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Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients

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Abstract: Hydroxyurea (HU) is frequently given as treatment for myelofibrosis (MF), but data on its efficacy and tolerability are scarce. The results of HU therapy were evaluated in 40 patients with hyperproliferative manifestations of primary (n= 32), post-polycythemia vera (n= 6) or post-essential thrombocythemia (n= 2) myelofibrosis. Median interval between diagnosis and HU start was 6.2 months (range: 0-141.7). Reasons for treatment were: constitutional symptoms (55%), symptomatic splenomegaly (45%), thrombocytosis (40%), leukocytosis (28%), pruritus (10%), and bone pain (8%). The starting dose was 500 mg/day, subsequently adjusted to the individual efficacy and tolerability. Response was: bone pain 100%, constitutional symptoms 82%, pruritus 50%, splenomegaly 40%, and anemia 12.5%. According to the International Working Group for Myelofibrosis Research and Treatment criteria, clinical improvement was achieved in 16 patients (40%). Median duration of response was 13.2 months (range: 3-126.2). Worsening of the anemia or appearance of pancytopenia were observed in 18 patients, requiring administration of erythropoietin-stimulating agents (n=17) and/or danazol (n=9). Oral or leg ulcers appeared in 5 patients and one had gastrointestinal symptoms. HU is an effective and generally well-tolerated therapy for the hyperproliferative manifestations of MF. The accentuation of the anemia often induced by HU is usually manageable with concomitant treatment.

Response to Reviewers: Answers to the comments by reviewer 1:

1. Retrospective design of the study. As already stated in the Introduction and in the Discussion, although there is limited bibliographic support for the use of hydroxyurea (HU) in MF, in clinical practice, this drug has been considered for many years (and still is) as the standard therapy for the hyperproliferative manifestations of this disease. Actually, until the recent development of the JAK2 inhibitors, no real alternative therapy to HU was available for comparison. As a result, for the time being, a retrospective study is the only possibility to assess the efficacy and tolerability of HU in MF. Having said this, it must be remarked that the data from the present study have been generated in a single institution, in which the drug was used following uniform rules for the starting dose, the dose adjustments and the use of adjuvant drugs for the treatment of the associated anemia. Moreover, more than 80% of the patients in the study were treated by the same physician, with long-lasting and specific dedication to MF.

2. Selection of the patients. As stated in the Patients and Methods, the 40 patients included in the study were the only ones receiving HU among the 157 with MF followed in our institution during the study period. As also stated in the same section, HU was given to these 40 patients exclusively as a treatment for the hyperproliferative manifestations of MF (i.e., constitutional symptoms, symptomatic splenomegaly, pruritus, bone pain, leukocytosis, and thrombocytosis). This means that a patient with anemia but without any of the above mentioned manifestations did not receive HU but, instead, therapies specifically aimed at treating the anemia, such as androgens, ESA or immunomodulatory drugs (depending on the time period).

3. There is no clear indication about the HU dosage employed in the patients. As detailed in the Patients and Methods, in all patients the starting HU dose was 500 mg daily and it was subsequently modified according to the efficacy and tolerability in each individual patient. As it can be inferred from the median HU dose received by the subgroups of patients receiving HU only or HU plus anemia therapies and by the responders, in the majority of patients the HU dose was escalated, whereas in some patients the starting dose had to be subsequently reduced due to excessive effect or HU-related toxicity.

4. Which were the clinical end-points used for titrating HU?. As now detailed in the Patients and Methods (page 4, final sentence of the second paragraph), the clinical end-point for titrating the HU dosage was the disappearance of the symptoms that motivated HU start or the improvement or normalization of the clinical and hematological parameters (spleen size in case of symptomatic splenomegaly, leukocyte and platelet counts in case of leukocytosis or thrombocytosis) that led to HU institution. In a proportion of patients, the subsequent appearance of hematologic and non-hematologic toxicity led to a dose reduction. Therefore, the main end-point for HU titration was efficacy, whereas toxicity also contributed in some patients.

