilic dermatosis $n=5$ (25%), systemic vasculitis $n=4$ (20%), organ-limited AIMs $n=4$ (20%), connective tissue disease $n=3$ (15%), inflammatory arthritis $n=3$ (15%) and immune cytopenia $n=1$ (5%). Three patients (15%) had incomplete classification criteria (Behcet like syndrome, giant cell arteritis, relapsing polychondritis). No undefined AIM was recorded. AIMs diagnosis are detailed in Table 2.

At AIMs diagnosis 17 patients (85%) presented with general symptoms, including fever $n=8$ (40%), weight loss $n=8$ (40%), anorexia $n=12$ (60%) or asthenia $n=15$ (75%). Furthermore, the main clinical manifestations in AIMs patients involved skin (60%), joints (45%), vessels (30%) (vasculitis in 20%, Raynaud syndrome in one patient (5%) and extensive veinous thrombosis associated with anti-phospholipid syndrome (APLS) and livedo in one patient (5%)), lungs (20%), digestive tract (20%) and kidneys (10%). No specific neurologic or cardiac involvement were observed.

Eleven patients (55%) presented with a non-infectious inflammatory syndrome (defined as a C Reactive protein (CRP) > 30 mg/dL), with a mean CRP level of 146 mg/dL (SD 97.8) at AIMs diagnosis. Presence of an inflammatory syndrome was more frequently observed in systemic vasculitis and neutrophilic dermatosis ($p=0.013$). Immunologic abnormalities were diverse: positive anti-nuclear factors ($n=5$), rheumatoid factor ($n=5$), complements anomalies ($n=2$), 12 weeks persistent APL-antibodies ($n=1$), and anti-CCP ($n=1$). No native DNA antibodies, cryoglobulinemia or ANCA positivity was observed. At least one biopsy was performed in fourteen patients (skin = 11, kidney = 2, muscle = 1) with informative results.

Hematologic characteristics:

Hematologic characteristics of each group are detailed in Table 1. MDS/CMML WHO classification at diagnosis were significantly different between the two groups ($p<0.001$). AIMs patients presented more frequently with CMML1 (35% vs 9.1%) or MDS with MLD (15% vs

3.6%). Controls more frequently presented as RAEB2 (45% vs 10%). RAEB1 repartition between the two groups was similar (30% vs 29%). No correlation was found between WHO classification and AIMS subtypes. Number of AZA cycles or prior bone marrow transplantation rates were similar between both groups.

At AZA onset, IPSS score was significantly different between the two groups ($p < 0.001$). In AIMS group, 48% of patients were low or intermediary-1 (Int-1) IPSS score versus 19% in control group. We observed a trend for IPSS-R ($p = 0.069$) with more low and very-low IPSS-R categories in the AIMS group. Consistently, bone marrow blasts were higher in the control group ($13.9 (\pm 8.58)$ vs $9.89 (\pm 7.58)$, $p < 0.01$) whereas monosomal karyotypes and IPSS-R cytogenetic prognosis were comparable between the two groups ($p = 0.43$ and 0.55 respectively). AML transformation rates were similar in both groups: 60% in AIMS group and 53% in control group ($p = 0.55$).

Cardiovascular and prior cancer:

Classical cardiovascular risk factors and history of major cardiovascular event repartition were homogenous between the two groups. Similarly, prior cancer, chemotherapy, radiotherapy and surgery rates were not statistically different in the two groups (Table 3).

Hospitalizations related to infections:

Percentage of patients who were hospitalized for at least one infection after MDS/CMML diagnosis was similar, 63% in the control group versus 55% in the AIMS group ($p = 0.55$). The mean number of hospitalizations, cumulative duration of hospitalizations, and death attributed to infections were similar in the two groups (Table 3).

AIMs treatments before AZA onset:

Eighteen patients had received a specific AIMS treatment (90%) before AZA onset. A patient with extra-membranous glomerulonephritis was treated only by anti proteinuric treatment and achieved complete remission without AIM treatment except AZA. A patient developed a Sweet syndrome after AZA introduction. Mean number of treatments used was 1.40 (SD 1.35).

