Leukemia Research 43 (2016) 13–17

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia

Jean-Baptiste Fraison[a,*,1], Arsène Mekinian[b,1], Eric Grignano[c], Jean-Emmanuel Kahn[d], Jean-Benoit Arlet[e], Olivier Decaux[f], Guillaume Denis[g], Anne-Laure Buchdahl[h], Mohamed Omouri[i], Gwenola Maigne[j], Achille Aouba[j], Nathalie Leon[k], Sabine Berthier[l], Eric Liozon[m], Sophie Park[n], Claude Gardin[o], Olivier Lortholary[p], Julien Rossignol[c], Pierre Fenaux[q], Olivier Fain[b,1], Thorsten Braun[o,1]

[a] Service de Médecine Interne, Hôpital Jean Verdier, Assistance Publique des Hôpitaux de Paris, Université Paris XIII, France
[b] Service de Médecine Interne, DHU i2B, Inflammation-Immunopathologie-Biothérapie (DHU i2B), Hôpital Saint Antoine, Assistance Publique des Hôpitaux de Paris, Université Paris VI Sorbonne, 75012 Paris, France
[c] Service d'hématologie, Institut de Cancérologie Gustave Roussy, 94800 Villejuif, France
[d] Service de Médecine Interne, Hôpital Foch, Suresnes, France
[e] Service de Médecine Interne, Hôpital Européen Georges Pompidoux, Université Paris V, Paris, France
[f] Service de Médecine Interne, Centre Hospitalier Universitaire de Rennes, France
[g] Service de Médecine Interne, Centre Hospitalier de Rochefort, France
[h] Service de Médecine Interne, Centre Hospitalier de Douai, France
[i] Service de Rhumatologie, Centre Hospitalier de Romilly, France
[j] Service de Médecine Interne, Centre Hospitalier Universitaire de Caen, France
[k] Service de Rhumatologie, Centre Hospitalier Universitaire de Caen, France
[l] Service de Médecine Interne, Centre Hospitalier Universitaire de Dijon, France
[m] Service de Médecine Interne, Centre Hospitalier Universitaire de Limoges, France
[n] Service d'Hématologie, Centre Hospitalier Universitaire de Grenoble, France
[o] Service d'Hématologie, Hôpital Avicenne, Université Paris XIII, Bobigny, France
[p] Service de Maladies Infectieuses, Hôpital Necker, Université Paris V, Paris, France
[q] Service d'Hématologie, Hôpital Saint Louis, Université Paris VII, Paris, France

ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form 4 February 2016
Accepted 14 February 2016
Available online 20 February 2016

Keywords:
Azacitidine
Myelodysplastic syndromes
Auto immune disorders

ABSTRACT

This retrospective study describes efficacy of Azacitidine on autoimmune disorders (AID) associated with MDS/CMML in 22 patients. Response of AID to Azacitidine was observed in 19 patients (86%). Reduction or discontinuation of steroids and/or immunosuppressive therapy (IST) was possible in 16 cases (73%). Hematologic response was seen in 55% of the patients. MDS/CMML and AID evolution was concordant in 13 cases (59%): both favorable (n = 11), both unfavorable (n = 2), but AID improved while MDS/CMML worsened (n = 8) and vice versa (n = 1). Azacitidine frequently seems effective in controlling steroid-dependent AID associated with MDS/CMML, but prospective studies are necessary to confirm those findings.

1. Introduction

Autoimmune disorders are observed in 10–30% of MDS and CMML, typically diagnosed concomitantly or shortly before or after MDS/CMML [1].

Most common AID associated with MDS/CMML include relapsing polychondritis, vasculitis, non-erosive and seronegative arthritis [2,3] and Sweet's syndrome [4]. While AID associated with MDS/CMML usually respond to corticosteroids [2], many patients

* Corresponding author at: Service de Médecine Interne, Av du 14 Juillet, Hôpital Jean Verdier, APHP, Université Paris XIII, 93140 Bondy, France.
E-mail addresses: jeanbaptiste.fraison@aphp.fr, jbfraison@gmail.com (J.-B. Fraison).
[1] Contributed equally to this work.