5. About one third of the patients had HU-induced anemia: was this related to the amount of drug employed?. As now provided in the Results (page 5, third paragraph), median HU dose received by patients with HU-induced anemia (643 mg/day) was lower than the median dose of patients not requiring treatment for the anemia (1,000 mg/day). The interpretation to this fact is that development or worsening of a pre-existing anemia was considered a side effect of HU and, as such, it led to lower dose escalation or to dose reduction. Anyway, the difference between the two groups did not reach statistical significance. This aspect is now commented in the Discussion (page 7, third paragraph).

6. The data could be presented as a letter to the Editor. We respectfully think that it is not possible to include all the data in a short format, since, by doing this, most of the details would be missed. Moreover, although the study is 100% clinical, we are convinced that the results provided will be frequently quoted in the future, as this type of information is lacking in the medical literature. Unfortunately, letters to the editor do not receive the same number of citations than regular papers do.

Answers to the comments by reviewer's 2:

1. It seems that a selection of patients was done. To what extent these results can be applied to patients with myelofibrosis?. As explained in the answer to point 2 by reviewer 1, there was a selection of patients, which was based on the presence of hyperproliferative manifestations of MF. But this is the rule for all treatments currently employed in MF. Since no available therapy can cover all the manifestations of the disease, the treatment of MF is always adjusted to the characteristics of the disease in every individual patient.

2. The question of Epo requiring anemia should be discussed. See answer to point 5 by referee 1.

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7 **Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative**
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9 **manifestations of myelofibrosis: results in 40 patients**

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15 **Running title:** Hydroxyurea in myelofibrosis
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Summary

Hydroxyurea (HU) is frequently given as treatment for myelofibrosis (MF), but data on its efficacy and tolerability are scarce. The results of HU therapy were evaluated in 40 patients with hyperproliferative manifestations of primary (n= 32), post-polycythemia vera (n= 6) or post-essential thrombocythemia (n= 2) myelofibrosis. Median interval between diagnosis and HU start was 6.2 months (range: 0-141.7). Reasons for treatment were: constitutional symptoms (55%), symptomatic splenomegaly (45%), thrombocytosis (40%), leukocytosis (28%), pruritus (10%), and bone pain (8%). The starting dose was 500 mg/day, subsequently adjusted to the individual efficacy and tolerability. Response was: bone pain 100%, constitutional symptoms 82%, pruritus 50%, splenomegaly 40%, and anemia 12.5%. According to the International Working Group for Myelofibrosis Research and Treatment criteria, clinical improvement was achieved in 16 patients (40%). Median duration of response was 13.2 months (range: 3-126.2). Worsening of the anemia or appearance of pancytopenia were observed in 18 patients, requiring administration of erythropoietin-stimulating agents (n=17) and/or danazol (n=9). Oral or leg ulcers appeared in 5 patients and one had gastrointestinal symptoms. HU is an effective and generally well-tolerated therapy for the hyperproliferative manifestations of MF. The accentuation of the anemia often induced by HU is usually manageable with concomitant treatment.

Key words: Myelofibrosis, Primary Myelofibrosis, Treatment, Hydroxyurea

Introduction

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm (MPN) of clonal origin [1] characterized by bone marrow fibrosis, extramedullary hemopoiesis with splenomegaly, anemia with dacryocytes, and a leukoerythroblastic blood picture [2]. MF can present as a *de novo* disorder (primary myelofibrosis or PMF) or appear as an evolutive form of a previously known polycythemia vera or essential thrombocythemia (post-PV MF or post-ET MF) [3]. The recent finding of the V617F mutation in the *JAK2* gene in a high proportion of MF patients [4] and the MPL mutation in some PMF patients [5] has contributed to a better understanding of the pathogenesis of the disease.