As a first AIMS treatment line, fourteen patients received steroids (70%), alone $n = 9$ (45%) or in combination $n = 5$ (25%) with Cyclophosphamide ($n = 1$), Methotrexate ($n = 2$), Leflunomide ($n = 1$), or Etanercept ($n = 1$). Four patients received other AIMS treatments with no systemic steroids: Colchicine ($n = 1$), Salazopyrine ($n = 1$), topical steroids alone ($n = 2$). One patient with APL syndrome received an adjuvant curative heparinotherapy.

Among all AIMs patients, six (30%) required a second line treatment including steroids in 5, alone in 1 patient and combined in 4 patients, with Methotrexate n=2, Azathioprine n=1, plasma exchanges n=1.

Two patients (10%) required a third line treatment, always combined with steroids (Rituximab n=1, Polyvalent immunoglobulins n=1). One patient with severe relapsing dermatomyositis required a fourth line treatment by Cyclophosphamide.

AIMS response to AZA:

One patient developed Sweet syndrome during AZA treatment that resolved with steroids alone and was not included in the analysis of AIMs response to AZA. Patients data are detailed in Table 4.

At AZA onset, eleven patients (58%) did not achieved AIMs complete response. Six had achieved a partial response (two with steroid dependence). Five patients experienced failure in AIMs treatments (Behcet like syndrome, sweet syndrome, pyoderma gangrenosum, dermatomyositis and leucocytoclastic vasculitis) with four of them dependent to high dose steroids (30-70 mg/day). Eight patients had achieved a complete response with no steroid-dependence.

After 3 AZA cycles, each of the five patients who experienced failure in AIMs treatment were in partial remission and 4 patients already in partial remission experienced a complete remission.

At cycle 6, five patients had stopped AZA for toxicity (n=2), progression of MDS/CMML and treatment switch (n=2) or death (n=1). Two of the three remaining patients that initially failed in AIMs response maintained partial remission and one achieved complete remission.

Finally, among all patients, 9/19 (47%) showed an improvement with AZA. Among the patients that were not in remission at AZA onset, 9/11 (82%) showed an improvement in AIMs response.

Steroid-dependence after AZA:

At AZA onset, a total of 6/19 patients were steroid dependent (31,5%). Mean prednisone dosage in steroid dependent patients was 43,3 mg/d (SD 22,5) versus 1,43 mg/d (SD 2,3) in non-steroid dependent patients ($p<0.001$). In steroid-dependent patients, mean amount of daily prednisone decreased from 43,3 mg/d to 21,83 mg/d at cycle 3 (n=6) and to 10,2 mg/d at cycle 6 (n=5) with only one patient (5,5%) staying dependent to steroids. AZA allowed an improvement in AIMs response in all steroid dependent patients.

MDS/CMML response to AZA:

According to IWG MDS/CMML criteria, no statistical difference in MDS/CMML response to AZA was observed between the two groups ($p=0.69$). In the control group and the AImS group respectively, complete response was observed in 26% and 10%, stable disease in 25% and 35%, partial response in 7.3% and 10% and marrow complete response without hematologic improvement in 10% and 10% respectively. Other patients experienced progression. Among the six AImS steroid dependent patients at AZA onset, one patient achieved a prolonged complete response, one patient a marrow complete response, three patients a stable disease, and one patient experienced progression. No correlation was found between AImS response and MDS/CMML response to AZA.

Survival:

Median overall survival (OS) in the entire cohort was evaluated at 20,6 months (SD 3,7). We did not observe a significant difference in OS between AImS and control group. Median OS in AImS group was 28,7 months (SD 5,0) and 20,3 months (SD1,9) in controls ($p=0,517$). We did not observe any difference in OS among patients who presented at least one infection related hospitalization in comparison with those who did not ($p=0,571$). OS in the entire cohort was significantly altered in patients with prior cancer, with an OS of 17,4 months and 28,5 months in patients with no prior cancer ($p=0,029$). The influence of a history of major cardio-vascular event on OS was at the limit of statistical significance ($p=0,07$). Hematological characteristics such as IPPS-R and AML transformation were found to influence OS in the entire cohort ($p=0,003$ and $0,012$ respectively), whereas surprisingly, IPSS was at the limit of statistical significance ($p=0,058$) (Figure 2).

