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Comparison of platelet count reduction in patients with essential thrombocythaemia treated with hydroxyurea and thromboreductin. Single centre experience (RCD code: VIII)

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Abstract

Essential thrombocythemia is one of the Ph-negative myeloproliferative neoplasms treated with hydroxyurea. An alternative strategy may be a therapy with thromboreductin. The aim of the study was to compare the effectiveness of hydroxyurea and thromboreductin treatment, defined by a decrease in the platelet count. The study group consisted of 154 patients with essential thrombocythemia diagnosed and treated at the Outpatient Clinic of Hematology in Krakow, Poland between 1995 and 2016. Patients were included in the study at the start of cytoreductive treatment. 102 patients was treated with hydroxyurea and 52 patients treated with thromboreducin. We set the limit values for the number of platelets on levels : <800 x 10^9/L, <600 x 10^9/L, <450 x 10^9/L and <350 x 10^9/L. Afterwards, the analysis of the time required to achieve each point was performed. A comparison of hydroxyurea and thromboreductin groups showed that the number of platelets at the beginning of therapy was significantly lower in patients treated with hydroxyurea. Platelets value in the last control was significantly lower in patients treated with thromboreductin than hydroxyurea. The change in total platelet count over the time was significantly higher in the thromboreductin group**.** Patients treated with thromboreductin had a faster platelets reduction lower than 450 x10^9/L. Tromboreductin is effective in reducing the number of platelets in patients with resistant essential thrombocythemia or intolerant of hydroxyurea regardless of age. JRCD 2018; 3 (8): 266–270

Key words: essential thrombocythaemia, thromboreductin, hydroxyurea, platelets reduction

Background

Essential thrombocythaemia (ET) is one of the Ph-negative myeloproliferative neoplasms. It is characterised by an increase in the number of thrombocytes in the peripheral blood and excessive proliferation of megakaryocytes in the bone marrow. Diagnosis of a patient with ET is based on World Health Organization (WHO) criteria, which are presented in Table 1 [1].

ET is diagnosed mainly in people between 50 and 60 years of age with the same frequency in both sexes. However, in the group of patients under 60 years old, prevalence is higher in females [2]. ET accounts for one third of cases of Ph-negative myeloproliferative neoplasms. The incidence rate for ET is 1 to 2 new cases per 100 000 persons per year [3].

Routine tests are available for several mutations, however, none of the currently known mutations are pathognomonic for ET. These mutations occur in a different percentage in each of the chronic Ph-negative myeloproliferative diseases [4]. The Janus kinase 2 gene mutation, JAK2 V617F, is the most frequent mutation of the JAK2 gene, which is present in 50–64% patients with ET [5]. Other routinely tested molecular abnormalities include the calreticulin gene (CALR) on chromosome 19p13.2, present in about 20% of cases [6], and the myeloproliferative leukaemia gene (MPL) on chromosome 1p34, which occurs in 4% of patients [7].

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Table 1. 2016 WHO diagnostic criteria for ET

Major criteria[a]
– Platelet count ≥450 × 10^9/L (≥450 000/ μL)
– Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
– No meeting WHO criteria for BCR-ABL1 CML, PV, OMF, myelodysplastic syndrome, or other myeloid neoplasms
– Presence of a JAK2, CALR, or MPL mutation
Minor criteria[a]
– Presence of a clonal marker or absense of evidence for reactive thrombocytosis

[a] Diagnosis of ET by the 2016 World Health Organization criteria requires all four of the following major criteria or the first three major criteria plus the minor criterion [1]. CML, chronic myeloid leukemia; ET, essential thrombocythemia OMF, osteomyelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

Not all patients with ET require antiproliferative or anticoagulant therapy at the time of diagnosis. Revision of the cardiovascular risk factors system resulted in the development of an updated scale: Revised IPSET thrombosis (International Prognostic Score for Essential Thrombocythemia). This system is based on risk factors such as age over 60 years, previous history of thrombosis, and presence of JAK2 F617V mutations. Patients are categorised into 4 groups: very low, low, intermediate, and high [8]. Estimation of the risk for thromboembolic complications determines the patient's qualification for cytoreductive treatment [9].