From the clinical point of view, MF is a heterogeneous disorder, with its spectrum ranging from patients who are asymptomatic at diagnosis and may not require treatment for years to others with symptoms mainly derived from anemia and splenomegaly and constitutional symptoms [6]. Except for allogeneic hemopoietic stem cell transplantation (allo-HSCT) [7, 8], therapy of MF remains mostly palliative and is usually adjusted to the disease characteristics in each patient [6]. In the “hyperproliferative” forms of the disease, characterized by constitutional symptoms, marked splenomegaly, leukocytosis and/or thrombocytosis, and, more rarely, aquagenic pruritus or bone pain, cytolytic treatment is usually administered [6]. Although hydroxyurea (HU) is the drug most frequently used in such cases, information on its efficacy is limited to a few reports including a scarce number of patients [9, 10]. In this context, the introduction in clinical trials of the *JAK2* inhibitors, which seem to be effective for the hyperproliferative manifestations of MF [11-13], has raised the need for information on the results of conventional therapy in such patients.

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2 The aim of the present study was to analyze, using modern criteria of response,
3 the efficacy and tolerability of HU in 40 patients with hyperproliferative manifestations
4 of MF treated in a single institution.
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7 8 **Patients and methods** 9

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11 Among 157 subjects consecutively diagnosed with PMF (n= 127), post-ET (n=
12 20) or post-PV (n= 10) MF at the Hematology Department of the Hospital Clínic of
13 Barcelona between 1991 and 2008, 40 patients received HU as treatment for
14 hyperproliferative manifestations of MF, including constitutional symptoms (weight
15 loss, night sweats, low grade temperature), symptomatic splenomegaly, pruritus, bone
16 pain, leukocytosis, and thrombocytosis. The latter 40 patients are the subject of the
17 present study and their main characteristics are described in the Results section. The
18 diagnosis of MF was made according to the criteria accepted at the time when the
19 patients were diagnosed, but in all cases the current WHO criteria [14] were fulfilled.
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22 In addition to the patients' demographic data, the following variables were analyzed:
23 type of symptoms or reason for starting HU, time lapse between MF diagnosis and
24 initiation of HU, response to treatment, time to response, maintenance HU dose, length
25 of response, need for additional therapies during HU treatment (i.e., use of
26 erythropoietin, darbepoetin-alfa or androgens), and HU-related side effects. The latter
27 included worsening of the anemia, defined as a decrease in the Hb level below 10 g/L or
28 need for transfusion, development of cytopenias, appearance of oral or leg ulcers, and
29 gastrointestinal symptoms. A complete medical history, physical examination, blood
30 counts, and comprehensive biochemistry tests were obtained before the start of HU and
31 at appropriate intervals, which varied depending on the patients' clinical situation but
32 did not exceed 3 months in any case. The starting HU dose was 500 mg daily and it was
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1 subsequently modified according to the efficacy and tolerability in each patient. The
2 clinical end-point for titrating the HU dosage was the disappearance of the symptoms
3 that motivated HU start or the improvement or normalization of the clinical and
4 hematological parameters (spleen size in case of symptomatic splenomegaly, and
5 leukocyte and platelet counts in case of leukocytosis or thrombocytosis) that led to HU
6 institution. In a proportion of patients, the subsequent appearance of hematologic and
7 non-hematologic toxicity led to a dose reduction.
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18 The response was evaluated using the criteria of the European Myelofibrosis
19 Network (EUMNET) [15] and those of the International Working Group for
20 Myelofibrosis research and Treatment (IWG-MRT) [16]. The minimum time to assess
21 the response was established as 3 months. In case of appearance or worsening of a
22 preexisting anemia, either erythropoietin/darbepoetin-alfa or danazol were administered,
23 depending on the patient's serum erythropoietin levels, as previously reported [17-19].
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38 Results

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41 Table 1 shows the main characteristics of the 40 patients. As can be seen, most
42 patients had PMF. Median interval between MF diagnosis and HU start was 6.2 months
43 (range: 0-141.7). The indications for starting HU treatment were: constitutional
44 symptoms (n= 22, 55%), symptomatic splenomegaly (n= 18, 45%), thrombocytosis (n=
45 16, 40%), leukocytosis (n= 11, 28%), pruritus (n= 4, 10%), and bone pain (n= 2, 8%).
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As can be inferred from the above figures, some patients had more than one feature of hyperproliferation, including 20 patients with two and 4 with three or more features.