Discussion:

Although AImS association with MDS/CMML is well established, treatment strategies in steroid dependent or refractory patients remains challenging. To our knowledge, this work is the first to focus on AZA efficacy in AImS management in a “real-life” cohort of high-risk MDS/CMML. In our group of MDS/CMML related AImS, 58% of patients did not achieve a complete response with traditional AImS treatments before AZA ($n=11$). Among them, 82% showed an improvement after AZA introduction ($n=9$). Among all AImS patients, 47% showed an improvement in AImS response, with a remarkable decrease in steroid dependence rate (31,5% before and 5% after AZA). These results are concordant with those observed by Fraison et al. in a cohort of 22 MDS/CMML related AImS in whom AZA improved clinical signs of AImS in 86% of the cases and permitted a decrease in steroid dosage in 64% (7). Several

case reports are consistent with a positive influence of AZA in AIMs management (15–18). Yet, larger prospective trials are needed to confirm this hypothesis.

We did not identify any difference neither in overall survival, nor in AML transformation between the two groups as already underlined in several studies (8), with a similar response to AZA. Classical hematologic prognosis factors such as IPSS, IPSS-R and AML transformation had an influence on patients' outcomes.

Surprisingly, in the whole cohort, survival was not influenced by the occurrence of infectious related hospitalizations, maybe thanks to the effectiveness of modern antimicrobial strategies in immunocompromised hosts such as MDS/CMML or AIMs patients.

In addition, infectious related hospitalization rates and durations were similar in both groups, implying that infection rates and intensity did not seem affected by immunosuppressive or steroid treatments received by AIMs patients. This could be explained by the aggressiveness of hematologic malignancies themselves in higher risk MDS/CMML, leading to an equivalent level of immunosuppression in which AIMs themselves or treatments may have a lower impact. Prior cancer or cardiovascular event were related to a worse outcome, highlighting the fact that comorbidities and past medical history may have a greater influence on survival than AIMs or treatment related complications. Therapy related MDS/CMML are known to be associated to poorer karyotypes, treatment response and outcome (19,20). We did not exclude patients that had priorly received genotoxic therapies, to stay close to a “real-life” cohort. The repartition of therapy related MDS/CMML was similar in both groups as prior cancer, chemotherapy or radiotherapy use was comparable in each group.

In our study, CMML-1, RAEB-1 and MDS-MLD, were the most frequent WHO subtypes associated with AIMs at MDS/CMML diagnosis, consistently with Mekinian et al. (15). AIMs patients also presented with more favorable prognosis factors at AZA introduction (WHO subtypes and IPSS) supporting the idea that in a real-life management, AIMs could have favored an earlier introduction of AZA. On the other hand, AIMs clinical manifestations may have favored earlier medical explorations and diagnosis of MDS/CMML in some cases. Yet, more favorable IPSS in AIMs group at AZA onset and the absence of difference in OS between the two groups may underline a lack of power from our study.

Consistently with published data, no correlation was found between timing of AIMs emergence and AIMs subtype or WHO classification. In the whole AIMs group, main clinical manifestations at diagnosis were consistent with literature data, with a predominance of general symptoms with fever, skin and joints involvement (6,8).

A 77 year-old male presented with franc deterioration of general status, fever, arthralgias, mouth and genital sores and diarrhea related to terminal ileitis. Colonoscopy and histopathology were non consistent with Crohn's disease. Karyotype showed trisomy 8 that lead us to diagnose a Behcet-like syndrome as previously described in literature with typical

digestive involvement (21–23). Interestingly, we observed two cases of MDS/CMML related nephrotic syndromes, one extra-membranous glomerulonephritis (EMG) and one membranoproliferative glomerulonephritis (MPGN). MPGN patient met partial response with steroid dependence and anti-proteinuric treatment and achieved complete response after AZA treatment. Association between MDS/CMML and glomerulonephritis seems rare but described in case reports (24). EMG patient experienced a complete response with exclusive anti-proteinuric treatment before AZA introduction, raising the doubt of a fortuitous association.

To assess the efficacy of AZA towards AIMs, we included patients that had received AZA treatment for MDS/CMML treatment. This made our recruitment different from those found in other works about MDS/CMML related AIMs. For comparison, patients with Int-2 or High IPSS represented 71% of our cohort, but only 18% in Segulier et al. and 26% in Mekinian et al. cohorts (8,15). Fraison et al. focused on 22 MDS/CMML related AIMs patients treated by AZA but with no control group, Int-2 and High IPSS represented as low as 50% of their patients (7). In our cohort, both AIMs and control group presented with a male predominance and with a similar age repartition. These findings contrast with other works where AIMs patients appeared younger (15,25) and without male predominance (25,26) as usually known in MDS (27). In Fraison's cohort, a male predominance was noted (73%), consistently with our results, suggesting that in higher risk MDS/CMML, AIMs may prevail in men (7).