The drug of choice for patients requiring antiproliferative therapy is hydroxyurea (HU), which is a widely used oral cytostatic [10]. Hydroxyurea acts by blocking ribonucleotide reductase and through direct damage to DNA. This results in cell arrest in the S phase of the cell cycle [11]. Its efficacy has been demonstrated in reducing the number of platelets and leukocytes [12]. Hydroxyurea toxicity is low, however, adverse effects are seen in about 5% of patients receiving HU due to Ph-negative myeloproliferative diseases. Side effects mainly involve the skin and oral mucosa and usually manifest as oral ulcers, rashes, and skin hyperpigmentation Lower extremity ulcers, diarrhoea, and vomiting appear only in a small percentage of cases [13]. An important issue may be that long-term cytostatic usage can result in changes to DNA structure, which in turn could lead to the appearance of secondary cancers. The potential of hydroxyurea to accelerate the transformation of ET to acute myeloid leukaemia has been previously discussed [14].

An alternative therapy involves thromboreductin, which can be used both in first and second line therapy, especially in cases of hydroxyurea intolerance or treatment failure [15]. Thromboreductin is a phosphodiesterase III inhibitor of cyclic adenosine monophosphate (cAMP). The exact mechanism of action of thromboreductin is currently unclear. Recent studies indicate its effect on inhibiting the proliferation of megakaryocytes, delaying the maturation of megakaryocytes, and reducing their size, which in turn leads to a reduction in platelet production [16]. The most frequent side effects of thromboreductin are headache, diarrhoea, fluid retention, and tachycardia. It has been shown to be effective in reducing platelet count in more than 70% of cases [17].

In this article, we present a single center comparison of hydroxyurea and thromboreductin efficacy in the reduction of platelet counts in ET patients. Patients were treated with hydroxyurea, and in case of its intolerance or ineffectiveness, thromboreductin was implemented.

Methods

The study group consisted of 154 patients with ET diagnosed and treated at the Haematology Outpatient Clinic in Kraków, Poland, between 1995 and 2016. In all cases, the diagnosis was based on criteria which were in force in a given year. All diagnoses were verified in accordance with the current WHO 2016 guidelines [1].Patients were enrolled in the study from the moment they required platelet-reducing therapy. The decision to initiate treatment was made by a physician using risk stratification and in cases where the number of platelets was 600 × 10^9/L or more.

One hundred two patients were treated with hydroxyurea (n=102) and 52 with thromboreductin (n=52). In accordance with current ET treatment standards, each patient initially received HU. However, in the absence of a satisfactory decrease in platelet count or intolerance to hydroxyurea, treatment with thromboreductin was initiated. In addition, each patient treated with HU received acetylsalicylic acid at a dose of 75 mg /day.

A lack of satisfactory response was defined according to guidelines of the European Leukaemia Net (ELN) and the International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG – MRT). When the number of platelets exceeded more than 600 × 10^9/L after 3 months of hydroxyurea treatment at a dose of at least 2g/day (2.5 g /day for patients weighing over 80 kg), the treatment was considered unsatisfactory. Similarly, treatment was deemed ineffective in cases where platelet count was greater than 400 × 10^9/L, reduction of WBC was less than 2.5 × 10^9/L, or haemoglobin level was less than 10 g/dl, regardless of hydroxyurea dose [18].

Appearance of lower extremity ulcers, skin-mucosal toxicity with unacceptable intensity, or fever associated with drug administration was considered as hydroxyurea intolerance.

Only patients receiving single drug treatment, either hydroxyurea or thromboreductin, were included in the analysis. Patients receiving these two drugs simultaneously were not included in the study. Platelet counts were measured in patients treated with hydroxyurea. This was initially performed monthly, and subsequently, every 3 months. Patients treated with thromboreductin were examined monthly according to the guidelines of the thromboreductin National Health Insurance treatment program. The average dose of HU administered was 1.5 g/day (minimal dose 0.5 g/day, maximum dose 2.5 g/day), while the average dose of thromboreductin was 2 mg/day (minimal dose 0.5 mg/day, maximum dose 6 mg/day).

No clinically significant adverse reactions were observed during thromboreductin treatment (according to version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, NCI-CTCAE v4.0).

