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Hydroxyurea: An Old Drug in Need of New Clinical Trials in Myeloproliferative Neoplasms

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Abstract: Hydroxyurea (Hu) has been a front-line therapeutic agent for myeloproliferative neoplasms (MPN) for many years and still enjoys the endorsement of experts in the field. However, several publications have reported sub-optimal response, the need for treatment interruption because of cytopenias and lack of sustained response. In all these studies, Hu was used as continuous therapy at a daily dose ranging from 500mg to 3000mg. At our Centre we have used Hu as intermittent therapy (akin to schedules used in patients with solid tumours) at 20-30mg/Kg doses, given as a single dose, twice or thrice weekly. We have consistently observed sustained responses without troublesome cytopenias. In this report we present our experience in 118 patients treated with intermittent Hu during the past 30 years (median follow-up 8.5 yrs): polycythemia vera – 29; essential thrombocythemia – 84; primary myelofibrosis – 5. Based on the pharmacokinetics of Hu and our experience, we speculate that the efficacy of intermittent Hu therapy without troublesome myelotoxicity over long periods of time is attributable to the following: i) higher plasma level from intake of Hu as a single dose; ii) higher uptake of Hu by cells with higher mitotic activity (i.e., the abnormal clone); and iii) unhindered, normal haemopoiesis on the drug free days each week. We hope that this article will generate interest and contemplation, leading to randomized clinical studies to compare the two dosage schedules (Continuous Vs Intermittent) in MPN patients.

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Introduction

Hydroxyurea (Hu) was introduced into the therapeutic armamentarium in the 1980s to treat patients with chronic myeloproliferative disorders [1]. Since then it has been a frontline agent for cyto-reductive therapy in all myeloproliferative neoplasms (MPN); i.e., polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (MF) and MPN-unclassified (MPN-u) [2–7]. However, several recent reports have described marked oscillation of blood counts, the need for treatment interruption and sub-optimal or lack of sustained response to Hu therapy [8–10]. In all these reports Hu was used as continuous therapy (Hu-Cont) at a daily dose of 500mg to 3000mg.

Based on our experience in a small number of MF patients in the late 1980s and early 1990s [11], we have used Hu as intermittent therapy (Hu-Int) as a single dose of 20mg – 30mg/Kg twice or thrice weekly in all MPN patients at our Centre. This regimen is akin to those used in patients with solid tumours, the dosage being higher than that commonly used in the Hu-Cont protocols (often given in divided doses). In this report, we present our favourable experience over a 30-year period, along with the background information relating to pharmacology and pharmaco-kinetics of Hu and current literature pertaining to Hu-Cont therapy.

Hydroxyurea: Pharmacology And Pharmaco-Kinetics [12–16]

Hydroxyurea is a structural analogue of urea. It is an S-phase cell cycle-specific ribonucleotide reductase inhibitor and nucleotide depleting agent, thus limiting de nova DNA synthesis. Animal

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studies indicate that the cytotoxic effects of Hu are limited to those tissues with high rates of cellular proliferation and those cells that are actively synthesizing DNA.

More than 80% of the orally administered dose of Hu is readily absorbed and the peak levels are reached in 1-4 Hrs.

Studies have shown that higher concentrations are achieved if the regular dose is given in a large single dose than if it is administered in divided doses. The plasma half-life is 2-4 hrs. It is rapidly and widely distributed in the body. Up to 50% of the orally administered dose of Hu is metabolised in the liver and is excreted as respiratory carbon dioxide and in the urine as urea. The remaining portion is excreted intact in the urine. Treatment-related myelotoxicity and muco-cutaneous ulcers are two side effects which require interruption or cessation of Hu therapy in MPN patients on long term treatment [17].

Current Practice: Literature

Polycythaemia Vera (PV): Hu is considered to be the front-line therapeutic agent for cytoreduction in PV patients who are over 60 years of age and/or with past history of thrombosis or significant leucocytosis ("high risk patients") [18]. Hu at a starting dose of 500mg twice daily is the most commonly used regimen; the dose is titrated on the basis of response and blood counts [18]. A large study reported by Barbui et al. has shown beneficial effects of Hu therapy in high-risk PV patients [19]. However, several studies have reported resistance, intolerance or disease progression in 10% to 30% of patients [20–23], necessitating cessation of Hu therapy. Parasuraman et al. [22]. have also reported sub-optimal response with elevated blood counts in up to 66% of patients who remained on Hu therapy. Dom et al. have reported lack of sustained response, as well as marked oscillation of blood counts during therapy [10]. In all these patients, change of therapy to long-acting interferon (IFN) has been recommended.