The distribution of AIMs subtypes was different from that observed by Mekinian et al. and Segulier et al. (8,15). We observed a higher prevalence of neutrophilic dermatosis (25% compared to 10% and 11% respectively). Consistently, in the largest retrospective cohort by Mekinian et al, neutrophilic dermatosis was statistically associated with higher risk MDS/CMML. Conversely, we observed lower rates of connective tissue diseases and inflammatory arthritis that were associated to lower risk MDS/CMML, under-represented in our cohort.

We observed only one case of immune cytopenia, whereas Segulier et al. observed a prevalence of 15% in their 81 patients' cohort. This difference could underline the fact that immune cytopenias may prevail in association with low risk MDS/CMML and may be more challenging to detect in higher risk patients with forefront major cytopenias.

Systemic vasculitis repartition among MDS/CMML varies from 4-60% of AIMs subtypes according to different series (8) and are known to be associated to CMML(15,28). Vasculitis represented 20% of AIMs in our cohort and CMML were highly represented but a lack of power may explain the absence of statistical association between AIMs subtypes and MDS/CMML WHO classification or risk groups.

In their literature review, Segulier et al. underlined the important discrepancies in AIMs subtype repartition among different works. The combination of an important heterogeneity in patient

phenotypes, AIMS subtype classifications, inclusion criteria and the retrospective methods used in most works may induce an important variability in AIMS identification.

In our cohort, no undefined AIMS were retained, due to the difficulty in retrospectively ruling out differential diagnosis to undefined clinical manifestations and the will to include only patients with authentic AIMS.

As previously underlined, the retrospective design and the small number of patients constitute the principal weaknesses of our work. Nevertheless, our study is the first to compare a real-life cohort of predominantly high risk MDS/CMML AZA treated patients with or without AIMS.

Conclusion

AIMs are commonly associated to high-risk MDS/CMML with various presentations. Although the presence of AIMS does not impact neither OS nor progression to AML, their management is crucial to improve patients' quality of life and to avoid serious or fatal complications of AIMS. Increasing evidence suggests that MDS/CMML specific therapies such as AZA, based on their immunomodulatory effect, may be effective in treating AIMS and sparing steroids concomitantly to MDS/CMML disease control. Larger and prospective studies are needed to address the place of AZA and to help physicians to choose the best therapeutic strategy.

Tables and figures:

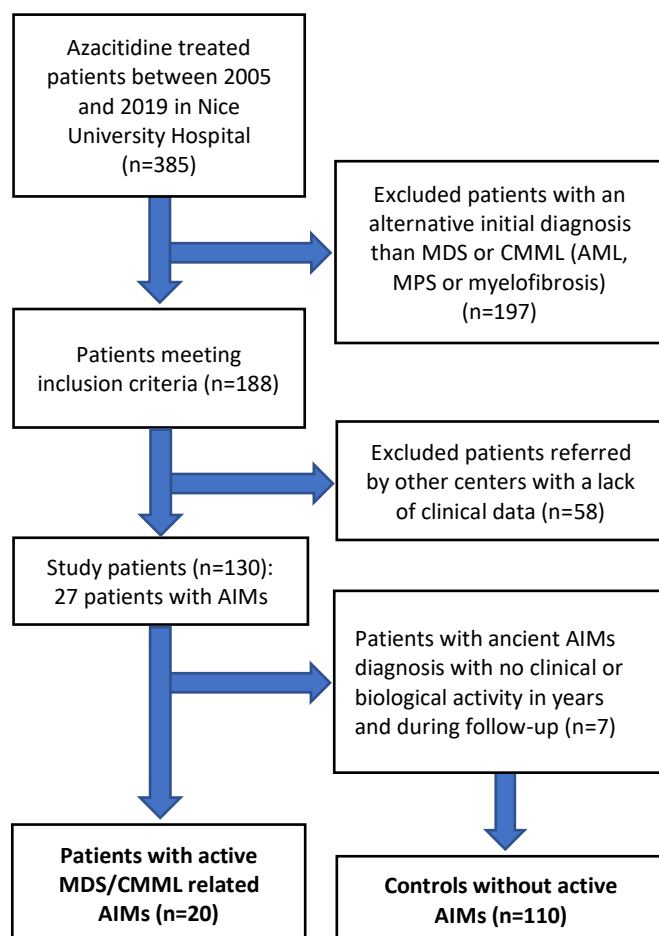


Figure 1 : Inclusion flow chart

MDS: myelodysplastic syndroms, CMML : chronic myelomonocytic leukaemia, AML : acute myeloïd leukaemia, MPS : myeloproliferative syndrom, AIMs : Autoimmune or inflammatory manifestations

