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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. Concurrent anti-platelet therapy was given on the basis of the results of whole blood platelet aggregation studies, achieving effective thromboprophylaxis. 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 further publications from Centres using intermittent Hu therapy and randomized clinical studies to compare the two dosage schedules (Continuous Vs Intermittent) in MPN patients.

Keywords: Myeloproliferative Neoplasms, Hydroxyurea, Intermittent Therapy

1. 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) [2-8]. 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 In all these reports Hu was used as continuous therapy (Hu-Cont) at a daily dose of 500mg to 3000mg [8-10].

Based on our experience in a small number of MF patients in the late 1980s and early 1990s, 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 [11]. 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.

1.1 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 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].

2. Current Practice: Literature

2.1 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 have also reported sub-optimal response with elevated blood counts in up to 66% of patients who remained on Hu therapy [22]. 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.

2.2 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 anagrelide, long-acting interferon or busulphan [5].

2.3 Myelofibrosis (MF)

Case reports on the use of Hu in patients with MF came from our Centre in Australia (using Hu-Int) and Lofvenberg and colleagues in Sweden (using Hu-Cont) in the late 1980s [6,7,11]. 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].

3. Materials & 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 results (up to July 2022) were presented to and approved by the Institutional Ethics Review Committee (Illawarra Private Cancer Care Institutional Board, July 2022; 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]. Whole blood platelet aggregation (WBPA) studies were performed at the time of diagnosis of MPN for risk assessment and repeated four weeks after commencement of anti-platelet therapy to ascertain efficacy; in patients with incomplete drug effect, treatment was revised and the study repeated until optimum effect was achieved [34]. Follow up of patients comprised assessment of quality of life, clinical examination and review of progress blood counts.

3.1 Hu Therapy

Initial treatment comprised Hu 20mg/Kg, given as a single dose (rounded to the nearest 500mg capsule), 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.

4. 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 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.

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
PV	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
PV = Polycythemia 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 (x10^9/l	Platelet Count	
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 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 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.

WBPA studies showed varying degrees of platelet hyper-activity in 115 patients. Based on these results, the patients were commenced on anti-platelet therapy comprising aspirin (dose ranging from 100mg twice or thrice weekly to 400mg daily) and clopidogrel (75mg) alone or in combination with aspirin or odourless garlic. None of the patients developed thrombosis during the follow-up period (median 8 yrs). Details of WBPA studies, risk assessment and thromboprophylaxis have been published [34].

5. Discussion

There is no standardised dose schedule for Hu therapy in MPN patients. Review of the literature suggests HU-Cont regimen to be in common use; in particular, a starting dose of 500mg twice daily and titrated on the basis of response and blood counts [18,35-37]. There is paucity of reports on the Hu-Int regimen as used at our Centre. 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 [38].

There has been a long-held concern that long-term use of Hu in MPN patients may result in treatment-related acute leukaemia [1,39]. 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 [40,41]. 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 [42]. 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 [43].

MF is a clonal stem cell proliferative disorder, akin to PV and ET; the accompanying fibrosis is reactive, as are the common clinical constitutional symptoms [44]. The latter are attributable to inflammation, and amenable to canonical 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) [32]. However, none of the JAK-2 inhibitors have any impact on the proliferating clone or the course of the disease [31,32]. 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.

To the best of our knowledge, this is the first long-term observational study, albeit from a single Centre, on the use of Hu-Int regimen in MPN patients. As described, patients on this regimen have shown sustained responses without myelotoxicity or the need for treatment interruption. This regimen has also complemented the WBPA study-based thromboprophylaxis; none of the patients developed thrombosis while on the prescribed, individualised anti-platelet therapy [34]. We hope that this article will generate interest and contemplation, leading to publications from other Centres using the Hu-Int regimen and also Clinical Trials comparing the efficacy of Hu-Int versus Hu-Cont in MPN patients.