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Table 2 shows the therapeutic response for each hyperproliferative feature using the EUMNET criteria. According to these criteria, overall clinical and hematological response was: complete plus major response 30%, moderate plus minor response 32%, and failure 38%. When the IWG-MRT criteria were employed, a clinical improvement was registered in 16 of the 40 patients (40%), including disappearance of the palpable splenomegaly in 4 patients, a reduction in spleen size $\geq 50\%$ in 12 patients, and a Hb value increase > 2 g/dL in 5 patients. It must be noted that the latter criteria require a bone marrow biopsy to consider a possible complete or partial response and no patient had the marrow biopsy repeated for the response assessment. Median duration of the response was 13.2 months (range: 3-126.2). In responding patients, median maintenance daily HU dose was 700 mg (range: 500-2,000).

Hematologic toxicity was observed in 18 patients (45%), consisting of the appearance or worsening of a preexistent anemia (n= 14) or pancytopenia (n= 4). Overall, 26 patients required concomitant administration of erythropoietin/darbepoetin-alfa (n= 17) or danazol (n= 9) due to anemia at HU start or that appeared or worsened during HU therapy. Twelve patients responded to erythropoietin or darbepoetin-alfa. On turn, 7 patients responded to danazol, but in all cases the responses were short-lived. Median HU dose received by patients who develop HU-induced anemia was 643 mg/day (range: 143-1,500) versus 1,000 mg/day (range: 143-1,500) for patients not requiring a specific treatment for the anemia, with the difference between the two groups not being significant (Mann-Whitney U test). Non-hematologic side effects consisted of oral or leg ulcers, which were observed in 5 patients (12.5%), and gastrointestinal symptoms in one patient (2.5%). Median daily HU dose in patients developing ulcers was 1,340 mg (range: 500-2,000).

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At this writing, 26 patients have died. Causes of death included: disease progression (n=8, including acute transformation, observed in 5 patients), infection (n=5), bleeding (n=3), thrombosis (n=3), complications of allo-HSCT (n=2), liver failure and cardiac insufficiency (one case each), and unknown causes (3 patients). Of the 14 patients alive, 13 continue receiving HU. Among non-responders, 5 patients eventually developed acute transformation, at a median of 18.8 months (range: 11.9-25.3) from HU start, 2 received a standard or a reduced intensity conditioning allo-HSCT and died form complications related to the procedure, and 2 required splenectomy or splenic radiation as salvage therapy for symptomatic splenomegaly.

Discussion

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Except for allo-HSCT [7, 8], the therapy of MF remains essentially palliative and is usually adjusted to the characteristics of the disease in every individual [6]. Thus, a wait-and-see approach is often adopted in asymptomatic patients, delaying treatment start until a change in the clinical situation is observed. In patients with anemia, besides transfusion therapy, treatment is based on the use of androgens [19, 20], erythropoietin or erythropoietin-stimulating agents [17, 18] and, more recently, immuomodulatory drugs such as thalidomide, lenalidomide or pomalidomide [21-23]. With regard to symptoms of hyperproliferation of MF, they are usually managed with oral cytoreductive drugs, mainly HU [9, 10], but also busulfan [24] or melphalan [25]. Other treatment modalities include interferon-alfa [26], as well as splenectomy [27] or splenic radiation [28] for symptomatic splenomegaly refractory to drug treatment. However, a substantial proportion of patients does not respond to the above therapies or fail after

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achieving a response. This fact has stimulated the search for newer, more effective therapies for MF. In this sense, the discovery of the *JAK2* mutation [4] has been taken as a basis for the development of molecularly targeted therapies, the so-called *JAK2* inhibitors. The preliminary results of the clinical trials with these drugs indicate their efficacy in the hyperproliferative manifestations of MF [11-13]. Therefore, for comparison purposes, HU seems to be the logical reference.