		Controls, n=110 (%)	AIMs, n= 20 (%)	p
Age at diagnosis, mean (\pm SD)		69.2 (\pm 9.69)	68.0 (\pm 9.25)	0.51
Sexe, n (%)	Male	66 (60%)	12 (60%)	1
	Female	44 (40%)	8 (40%)	
Performans status,	0	38 (36%)	8 (40%)	0.91
	1	49 (46%)	8 (40%)	
	2	17 (16%)	4 (20%)	
	3	3 (2.8%)	0 (0%)	
Anterior MDS treatment, mean (\pm SD)		0.436 (\pm 0.873)	0.550 (\pm 1.15)	0.85
Allo-HSC graft, n(%)		22 (20%)	4 (20%)	1
Delay diagnosis – AZA		16.4 (\pm 35.2)	18.9 (\pm 26.1)	0.098
Nb AZA cycles, mean		11.5 (\pm 11.6)	13.8 (\pm 14.6)	0.72
WHO 2016 at diagnosis, n(%)	RAEB2	50 (45%)	2 (10%)	<0.01
	RAEB1	32 (29%)	6 (30%)	
	CMML1	10 (9.1%)	7 (35%)	
	MDS MLD	4 (3.6%)	3 (15%)	
	MDS SLD	4 (3.6%)	1 (5%)	
	CMML2	3 (2.7%)	1 (5%)	
	MDS Del(5q)	3 (2.7%)	0 (0%)	
	MDS U	3 (2.7%)	0 (0%)	
	MDS RS SLD	1 (0.91%)	0 (0%)	
	RAEB2	74 (67%)	9 (45%)	
	RAEB1	17 (15%)	4 (20%)	
	AML MLD	16 (15%)	2 (10%)	
WHO 2016 at AZA onset, n(%)	CMML2	1 (0.91%)	2 (10%)	<0.01
	AML	1 (0.91%)	1 (5%)	
	GS	0 (0%)	1 (5%)	
	MDS MLD	0 (0%)	1 (5%)	
	MDS U	1 (0.91%)	0 (0%)	
	Blast BM %, mean	13.9 (\pm 8.58)	11.3 (\pm 9.76)	
	IPSS, n(%)	42 (42%)	4 (20%)	
	Intermediate-2	39 (39%)	7 (35%)	
IPSS-R category, n(%)	Intermediate-1	19 (19%)	5 (25%)	0.075
	Low	0 (0%)	4 (20%)	
	Very high	24 (22%)	4 (20%)	
	High	53 (49%)	8 (40%)	
	Intermediate	28 (26%)	5 (25%)	
IPSS-R score, mean	Low	3 (2.8%)	1 (5%)	0.15
	Very low	0 (0%)	2 (10%)	
	IPSS-R karyotype prognosis, n(%)	5.45 (\pm 1.60)	4.70 (\pm 1.87)	
	Good	55 (56%)	13 (68%)	
	Intermediate	22 (22%)	2 (11%)	
Monosomal karyotypes, n(%)	Very poor	11 (11%)	2 (11%)	0.7
	Poor	9 (9.2%)	1 (5.3%)	
	Very good	1 (1%)	1 (5.3%)	
AML progression, n(%)		58 (53%)	12 (60%)	0.55
Follow-up, mean, months (SD)		38.8 (\pm 43.0)	43.2 (\pm 33.4)	0.1
Death, n(%)		69 (63%)	11 (55%)	0.51

Table 1: Baseline demographical and hematological characteristics in AIMS and control groups.

