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Use of 5-azacitidine for therapy-related myeloid neoplasms in patients with concomitant active neoplastic disease

M. Annereau[a,1], C. Willekens[b,1], L. El Halabi[b], C. Chahine[b], V. Saada[c], N. Auger[c], A. Danu[b], E. Bermudez[a], J. Lazarovici[b], D. Ghez[b], A. Leary[d], B. Pistilli[d], F. Lemare[a], E. Solary[b,e], S. de Botton[b,e], R.-P. Desmaris[a,1], J.-B. Micol[b,e,*,1]

[a] Gustave Roussy, Université Paris-Saclay, Département de Pharmacie, Villejuif F-94805, France
[b] Gustave Roussy, Université Paris-Saclay, Département d'hématologie, Villejuif F-94805, France
[c] Gustave Roussy, Université Paris-Saclay, Département de biologie et pathologie médicales, Villejuif F-94805, France
[d] Gustave Roussy, Université Paris-Saclay, Département de médecine oncologique, Villejuif F-94805, France
[e] Inserm UMR1170, Gustave Roussy, Université Paris-Saclay, Villejuif F-94805, France

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ABSTRACT

Background: Patients diagnosed with therapy-related myeloid neoplasms (TRMN) with concomitant active neoplastic disorder (CAND) are usually proposed for best supportive care (BSC). We evaluated the feasibility of using 5-azacytidine (AZA) in this setting.
Methods: All patients referred to Gustave Roussy between 2010 and 2015 for TRMN diagnosis (less than 30% blast) and eligible for AZA treatment were included. Patients with CAND proposed for BSC were also described. Patient's outcomes were analyzed based on the presence or not of a CAND.
Results: Fifty-two patients with TRMN were analyzed, including 19 patients with CAND (14 eligible for AZA) and 33 without CAND eligible for AZA. The 5 patients with CAND ineligible for AZA had a worst performance status ($p = 0.016$) at diagnosis and a shorter overall survival (OS) (0.62 months). Baseline characteristics of patients eligible for AZA were similar in the 2 groups except a trend for best performance status in patients with CAND ($p = 0.06$). Overall response rate (71.4% vs 60.3%), transfusion independence (50.0% vs 45.5%) and OS (12.7 months vs 10.8 months) were similar between patients with and without CAND respectively ($p = ns$).
Conclusion: Here we report the feasibility and efficacy of AZA for selected patients with TRMN and a CAND.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis leading to blood cytopenias and risk of progression to acute myeloid leukemia (AML). Hypomethylating agents, such as 5-azacitidine (AZA) and decitabine, are the standard of care for high-risk MDS patients (as defined by the IPSS score) [1] unfit for intensive chemotherapy and ineligible for allogeneic stem cell transplantation. These treatments have been shown to prolong overall survival [2] and improve quality of life compared to best supportive care (BSC) [3]. The most common adverse events associated with hypomethylating agents are peripheral blood cytopenias, gastrointestinal toxicity and injection site reactions with subcutaneous injections of AZA [4], but these treatments are usually well tolerated.

Therapy-related myeloid neoplasms (TRMN) include therapy-related AML (t-AML) and therapy-related MDS (t-MDS) arising after cytotoxic chemotherapy (alkylating agents and topoisomerase II inhibitors) and/or radiotherapy administered for a prior neoplasm. Alkylating agent related t-MDS/AML are usually associated with adverse cytogenetic features, including chromosome 5 and 7 abnormalities, complex karyotype, *TP53* mutations or deletions. t-AML/MDS with abnormalities of chromosome 11q23 are more common in patients exposed to topoisomerase II inhibitors [5]. Unfortunately these patients have a short median survival [6]. Recently some authors reported the feasibility and efficacy of AZA

* Corresponding author at: Department of Hematology, Gustave Roussy, Université Paris-Saclay, 114 Rue Edouard Vaillant, Villejuif F-94805, France.
E-mail address: jeanbaptiste.micol@gustaveroussy.fr (J.-B. Micol).
[1] These authors contributed equally to this work.

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in cases of TRMN, with similar results as seen in de novo MDS patients [7–10].

At diagnosis of t-MDS/AML, some patients may present a concomitant active neoplastic disorder (CAND). Given that these patients are usually ineligible for allograft or clinical trials and that cytopenias prohibit treatment of the concomitant neoplastic disorder, BSC is often provided. Tolerability and efficacy of specific treatments for t-MDS/AML in these hopeless situations have never been described. We report here our experience in treating patients diagnosed with high-risk t-MDS/AML and CAND with AZA.

2. Patients and methods

2.1. Patients

Patients treated with at least 1 cycle of AZA in our hematology unit for t-MDS or t-AML (with 20–30% blasts), from January 2010 to December 2015, were retrospectively studied. Patients with CAND proposed for BSC were also described as a control group. t-MDS/AML was defined according to WHO 2016 classification [10].

Patients with t-MDS/AML eligible for AZA treatment were separated into 2 cohorts: patients with a CAND (solid tumor, lymphoma, or myeloma) and patients with a previous history of solid tumor or lymphoma in complete remission (CR). Patients with a previous myeloproliferative neoplasm were excluded.