Although HU is widely used in MF, published data on its efficacy and tolerability in these patients are limited. Löfvenberg et al [9] reported the therapeutic results in 10 PMF patients, who were part of a series of 59 MPN patients treated with HU, reporting a favorable response in 8 of them. Although toxicity was considered moderate, 21 episodes of accentuation of anemia were registered during HU treatment. In some patients, the response was associated with reversal of bone marrow fibrosis [29]. On turn, Manoharan [10] described the results of intermittent HU therapy in 10 PMF patients. In this latter study, in which HU was administered twice or thrice weekly at a dose of 1 to 2 g to treat hyperproliferative manifestations of MF, 4 patients had a good response and 4 a partial response, with no hematologic toxicity being observed. It must be remarked that both studies, in addition to including a small number of patients, had the limitation of the lack of well recognized criteria of response in MF at that time.

The present study included 40 MF patients who were uniformly treated at the same institution and in whom the response to treatment was assessed using modern criteria of response [15, 16]. In a substantial proportion of patients, HU was effective in controlling the manifestations of MF, especially the hyperproliferative signs or symptoms, and, overall, 40% of the patients fulfilled the stringent IWG-MRT category of clinical improvement [16]. Median duration of the response exceeded one year, although there was a wide variability. The HU dose necessary to maintain the response

1 was also variable, ranging from 500 mg to 2 g daily. Of note, 5 of the 24 resistant
2 patients eventually developed acute transformation.
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4 In our patients, HU therapy was often associated with hematologic and non-
5 hematologic side effects. Accentuation of anemia was the most frequent adverse effect,
6 being observed in almost a half of the patients. This complication could be successfully
7 managed in many cases with the addition of erythropoietin or erythropoietin-stimulating
8 agents, especially in patients with inadequate erythropoietin serum levels and non-
9 transfusion-dependant anemia. In patients not eligible for the above agents because of
10 their adequate erythropoietin levels or who did not respond to them, responses could
11 also be obtained with danazol, but they were usually short-lived. **Although the**
12 **difference was not significant, as a whole, patients with HU-induced anemia received**
13 **less HU than patients not requiring the addition of a specific treatment for the anemia.**
14 **This fact should not be surprising, since development or worsening of a pre-existing**
15 **anemia was considered as a side effect of HU and, as such, it led to lower dose**
16 **escalation or to dose reduction.** With regard to non-hematologic toxicity, oral or leg
17 ulcers were the most frequently registered side effect, although they were observed in a
18 minority of patients.
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42 In conclusion, HU is an effective and relatively well-tolerated therapy for the
43 hyperproliferative manifestations of MF. Accentuation of the anemia, usually
44 manageable with concomitant therapy, is the most frequent side effect of treatment.
45 Durability of the responses is variable, but can long-lasting. Anyway, given the
46 palliative nature of HU, newer more effective and durable therapies for the
47 hyperproliferative forms of MF are needed.
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Table 1. Main clinicohematological characteristics in 40 patients with myelofibrosis at the start of hydroxyurea therapy

Age at HU start *	64 (28-84)
Sex (M/F)	28/12
MF type:	
Primary	32
Post-ET	6
Post-PV	2
Hb, g/dl *	11 (7-16.3)
WBC x 10 ⁹ /L *	14 (4-46)
Platelets x 10 ⁹ /L *	348 (47-1250)
Splenomegaly **	
≥20	10
10-19	4
<10	26

HU: hydroxyurea; *median (range); **cm below costal margin; ET: essential thrombocythemia; PV: polycythemia vera

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2 Table 2. Response by specific features in 40 patients with myelofibrosis treated with
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	No. of patients	Response rate
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* Responses include complete plus partial response according to the EUMNET criteria