References

1. Spivak, J. L., & Hasselbalch, H. (2011). Hydroxycarbamide: a user's guide for chronic myeloproliferative disorders. *Expert review of anticancer therapy, 11*(3), 403-414.
2. Fruchtman, S. M. (1997). From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. *Semin. Hematol., 34*, 17-23.
3. Cortelazzo, S., Finazzi, G., Ruggeri, M., Vestri, O., Galli, M., Rodeghiero, F., & Barbui, T. (1995). Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *New England Journal of Medicine, 332*(17), 1132-1137.
4. Donovan, P. B., Kaplan, M. E., Goldberg, J. D., Tatarsky, I., Najean, Y., Silberstein, E. B., ... & Wasserman, L. R. (1984). Treatment of polycythemia vera with hydroxyurea. *American Journal of Hematology, 17*(4), 329-334.
5. Tefferi, A., Vannucchi, A. M., & Barbui, T. (2024). Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. *American journal of hematology.*
6. Manoharan, A. (1988). Myelofibrosis: prognostic factors and treatment. *British journal of haematology, 69*(3), 295-298.
7. Löfvenberg, E., & Wahlin, A. (1988). Management of polycythaemia vera, essential thrombocythaemia and myelofibrosis with hydroxyurea. *European journal of haematology, 41*(4), 375-381.
8. Tefferi, A., Elliott, M. A., Kao, P. C., Yoon, S., El-Hemaidi, I., & Pearson, T. C. (2000). Hydroxyurea-induced marked oscillations of platelet counts in patients with polycythemia vera. *Blood, The Journal of the American Society of Hematology, 96*(4), 1582-1584.
9. Tauscher, J., Siegel, F., & Petrides, P. E. (2010). Hydroxyurea induced oscillations in twelve patients with polycythemia vera. *Haematologica, 95*(7), 1227.
10. Dom, M. J., Pedersen, R. K., Knudsen, T. A., Andersen, M., Skov, V., Kjær, L., ... & Ottesen, J. T. (2021). Data-driven analysis of the kinetics of the JAK2V617F allele burden and blood cell counts during hydroxyurea treatment of patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis. *European Journal of Haematology, 107*(6), 624-633.
11. Manoharan, A. (1991). Management of myelofibrosis with intermittent hydroxyurea. *British journal of haematology, 77*(2), 252-254.
12. Tracewell, W. G., Trump, D. L., Vaughan, W. P., Smith, D. C., & Gwilt, P. R. (1995). Population pharmacokinetics of hydroxyurea in cancer patients. *Cancer chemotherapy and pharmacology, 35,* 417-422.
13. Wawra, E., & Wintersberger, E. (1983). Does hydroxyurea inhibit DNA replication in mouse cells by more than one mechanism?. *Molecular and cellular biology, 3*(3), 297-304.
14. Young, C. W., Schochetman, G., & Karnofsky, D. A. (1967). Hydroxyurea-induced inhibition of deoxyribonucleotide synthesis: studies in intact cells. *Cancer Research, 27*(3), 526-534.