http://dx.doi.org/10.1016/j.leukres.2016.02.005
0145-2126/

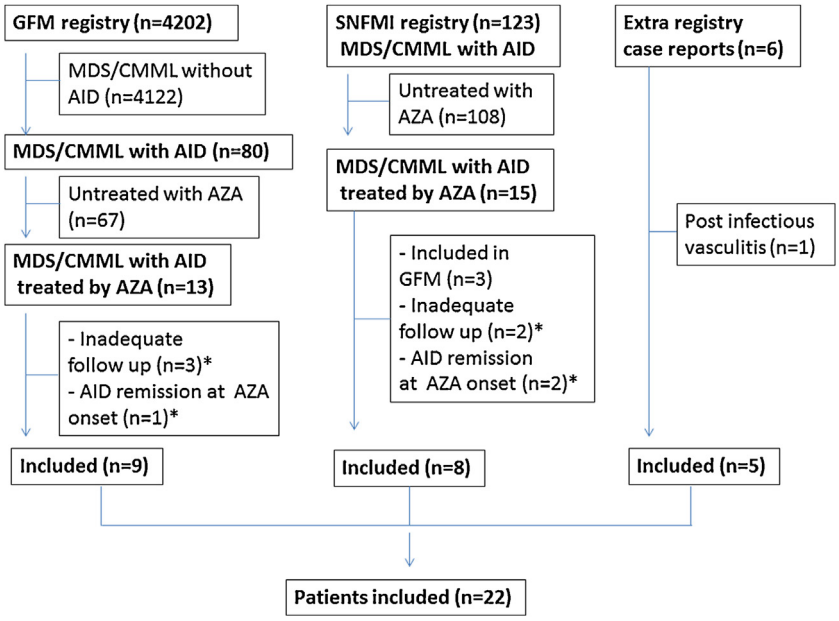

Fig. 1. Patient flow chart.

remain steroid dependent or resistant, requiring additional IST, a situation which increases the risk of severe cytopenias and infections in the context of MDS/CMML [1].

Azacitidine significantly improves survival in higher risk MDS [5] and in myelodysplastic type CMML [6,7] and is also approved outside Europe for the treatment of lower risk MDS. Eight patients with MDS/CMML and AID treated with Azacitidine have been reported to our knowledge [8–12].

2. Methods

We retrospectively analyzed the efficacy of Azacitidine in MDS/CMML patients with concomitant AID seen between 2007 and May 2014 in registries of the Société Nationale Française de Médecine Interne (SNFMI) and of the Groupe Francophone des Myélodysplasies. The SNFMI registry included 123 MDS/CMML patients with AID in 26 centres) [13], while the GFM registry included 4202 MDS/CMML in 30 centres of whom 80 also had documented AID. The GFM registry has been so far the basis for many publications of the GFM or that included the GFM [14–16].

Inclusion criteria for the present study were (i) complete or atypical AID according to usual international criteria [17], (ii) MDS or non-proliferative CMML (i.e., with WBC < 13G/L), classified according to WHO 2008 criteria [18] but also including patients with up to 30% marrow blasts, (iii) treatment with at least one cycle of Azacitidine.

Patients were excluded if AID were caused by infectious disease, AID were in remission without steroids or IST at Azacitidine onset, or if IST was administered more than 12 months before diagnosis of MDS, suggesting MDS secondary to IST.

Complete/partial remission (CR/PR) of AID after Azacitidine were defined by complete/partial disappearance of clinical or biological signs with stable dose or decrease/discontinuation of steroids or IST, as previously defined [2]. Hematological response to Azacitidine was classified according to IWG 2006 criteria [18].

For statistical analysis, Wilcoxon test was used for analysis of paired quantitative variables and Fisher's exact test for paired qualitative variables using R 3.2.1 (2015) with package Rcmdr 2.1-7 (2007).

3. Results

Among patients with both MDS/CMML and AID included in the 2 registries, twenty eight patients had received Azacitidine (flow chart in Fig. 1). Six were excluded, because AID were in remission without IST at Azacitidine onset (n = 2), of inadequate follow-up (n = 3) and as vasculitis was post-infectious (n = 1). Median age of the 22 remaining patients was 70 years (range 41–84), including 6 females and 16 males (73%). (Table 1)

Diagnosis of MDS/CMML preceded AID diagnosis (n = 8; by a median of 17 months), was concomitant with (n = 7) or followed AID diagnosis (n = 7; by a median of 20 months).

3.1. AID and MDS characteristics

At MDS/CMML diagnosis, 14 patients had low or int-1 IPSS and 8 had int-2 or high IPSS. The 2 cases of CMML with WBC below 13G/L were classifiable by IPSS. AID diagnosis included: Behçet's disease (n = 4), polymyalgia rheumatica (n = 3), polymyalgia rheumatica with giant cell arteritis (n = 1), giant cell arteritis (n = 1), relapsing polychondritis (n = 3), polychondritis with Sweet's syndrome (n = 1), Sweet's syndrome (n = 1), systemic lupus erythematous (n = 2), seronegative polyarthritis (n = 2), Sjögren's syndrome with anti-phospholipid syndrome (n = 1), adult onset Still's disease (n = 1), large vessel vasculitis (n = 1) and unclassified small vessel vasculitis (n = 1). Twelve (55%) AID were considered atypical and 10 (45%) fulfilled complete diagnostic criteria.

3.2. AID features at Azacitidine onset

At Azacitidine onset, AID was still active (n = 15), in PR (n = 5) and in CR (n = 2). Nineteen patients still reported clinical symptoms related to AID including asthenia (n = 17), weight loss (n = 8), fever >38.5 °C (n = 8), rheumatologic signs (n = 15), skin involvement (n = 10), oral aphtosis (n = 4) (Table 1). Twenty (91%) patients were receiving steroids (median: 23 mg/day) for a median duration of 11 months (range 1–101) with no efficacy (n = 13), partial efficacy (n = 5) and full efficacy on AID (n = 2). In patients where steroids were ineffective, they were however generally continued to avoid AID flare. The median duration of steroid use, in the 18