Statistical analysis was performed using Statistica 10.0 software (Statsoft, Inc 2007). Continuous variables were expressed as means with range values, while dichotomous variables were expressed

Table 2. Characteristics of patients with ET treated with thromboreductin vs. hydroxyurea

	Thromboreductin			Hydroxyurea		
	n = 52 (100%) Female: 35 (67.3%) Male: 17 (32.7%)			n = 102 (100%) Female: 76 (75.51%) Male: 26 (25.49%)		
Age	Population	Female	Male	Population	Female	Male
< 60 years	n = 30 (%)	21 (70.00)	9 (30.00)	n = 32 (%)	22 (68.70)	10 (31.30)
>60 years	n = 22 (%)	14 (63.63)	8 (36.37)	n = 70 (%)	54 (77.14)	16 (22.85)
	Platelet count ($\times 10^9$/L)		Time (months)	Platelet count ($\times 10^9$/L)		Time (months)
Gender:						
Female (min: max)	(159: 654)		(24: 1334)	(200: 750)		(22: 1334)
Median	406 000		88	430 000		89
Standard deviation	109 320		211.7	103 170		204.27
Male (min: max)	(124: 689)		(23: 149)	(268: 672)		(22: 174)
Median	480 000		66	449 000		100
Standard deviation	143 040		49.64	108 480		44.23
Age						
<60 years	(300: 689)		(25: 167)	(250: 650)		(22: 220)
Median	470 000		76.5	440 000		82
Standard deviation	115 720		44.74	94 280		50.43
>60 years	(124: 542)		(23: 1334)	(200: 750)		(22: 1334)
Median	397 000		76	430 000		99.5
Standard deviation	114 981		255.71	109 060		211.31

as number or percentage. In order to compare features and treatment results between the groups, the Mann-Whitney U test and Chi-squared test with Fisher's amendment were used, depending on the type of variables being assessed.

Results

The study group consisted of 154 patients: 102 patients treated with HU and 52 patients treated with thromboreductin (111 females and 43 males). The average age was 60.7 years (ranging from 22 to 93 years of age), while 92 patients (n = 92) were over 60 years of age and 62 patients (n = 62) were under 60 years of age. Characteristics of the study group are presented in Table 2.

Patients were divided into two groups based on the medication received, either hydroxyurea (n = 102) or thromboreductin (n = 52).

Platelet count was measured at the beginning of treatment and upon completion of the study. Comparison of these two groups showed that the number of platelets at the time of cytostatic treatment implementation was significantly lower in patients treated with hydroxyurea ($P < 0.05$). Platelet numbers in the final measurement were significantly lower in patients treated with thromboreductin when compared to those treated with hydroxyurea ($P < 0.05$).

Duration of therapy in both groups did not significantly differ. Patients treated with HU were significantly older ($P < 0.05$) than those treated with thromboreductin.

The following were chosen as limit values for platelet numbers: $<800 \times 10^9$/L, $<600 \times 10^9$/L, $<450 \times 10^9$/L and $<350 \times 10^9$/ul. The time required to achieve each point was measured. There were no differences between groups in lowering the platelets value below $<800 \times 10^9$/L and $<600 \times 10^9$/L.

The reduction in total platelet count over time was significantly higher in the thromboreductin group ($P < 0.05$).

Patients treated with thromboreductin had a more rapid reduction in platelet count, reaching $<450 \times 10^9$/L before patients treated with HU ($P < 0.05$). Furthermore, there was no statistically significant difference in the rate of reduction of platelets below 350×10^9/L.

For further analysis, patients in hydroxyurea and thromboreductin groups were divided into subgroups with regard to age (above or below 60 years Within the hydroxyurea group, there were no statistically significant differences between the 2 subgroups, both in the number of platelets at final measurement and in the change in platelet number during the entire time of therapy ($P > 0.05$). Similarly, there was no significant difference between the 2 subgroups in the time needed to achieve platelet reduction to below 450×10^9/L and 350×10^9/L ($P > 0.05$).

In the thromboreductin group, the number of platelets in the final evaluation showed no significant difference with regard to the age of patients. However, there was a statistically significant difference in the time needed to obtain a platelet count $< 450 \times 10^9$/L between the 2 age subgroups. Younger patients achieved a desirable decrease in platelet count, which was proportional to the previously mentioned value, less often and after a longer period of time ($P <0.05$). However, there was no such difference in the time needed to reach a platelet count below 350×10^9/L.