Essential Thrombocythemia (ET) – Hu remains as the preferred first-line therapeutic agent in high-risk ET patients (Triple A Risk Model) and also in patients with high risk for thrombosis (age over 60 yrs, history of thrombosis, JAK-2+^{ve} and in patients with significant leucocytosis [5,24,25]. Hu dosage schedule has ranged from 500mg twice daily or 1000mg daily to 15mg/kg daily, to lower the platelet count as well as the leucocyte count; the dose is modified according to the haematological response. Campbell et al. have highlighted the fact that the actual thrombosis risk is influenced by leucocytosis, not the platelet count [26]. As in the case of PV patients, intolerance or resistance to Hu therapy has been observed in about 25% of patients, [27–28]. In these patients, 2nd line treatment comprises either long-acting interferon or busulphan [5].

Myelofibrosis (MF) – Case reports on the use of Hu in patients with MF came from our Centre in Australia (using Hu-Int) [6,11]. and Lofvenberg and colleagues in Sweden (using Hu-Cont) [7]. in the late 1980s. The favourable clinical responses described in these early reports were validated by Martinez-Trillos and colleagues in 40 MF patients treated with Hu-Cont at a starting dose of 500mg [29]. The observed responses included resolution of bone pain (100%), resolution of constitutional symptoms (82%), resolution of pruritus (50%), decrease in spleen size (40%) and improved haemoglobin level (12%). The study also documented worsening anaemia or cytopenias in 18 of 40 patients. The median duration of response was 13.2 months; thus at 12 months, 80% of patients were in need of an alternative treatment [17,29]. More recently, Pugliese and colleagues have reported deeper and more durable responses in MF patients with hyperproliferative disease (leucocytosis and/or thrombocytosis) treated with a combination of Hu (Hu-Cont) and ruxolitinib [30]. Based on these studies, the current recommendation is to use Hu in MF patients with hyperproliferative disease and/or splenomegaly [31,32].

Current Practice: Our Centre

Material and Methods

This retrospective study comprised critical review of management of all MPN patients referred to our Centre up to June 2023. The concepts of the Study (initiated in 2021), methodology and the

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results (up to July 2022) were presented to and approved by the Institutional Ethics Review Committee (22-006). Diagnosis of MPN was made on the basis of abnormal blood counts, a positive driver mutation result and/or bone marrow examination [33]. Follow up of patients comprised assessment of quality of life, clinical examination and review of progress blood counts.

Hu Therapy

Initial treatment comprised Hu 20mg/Kg, given as a single dose, twice or thrice weekly. Depending on the response at six or eight weeks, treatment was revised by either altering the dose (25mg or 30mg/Kg) or the frequency. Once a stable haematological state was achieved, patients were reviewed at two or three monthly intervals for the long-term.

Results

A total of 145 patients with MPN were referred to our Centre for diagnosis and treatment. Of these 27 patients have been excluded from this analysis and review for the following reasons: i) patients not in need of cyto-reductive therapy (N=20); ii) patients developing a febrile reaction to Hu (N=2); and, iii) patients going on long-acting interferon therapy as first-line treatment (N=5). Clinical details of the remaining 118 patients on long-term Hu therapy are shown in Table 1. Table 2 summarises the clinical course of three ET patients who were referred to our Centre because of sub-optimal response to continuous Hu therapy at the dose of 0.5-1gr daily.

Table 1. Clinical details of MPN patients on longterm hydroxyurea therapy.

MPN	Number M:F	Diagnosis				Age at Dx (yrs)		Follow-up (yrs)	
		JAK-2	CALR	MPL	BM	Range	Mean	Range	Median
PRV	29; 15:14	27	-	-	2	47-86	65.5	1-20.5	10.5
ET	84, 30:54	56	16	3	9	40-82	63.1	1-30	7.75
MF	5 5:0	4	1	-	5	54-82	69.2	4-9	6
Total	118	87	17	3	16	40-86	64	1-30	8.5

MPN = Myeloproliferative neoplasms; PRV = Polycythemia Rubra Vera; ET = Essential thrombocythemia; MF = Myelofibrosis (Primary); JAK-2, CALR, MPL = Driver mutations; BM = Bone marrow examination.

Table 2. Summary of Clinical Course – Hu Cont Vs Hu Int Therapy.

Patient Sex/Age (yrs)	**Diagnosis**	**Hu-Cont Therapy**		**Hu-Int Therapy**		**Follow-up (yrs)**
		Dose/wk	Platelet Count (10^9/l)	Dose/wk	Platelet Count (x10^9/l)	
1. B.Mc M/65	ET, JAK-2 +ve	6.5grms[x]	655	6grms[xx]	420	6
2. G.DeF M/61	ET, CALR+ve	7grms[y]	812	5grms[yy]	340	11
3. EH F/72	ET, JAK-2+ve	4grms[z]	350	3grms[zz]	260	4.5

X - 500mg-1000mg daily; XX - 2grms thrice weekly; Y --1000mg daily; YY - 2.5grms twice weekly; Z - 500mg daily x 6 days, 1000mg x 1 day; ZZ -1.5grms twice weekly.