AIMs: auto immune or inflammatory manifestations, HSC: hematopoietic stem cells, AZA: Azacitidine, WHO : world health organization, MDS: myelodysplastic syndrome, SLD: single lineage dysplasia, MLD: multilineage dysplasia, RS : ring-sideroblast, U : undefined, RAEB : refractory anemia with excess blasts, CMML : chronic myelomonocytic leukemia, GS : granulocytic sarcoma, AML : acute myeloid leukemia, BM : bone marrow, IPSS: International Prognosis Scoring System, IPSS-R : IPSS-Revised

AIMs Subtype	Diagnosis	
Neutrophilic dermatosis n=5, (25%)	Sweet syndrome (n=3)	(+)
	Pyoderma Gangrenosum (n=2)	(+)
Vasculitis, n=4 (20%)	Behcet-like syndrome (n=1)	(-)
	Giant cell arteritis (n=1)	(-)
	Polyarteritis nodosa (n=1)	(+)
	Leucocytoclastic vasculitis (n=1)	(+)
Organ limited AIM, n=4 (20%)	Psoriasis (n=2)	(+)
	Nephrotic syndrome (n=2)	(+)
Connective tissue disease, n = 3 (15%)	Relapsing polychondritis (n=1)	(-)
	Dermatomyositis n=1)	(+)
	Anti-phospholipid syndrome (n=1)	(+)
Inflammatory arthritis, n=3 (15%)	Rheumatoid arthritis (n=1)	(+)
	RS3PO (n=1)	(+)
	Spondyloarthritis (n=1)	(+)
Immune cytopenia, n=1 (5%)	Immune thrombocytopenic purpura (n=1)	(+)

Table 2: AIMs diagnosis and classification

The (+) sign indicates complete classification criteria, (-) indicates incomplete classification criteria

AIM: auto immune or inflammatory manifestation, RS3PO: Remitting seronegative symmetrical synovitis with pitting oedema.

	Controls n=110 (%)	AIMS n=20 (%)	p
Before MDS/CMML cardio vascular events:			
Hypertension n(%)	49 (45%)	5 (25%)	0.096
Diabetes, n(%)	16 (15%)	3 (15%)	1
Dyslipidemia, n(%)	33 (30%)	5 (25%)	0.63
Tobacco use, n(%)	37 (35%)	6 (32%)	0.78
Obesity, n(%)	7 (10%)	1 (5%)	0.68
Major CV event, n(%)	22 (20%)	2 (10%)	0.37
Thromboembolic venous event, n(%)	7 (7.7%)	2 (11%)	0.64
Before MDS/CMML history of cancer:			
Cancer history, n(%)	29 (27%)	4 (20%)	0.53
Active solid cancer, n(%)	11 (41%)	1 (25%)	1
Delay cancer – MDS/CMML, months (SD)	97.7 (±84.9)	72.0 (±67.8)	0.6
Chemotherapy, n(%)	19 (68%)	2 (50%)	0.59
Radiotherapy, n(%)	10 (36%)	3 (75%)	0.28
Surgery, n(%)	15 (56%)	3 (75%)	0.62
After MDS/CMML diagnosis history of infections:			
Infection related hospitalization	68 (63%)	11 (55%)	0.5
Nb infection related hospitalization, n(SD)	2.40 (±1.59)	3.09 (±2.02)	0.25
Mean hospitalization time, days (SD)	12.7 (±9.32)	13.0 (±7.33)	0.65
Hospitalization cumulative duration, days (SD)	28.6 (±21.3)	34.2 (±18.1)	0.21
Infectious cause of death	30 (36%)	2 (14%)	0.13

Table 3: Comparative data about cardiovascular events, prior cancer and infectious complications in both groups

AIMs: auto immune or inflammatory manifestations, CV: cardiovascular, Nb: number.