CAND was defined by the presence of prior cancer metastasis at diagnosis of t-MDS/AML or diagnosis of t-MDS/AML during treatment (chemotherapy, radiotherapy or monoclonal antibody) for solid cancer or lymphoma not in CR. Patients in CR treated with hormonal therapy were not considered as CAND. Characteristics of the prior and concomitant cancer were retrospectively assessed at the time of t-MDS/AML diagnosis.

2.2. Treatment and toxicity

AZA was administered subcutaneously at the approved FDA/EMA indication and dosing (75 mg/m^2 during 7 days every 28 days). A dose adjustment with a 5-day schedule was applied in some patients in case of response. Delay between AZA cycles was defined as the time between the day 1 of AZA cycle and day 1 of the next cycle of AZA.

Concomitant treatment used for the CAND (chemotherapy, radiotherapy, monoclonal antibody) during AZA therapy was also assessed. Toxicity, especially transfusion requirements, and subsequent AZA schedule modifications were evaluated. A t-student test was performed to compare AZA cycle delay between t-MDS/AML patients with CAND and t-MDS/AML patients with previous cancer in remission.

2.3. Outcome

Hematological response was evaluated at best time point by peripheral blood count, bone marrow aspiration, cytogenetic studies, and transfusion requirement according to the IWG 2006 criteria [11]. Overall response rate (ORR) was defined by the addition of complete response (CR), partial response (PR), marrow CR (mCR), and stable disease (SD) with hematological improvement (HI), according to IWG 2006 criteria. Overall survival (OS) was calculated from the date of t-MDS/AML diagnosis to the date of death from any cause. Surviving patients were censored at last known contact date. Causes of death were separated in deaths related to t-MDS/AML, deaths related to the prior cancer/CAND, and death due to infections. OS curves were estimated using the Kaplan-Meier method and compared using a log rank test with a p-value of 0.05 or less considered significant. All statistical tests were carried out with the STATA® software 12.

3. Results

3.1. Baseline characteristics of patients with CAND

Fifty-two patients with t-MDS/AML were analyzed. Five patients who presented TRMN with CAND proposed for BSC were described (Table 1) and compared to patients with TRMN with CAND eligible for AZA. Performance status of these 5 patients was worst (p = 0.016) despite no differences in the staging of TRMN. Patients eligible for AZA were next divided into 2 groups depending on the presence of CAND. Baseline and hematological characteristics of the patients are reported in Table 1. The two populations were similar except in ECOG status at baseline with a trend for better ECOG status in t-MDS/AML with CAND (p = 0.06).

Fourteen patients presented t-MDS/AML with CAND were eligible for AZA. Patients characteristics and treatments are described in details Table 2. Median age was 68.4 years (range: 47.9–84.5), CAND included breast cancer (n = 4), ovarian cancer (n = 4), non-Hodgkin lymphoma (n = 2), multiple myeloma (n = 1), lung cancer (n = 1), sarcoma (n = 1) and neuroendocrine pancreatic tumor (n = 1). Previous treatment of CAND consisted of chemotherapy-alone in 5 patients (35.7%), radiotherapy alone in 2 patients (14.3%), or both in 7 patients (50%). The median number of prior lines of treatment for CAND was 5 (range: 1–9). Median interval from primary cancer to diagnosis of t-MDS/AML was 5.9 years (range: 2.3–27.4).

t-MDS/AML patients were subdivided according to WHO classification as refractory cytopenia with multilineage dysplasia (RCMD; n = 1), refractory anaemia with excess of blasts (RAEB-1; n = 3), RAEB-2 (n = 8), and AML with 20–30% blasts (n = 2). Cytogenetic analysis was normal in 2 patients, complex in 4 patients, and monosomal in 7 patients (for the last patient the karyotype was not conclusive (failure of standard R-banding)). Chromosome 5 (-5/del(5q)) and 7 abnormalities (-7/del(7q)) were found in 3 patients and 7 patients respectively.

3.2. Treatment in t-MDS/AML patients with CAND

Among the 14 patients with CAND, 10 patients had metastatic solid cancer, 3 patients had an active lymphoid malignancy and 1 an active solid cancer. Six patients were concomitantly treated for the CAND in combination with AZA. Timeline of the co-administration is detailed Fig. 1 and Supplementary Fig. S1. Concomitant treatments for CAND included monoclonal antibody alone for 2 patients (bevacizumab [patient 3, Supplementary Fig. S1A] and rituximab [patient 4, Supplementary Fig. S1B]), chemotherapy for 3 patients (1 patient received liposomal doxorubicin followed by paclitaxel, cisplatin, and bevacizumab [patient 1, Fig. 1A]; 1 paclitaxel plus trastuzumab [patient 5, Supplementary Fig. S1C] and the last one received carboplatin [patient 6, Supplementary Fig. S1D]) and proteasome inhibitor (bortezomib, patient 2, Fig. 1B) respectively. For one patient (patient 5), AZA was suspended during chemotherapy treatment. Two patients received radiotherapy during AZA treatment as antalgic treatment (patient 7) or local treatment (patient 8, cutaneous localisation of the NHL) and 4 others received hormonotherapy. Interestingly all the patients receiving a treatment active for the CAND were responders to AZA (including 4/6 in CR) compare to 4/8 responders for others patients.

3.3. Treatment results and toxicities in t-MDS/AML patients with CAND

t-MDS/AML patients with CAND received a median number of 9 cycles of AZA (range: 1–34). No unusual toxicities were seen