15. Gwilt, P. R., & Tracewell, W. G. (1998). Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clinical pharmacokinetics, 34*(5), 347-358.
16. McEvoy, G. K. (1994). AHFS drug information. *Oncology Issues, 9*(5), 12-13.
17. Cervantes, F. (2014). How I treat myelofibrosis. *Blood, The Journal of the American Society of Hematology, 124*(17), 2635-2642.
18. Vannucchi, A. M. (2014). How I treat polycythemia vera. *Blood, The Journal of the American Society of Hematology, 124*(22), 3212-3220.
19. Barbui, T., Vannucchi, A. M., Finazzi, G., Finazzi, M. C., Masciulli, A., Carobbio, A., ... & Tognoni, G. (2017). A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. *American journal of hematology, 92*(11), 1131-1136.
20. Alvarez-Larrán, A., Pereira, A., Cervantes, F., Arellano-Rodrigo, E., Hernández-Boluda, J. C., Ferrer-Marín, F., ... & Besses, C. (2012). Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood, The Journal of the American Society of Hematology, 119*(6), 1363-1369.
21. Kuykendall, A. T. (2023). Treatment of hydroxyurea-resistant/intolerant polycythemia vera: a discussion of best practices. *Annals of Hematology, 102*(5), 985-993.
22. Parasuraman, S., DiBonaventura, M., Reith, K., Naim, A., Concialdi, K., & Sarlis, N. J. (2015). Patterns of hydroxyurea use and clinical outcomes among patients with polycythemia vera in real-world clinical practice: a chart review. *Experimental Hematology & Oncology, 5*, 1-10.
23. Alvarez-Larrán, A., Kerguelen, A., Hernández-Boluda, J. C., Pérez-Encinas, M., Ferrer-Marín, F., Bárez, A., ... & Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas (GEMFIN). (2016). Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. *British Journal of Haematology, 172*(5), 786-793.
24. Tefferi, A., Loscocco, G. G., Farrukh, F., Szuber, N., Mannelli, F., Pardanani, A., ... & Vannucchi, A. M. (2023). A globally applicable “triple A” risk model for essential thrombocythemia based on A ge, A bsolute neutrophil count, and A bsolute lymphocyte count. *American journal of hematology, 98*(12), 1829-1837.
25. Passamonti, F., Thiele, J., Girodon, F., Rumi, E., Carobbio, A., Gisslinger, H., ... & Tefferi, A. (2012). A prognostic model to predict survival in 867 World Health Organization–defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. *Blood, The Journal of the American Society of Hematology, 120*(6), 1197-1201.
26. Campbell, P. J., MacLean, C., Beer, P. A., Buck, G., Wheatley, K., Kiladjian, J. J., ... & Green, A. R. (2012). Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. *Blood, The Journal of the American Society of Hematology, 120*(7), 1409-1411.
27. Rumi, E., & Cazzola, M. (2016). How I treat essential thrombocythemia. *Blood, The Journal of the American Society of Hematology, 128*(20), 2403-2414.
28. Nejadnik, B., Mascarenhas, J., Rappaport, K. M., Lu, B., Gagnon, B. M., & Verstovsek, S. (2017). Treatment of essential thrombocytopenia patients intolerant/resistant to hydroxyurea: A physician survey.
29. Martínez-Trillos, A., Gaya, A., Maffioli, M., Arellano-Rodrigo, E., Calvo, X., Díaz-Beyá, M., & Cervantes, F. (2010). Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. *Annals of hematology, 89,* 1233-1237.
30. Pugliese, N., Giordano, C., Nappi, D., Luciano, L., Cerchione, C., Annunziata, M., ... & Martinelli, V. (2019). Adding hydroxyurea in combination with ruxolitinib improves clinical responses in hyperproliferative forms of myelofibrosis. *Cancer Medicine, 8*(6), 2802-2809.
31. McLornan, D. P., Psaila, B., Ewing, J., Innes, A., Arami, S., Brady, J., ... & Harrison, C. N. (2024). The management of myelofibrosis: A British society for haematology guideline.
32. Tefferi, A., Pardanani, A., & Gangat, N. (2024). Momelotinib expands the therapeutic armamentarium for myelofibrosis: Impact on hierarchy of treatment choices. *American journal of hematology, 99*(2), 300-308.
33. Barbui, T., Thiele, J., Vannucchi, A. M., & Tefferi, A. (2015). Rationale for revision and proposed changes of the WHO diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis. *Blood cancer journal, 5*(8), e337-e337.
34. Manoharan, A., Gemmell, R., Cavanaugh, L., & Shadood, N. (2022). Thrombosis in myeloproliferative neoplasms: a single center experience of using whole blood platelet aggregation studies for risk assessment and thromboprophylaxis. *Clinical and Applied Thrombosis/ Hemostasis, 28,* 10760296221117482.
35. Büyükaşık, Y., Ali, R., Turgut, M., Saydam, G., Yavuz, A. S., Ünal, A., ... & Tuğlular, T. (2020). Patterns of hydroxyurea prescription and use in routine clinical management of polycythemia vera: a multicenter chart review study. *Turkish Journal of Hematology, 37*(3), 177.
36. Grunwald, M. R., Kuter, D. J., Altomare, I., Burke, J. M., Gerds, A. T., Walshauser, M. A., ... & Mesa, R. (2020). Treatment patterns and blood counts in patients with polycythemia vera treated with hydroxyurea in the United States: an analysis from the REVEAL study. *Clinical Lymphoma Myeloma and Leukemia, 20*(4), 219-225.
37. Ferrer-Marín, F., Hernández-Boluda, J. C., & Alvarez-Larrán, A. (2024). Essential thrombocythaemia: A contemporary approach with new drugs on the horizon. *British Journal of Haematology, 204*(5), 1605-1616.
38. Mascarenhas, J., Kosiorek, H. E., Prchal, J. T., Rambaldi, A., Berenzon, D., Yacoub, A., ... & Hoffman, R. (2022). A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. *Blood*, *The Journal of the American Society of Hematology, 139*(19), 2931-2941.
39. Spivak, J. L. (2010). An inconvenient truth. *Blood, The Journal of the American Society of Hematology, 115*(14),

2727-2728.
40. Gangat, N., Wolanskyj, A. P., McClure, R. F., Li, C. Y., Schwager, S., Wu, W., & Tefferi, A. (2007). Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. *Leukemia, 21*(2), 270-276.
41. Finazzi, G., Caruso, V., Marchioli, R., Capnist, G., Chisesi, T., Finelli, C., ... & ECLAP Investigators. (2005). Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood, 105*(7), 2664-2670.
42. Tefferi, A., Rumi, E., Finazzi, G., Gisslinger, H., Vannucchi, A. M., Rodeghiero, F., ... & Barbui, T. (2013). Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia, 27*(9), 1874-1881.
43. Wang, R., Shallis, R. M., Stempel, J. M., Huntington, S. F., Zeidan, A. M., Gore, S. D., ... & Podoltsev, N. A. (2023). Second malignancies among older patients with classical myeloproliferative neoplasms treated with hydroxyurea. *Blood Advances, 7*(5), 734-743.
44. Jacobson, R. J., Salo, A., & Fialkow, P. J. (1978). Agnogenic myeloid metaplasia: a clonal proliferation of hematopoietic stem cells with secondary myelofibrosis. *Blood, 51*(2): 189-94.