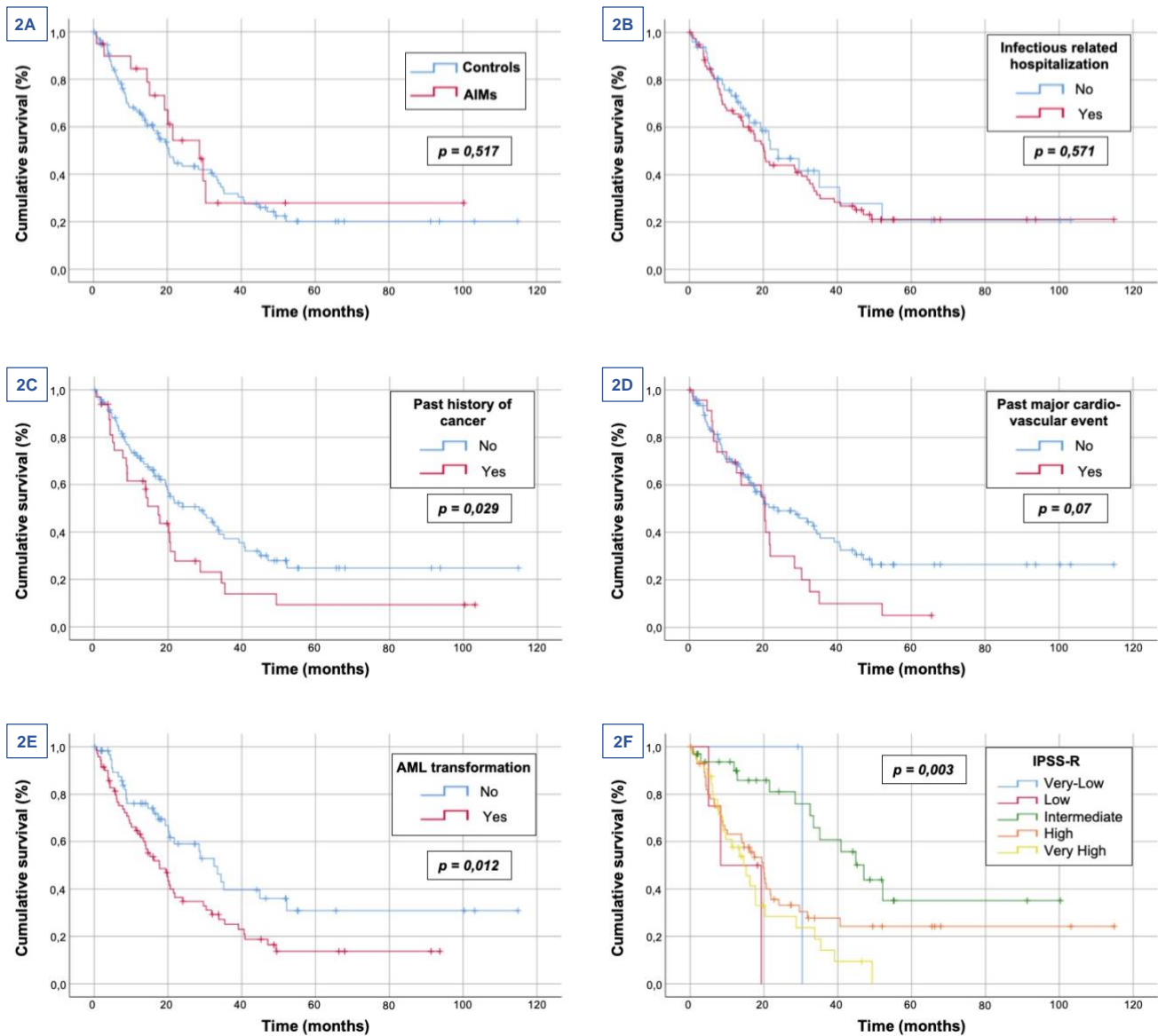


Figure 2: Overall survival from MDS/CMML diagnosis according to different parameters:

- 2A:** OS in patients with or without AIMs
- 2B:** OS in patients with or without infection related hospitalization
- 2C:** OS in patients with or without prior cancer
- 2D:** OS in patients with or without prior major cardiovascular event
- 2E:** OS in patients with or without AML transformation
- 2F:** OS regarding IPSS-R category