Treatment was well tolerated. The responses (i.e clinical wellbeing and normal or near-normal blood counts) were sustained and not associated with treatment-related cytopenias or muco-cutaneous ulcers. Accordingly, patients have continued the treatment without interruption over long periods of time.

Treatment of three PV patients was changed over to long-acting interferon at 8yrs, 10yrs and 16yrs, respectively, because of increasing Hu dosage requirements. Similarly, three ET patients were

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changed over to long-acting interferon at 5yrs, 17 yrs and 22yrs because of increasing Hu dosage requirement. Ruxolitinib therapy was given along with Hu to one of five MF patients because of troublesome constitutional symptoms at diagnosis. The other four patients received only Hu therapy. Ruxolitinib therapy was also added to Hu in three patients (PV-1; ET-2) who developed secondary myelofibrosis at 4yrs, 7yrs and 17yrs from the time of diagnosis. Three of the 118 patients developed acute leukaemia at 5yrs, 8yrs and 16yrs and succumbed after a short clinical course.

Effective thromboprophylaxis was achieved in all patients with the use of whole blood platelet aggregation studies for risk assessment and assessing the efficacy of anti-platelet therapy [34].

Discussion

The total weekly dose of Hu-Int used for MPN patients at our Centre is comparable to those commonly recommended in the Hu-Cont regimen. Our favourable results (i.e., sustained response, without myelotoxicity or the need for treatment interruptions) suggest that this is a better therapeutic model. As such, it negates the need to consider alternative therapies, such as long-acting interferon. Based on the review of Hu pharmaco-kinetics and our experience, we hypothesize that the better clinical outcome with Hu-Int is attributable to i) the higher plasma level of HU achieved with single dose intake; ii) the preferential uptake of Hu by the mitotically more active clonal proliferative cells; and iii) the unhindered, normal haemopoietic activity on the treatment-free days each week.

From the patients' viewpoint, Hu is a more convenient (less invasive) and cost-effective option than IFN for conditions which require long term treatment. The actual cost of pegylated IFN 180mcg (per week) in Australia is A$146, whilst 5g of Hu (per week) costs A$3.40. The cost difference between these agents is bound to be a major factor in the patients' compliance, particularly in resource-poor countries where the patient has to pay for the treatment. Furthermore, the clinical benefits with Hu have been shown to be on par with IFN therapy – a randomized phase 3 trial of interferon- versus Hu in patients with PV (N = 87) and ET (N = 81) by Mascarenhas et al. has reported i) similar clinical remission at 12 months; ii) similar reduction in spleen size; iii) similar incidence of thrombosis; and iv) similar rate of molecular response. The authors also reported a much better bone marrow histo-morphological response with Hu (23% Vs 5%) and higher incidence of adverse events with IFN [35].

There has been a long-held concern that long-term use of Hu in MPN patients may result in treatment-related acute leukaemia [1,36]. However, several recent studies have found no evidence to support this view. Two large non-controlled studies in ET (605 patients) and PV (1638 patients) do not support this concern about Hu-related leukaemogenicity [38,38]. This view is further supported by an International Working Group Study of 1545 PV patients; this study reported a cumulative hazard of leukaemic transformation, with death as a competing risk, at 2.3% at 10 years and 5.5% at 15 years [39]. Similarly, a very recent retrospective cohort study of 4023 MPN patients (PV-1688; ET-1976; MF-359) by Wang et al. has also concluded that Hu does not increase the risk of second malignancies including acute myeloid leukaemia and myelodysplastic syndrome [40].

MF is a clonal stem cell proliferative disorder, akin to PV and ET; the accompanying fibrosis is reactive [41], as are the common clinical constitutional symptoms. The latter are attributable to inflammation, and amenable to caronical JAK-STAT inhibition by JAK-2 inhibitors like ruxolitinib. Momelotinib also improves the haemoglobin level in MF patients with anaemia, through inhibition of Activin A Receptor type 1 (ACVR1) [33]. However, none of the JAK-2 inhibitors have any impact on the proliferating clone or the course of the disease [32,33]. On the other hand, chemotherapy agents have the potential to slow down the proliferation and improve the clinical outcome. The key to achieve this is to be able to administer Hu for the long term. Based on our experience, this may be possible with Hu-Int therapy.

The weakness of the main part of this article (namely the use of Hu-Int in MPN patients) is that this is a single arm, retrospective study from a single Centre. However, it shows a better clinical outcome over a long period of time (median 8.5 years), compared to the reports on the use of Hu-Cont therapy. We hope that this article will generate interest and contemplation, leading to Clinical Trials comparing the efficacy of Hu-Int versus Hu-Cont in MPN patients.

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