Discussion

The average life expectancy of patients diagnosed with ET is not significantly different from that of the general population. However, in patients less than 55 years of age, ET may cause a reduction in quality of life and life expectancy [19,20]. Therefore, it is important to prevent the occurrence of eventual complications, which may lead to the diminishment of life quality or even to death.

The most frequent adverse events caused by the disease are thromboembolic and haemorrhagic complications. For this reason, one of the most important goals of ET treatment is to prevent their occurrence [21].

Previous studies have shown that platelet counts above the upper limit correlate with a higher risk of thrombotic complications. It is recommended to keep platelet counts within normal range during the maintenance treatment [22].

On the other hand, a platelet count above 1000×10^9/L may be the cause of haemorrhagic complications due to acquired von Willebrand disease [23,24].

Investigation of thromboembolic or haemorrhagic complications were not goals of the current study, as we aimed only to examine platelet counts as an indicator of treatment effectiveness. Comparison of the two groups of patients in our study showed that those who received hydroxyurea at the initiation of treatment had platelet counts significantly lower than patients treated with thromboreductin at that time, while the final platelet count was significantly lower in the thromboreductin group. Subjects who received thromboreductin were previously ineffectively treated with HU or had unacceptable toxicity to HU. However, patients treated with thromboreductin achieved a reduction in platelet count to below 450×10^9/L in a shorter period of time.

Steurer and others achieved a rapid reduction in platelet count (initial median of 743, down to 441 after 6 months) after thromboreductin administration in a study in which 97 patients with myeloproliferative diseases (ET, policythaemia vera and myelofibrosis) were evaluated. The percentage of patients who obtained a platelet count below 600×10^9/L after 6 months of treatment was 77%. In addition, they assessed the percentage of thromboembolic complications, which in ET patients fell from 25% to 14% after switching to thromboreductin [25].

In the ANAHYDRET study, thromboreductin was compared to hydroxyurea in 259 previously untreated patients with ET. Thromboreductin was shown to be equally effective as hydroxyurea both in reducing the number of platelets (after 6, 12, and 36 months), as well as in the prevention of thrombotic complications [26]. Analysis of patients treated in our center, depending on age, with a cut-off limit of 60 years, also showed no difference in the number of platelets in the final estimation.

In our observation, the time to reduce platelet counts to below 450×10^9/L and 350×10^9/L in patients treated with HU did not differ significantly, regardless of patient age. Moreover, in the group treated with thromboreductin, the time needed to achieve a reduction in platelet count down to 350×10^9/L was the same in both age groups. However, it appeared that younger patients achieve a decrease in the number of platelets below 450×10^9/L less often and after a longer period of time.

Patients receiving thromboreductin are usually younger than those treated with HU [26]. Similarly, in our study, patients treated with HU were significantly older.

Based on prospective observations, it has been shown that administration of thromboreductin reduces the risk of major and minor thromboembolic events. Thromboreductin reduces the number of platelets below 600×10^9/L in the case of first and second line treatments [25].

Thromboreductin has a positive inotropic effect which can cause side effects within the cardiovascular system [28]. All of these potential adverse events may especially affect older patients with comorbidities, including cardiovascular disorders. This may influence the medical decision-making process regarding the use of thromboreductin in elderly patient groups.

Previous studies have shown that the side effects of thromboreductin are transient and occur mainly in the first weeks of treatment and that their percentage is no higher than for hydroxyurea [29]. Therefore, according to our experience, thromboreductin can also be used in patients over 60 years of age. The reduction in platelet number simultaneously reduces the risk of thromboembolic complications [30] which correlates with decreased long-term and serious adverse events.

Our study was retrospective, examining patients who had received either HU + acetylsalicylic acid or thromboreductin. However, patients in the thromboreductin group had previously been treated with HU. It cannot be excluded that this factor could influence the final results of the analysis. A comparison with studies in which patients were de novo treated with thromboreductin may not be completely reliable.

Conclusions

Thromboreductin is effective in reducing the number of platelets in ET patients with previous ineffective treatment using HU or those who poorly tolerate HU, regardless of age. Evaluation of treatment effectiveness with thromboreductin as a first line medication will be the subject of another analysis.

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