N, Age at MDS/CMML diagnosis, gender	WHO at AZA onset	IPSS	AIM subtype	AIM diagnosis	Temporal association	Anterior AIMS treatments	Best IWG response	Steroid dependence at AZA onset	AIM status at AZA onset	Prednisone dose at AZA onset (mg/j)	AIM status at AZA cycle 3	Steroid dependence after cycle 3	Prednisone dose after cycle 3 (mg/d)	AIM status at AZA cycle 6	Steroid dependence after cycle 6 (yes/no)	Prednisone dose after cycle 6 (mg/d)
1. 53(F)	RAEB2	Int-1	CTD	Myositis	Concomitant	Steroids/MTX/Pex IgIV/CYC	Marrow CR	1	F	60	PR	1	20	PR	1	20
2. 54(F)	RAEB1	Int-1	ND	PG	Concomitant	Steroids	Stable D	1	F	70	PR	0	30	CR	0	10
3. 58(F)	CMML2	Int-2	ND	Sweet	Secondary	Steroids	Stable D	1	F	30	PR	1	25	(Toxicity)		
4. 59(M)	AML MLD	High	Vasc	Leuc vasc	Concomitant	Steroids	Stable D	1	F	60	PR	1	45	PR	0	17,5
5. 72(M)	RAEB1	Low	CTD	APLS	Concomitant	Steroids	CR	1	PR	20	CR	0	10	CR	0	7
6. 75(M)	RAEB1	Low	OL	MPGN	Concomitant	Steroids	Progression	1	PR	20	CR	0	10	CR	0	7,5
7. 58(M)	RAEB2	Int-2	OL	Psoriasis	Old	Steroids/Eta/Ada	NE	0	CR	0	CR	0	0	(Progression)		
8. 62(M)	RAEB2	Int-2	IA	SPA	Recent	Salazo	Stable D	0	PR	0	PR	0	0	PR	0	0
9. 63(M)	GS	Int-1	OL	EMG	Recent	Anti Pu	Marrow CR	0	CR	0	CR	0	0	CR	0	0
10. 64(M)	RAEB2	Int-1	OL	Psoriasis	Concomitant	Topical S	Stable D	0	PR	0	CR	0	0	CR	0	0
11. 66(F)	RAEB2	High	ND	PG	Recent	Steroids/MTX/RTX	Stable D	0	PR	5	CR	0	0	CR	0	0
12. 66(M)	AML	High	IA	RA	Recent	Steroids/Lef/MTX	NE	0	CR	0	CR	0	0	CR	0	0
13. 72(F)	RAEB2	Int-2	IC	ITP	Concomitant	Steroids	CR	0	CR	5	CR	0	0	CR	0	0
14. 75(M)	RAEB2	Int-2	CTD	RP	Concomitant	Steroids	PR	0	CR	5	CR	0	0	CR	0	0
15. 77(F)	RAEB2	Int-2	Vasc	GCA	Secondary	Steroids	Stable D	0	CR	0	CR	1	40	CR	0	0
16. 77(F)	AML MLD	High	Vasc	PAN	Concomitant	Steroids/CYC/Azat	Progression	0	CR	0	(Death)					
17. 77(M)	RAEB1	Int-1	Vasc	Behcet	Secondary	Colchicine	Stable D	0	F	0	PR	0	0	(Toxicity)		
18. 79(M)	CMML2	Low	IA	RS3PO	Secondary	Steroids	Progression	0	CR	5	CR	0	5	CR	0	0
19. 88(M)	MDS MLD	Low	ND	Sweet	Concomitant	Topical S	Progression	0	PR	0	(Progression)					
20. 55(F)	RAEB2	Int-2	ND	Sweet	Concomitant	None	PR	0	(Sweet syndrome developed after AZA onset that resolved with steroids)							

Table 4: AIMS group patients characteristics before and after AZA treatment

RAEB: refractory anemia with excess blasts, CMML: chronic myelomonocytic leukemia, AML: acute myeloid leukemia, MLD: multilineage dysplasia, GS: granulocytic sarcoma, MDS : myelodysplastic syndrome, CTD: connective tissue disease, ND: neutrophilic dermatosis, Vasc: systemic vasculitis, OL: Organ-limited AIM, IA: inflammatory arthritis, IC: immune cytopenia, APLS: anti-phospholipid syndrome, MPGN: membrane-proliferative glomerulonephritis, SPA: spondyloarthritis, EMG: extra-membranous glomerulonephritis, PG: pyoderma gangrenosum, RA: rheumatoid arthritis, ITP: immune thrombocytopenia, RP: relapsing polychondritis, GCA: giant cell arteritis, PAN: periarteritis nodosa, RS3PO: remitting seronegative symmetrical synovitis with pitting oedema., MTX : methotrexate, Pex: plasma exchanges, IgIV: intravenous polyvalent immunoglobulins, CYC: cyclophosphamide, Eta: etanercept, Ada: adalimumab, Salazo : salazopyrine, Anti Pu : anti-proteinuric treatment, Topical S: topical steroids, RTX : rituximab, Lef : leflunomide, Azat : azathioprine, CR: complete response, Stable D: stable disease, PR: partial response, NE: non evaluable, F: failure

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