Case Report

Management of Essential Thrombocythemia in a Resource-limited Country: A Nigerian Case Study

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Abstract

Essential thrombocythemia (ET) is one of the classical clonal myeloproliferative neoplasms (MPNs) that constitute a clinical entity distinct from the other MPNs such as polycythemia vera and primary myelofibrosis despite the similarities in their molecular basis. The genetic basis of ET has been associated with the detection of the mutation of three mutually exclusive driver mutations, namely, Janus kinase 2 (JAK2), calreticulin, and myeloproliferative leukemia genes, making them important biomarkers in the diagnosis of ET. This condition is clinically characterized by thrombohemorrhagic complications and progression to myelofibrosis and acute myeloid leukemia. The reduction of the thrombotic complication and/or the associated hemorrhage constitutes the primary goal of the therapeutic practice for the management of ET. We report here seven cases of ET referred to the University College Hospital within a 3-year period (2014–2016). This case series describes the management practices and the therapeutic outcomes in the patients (using the resolution of the clinical presentations and decrease in platelet count). The report also highlights some of the challenges encountered in the management of ET in a resource-limited country like Nigeria.

Keywords: Essential thrombocythemia, hydroxycarbamide (hydroxyurea), myeloproliferative neoplasms, platelet count, resource-limited country, thrombosis

Introduction

Essential thrombocythemia (ET), one of the classical myeloproliferative neoplasms (MPNs), is a clonal hematopoietic stem cell disorder characterized by an isolated thrombocytosis. This disorder, like the other non-BCR-ABL1 MPNs (including polycythemia vera [PV] and primary myelofibrosis [PMF]), is associated with mutations in the Janus kinase 2 (JAK2) and/or other signaling molecules such as the myeloproliferative leukemia virus oncogene (MPL) and calreticulin (CALR) genes.[1,2]

According to the WHO classification for MPNs, ET diagnosis requires a consistent platelet count ≥450 × 10^9/L, detection of at least one of the three mutually exclusive driver gene mutations (JAK2, CALR, and MPL), and exclusion of reactive thrombocytosis and other myeloid malignancies associated with a raised platelet count (such as masked PV and prefibrotic PMF).[3-5]

The primary treatment goal in ET is the reduction of platelet count below the diagnostic threshold and resolution of the clinical presentation. The treatment choice for high-risk ET patients involves the combined use of antiplatelet and cytoreductive therapies (hydroxycarbamide and anagrelide) as the first-line treatment, while interferon-α and busulfan are as second-line treatment. There has also been recent development of molecularly targeted JAK2 inhibitors as third-line treatment.[6]

In this article, we explored the diagnosis and management of ET in a resource-limited country like ours characterized by limited access to more recent molecular diagnostic methods and newer therapeutic modalities as obtained in developed countries.

Case Report

This is a retrospective study of seven referred ET patients (four males and three females) managed at the Haematology Department of the University College Hospital, Ibadan, within a 3-year period (2014–2016).

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The demographic presentation of the patients along with their JAK2 V617F mutation status is shown in Table 1. There was a higher male preponderance (57.14%; 4/7) compared to the females (42.86%; 3/7). The median age at diagnosis was 62 years (range 48–72 years). Of seven patients, five were JAK2 V617F positive while one out of seven was negative, and the last patient (1/7) could not afford the test. BCR-ABL mutation assay was not conducted in all, but in one patient (conducted in the United Kingdom before the patient relocated to Nigeria) due to the cost and lack of easy assay accessibility.

Table 1: Cases, demographic characteristics and Janus kinase 2 V617F mutation status

Cases	Age (years)	Sex	JAK2 V617F mutation positivity	
			JAK2V617F Positive	JAK2V617F Negative
Case 1	52	Female	✓	X
Case 2	72	Male	X	✓
Case 3	62	Male	✓	X
Case 4	68	Female	✓	X
Case 5*	50	Male	*	*
Case 6	48	Female	✓	X
Case 7	72	Male	✓	X

*JAK2 V617F mutation assay was not conducted. ✓: Yes, X: No, JAK2: Janus kinase 2

The clinical features at presentation are shown in Table 2. The most prevalent symptoms were fatigue, intermittent claudication, headache, and dizziness. One of the patients had transient ischemic attack, another patient had extensive proximal DVT, and a third patient had decreased libido and evidence of inferior vena cava (IVC) thrombosis. Hypertension was the most common sign occurring in 5 (71.4%) patients, 2 (28.6%) had hepatomegaly, and only 1 (14.3%) had splenomegaly at presentation. Sickle cell disease was excluded by a detailed history and peripheral blood film examination.

The full blood count evaluation at diagnosis [Table 3] revealed a median hematocrit of 41% (range 35%–60%), the median WBC count of 7.3 × 10^9/L (range 5.4–12.5 × 10^9/L), and the median initial platelet count of 962 × 10^9/L (range 660–3770 × 10^9/L).

The bone marrow aspiration cytology evaluated at presentation revealed hypercellular marrow with megaloblastic erythropoiesis of the bone marrow as a common presentation in the sampled cases [Table 4]. Bone marrow trephine biopsies for histology were not done.

Table 2: Patient demographic characteristics and presenting symptoms and signs

Features	Clinical Features/ Presentations	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Symptom	Fatigue	✓	✓	X	✓	✓	✓	X
	Dizzy spell	✓	✓	X	✓	✓	✓	X
	Headache	X	✓	X	✓	✓	X	X
	Blurring of vision	X	✓	X	X	X	X	X
	Fainting	✓	✓	X		X	X	X
	Numbness	X	✓	X	X	X	✓	X
	Calf pain	X	✓	X	X	X	✓	X
	Intermittent Claudication	X	✓	X	X	X	✓	X
	Weight loss	X	✓	X	X	✓	X	X
	Others	X	Erythromelalgia	X	X	Left leg swelling	Calf swelling	TIA
		X	Pruritus	X	X	Abdominal pain and distension	Primary infertility	X
		X	X	X		Poor libido	X	X
Signs	Hypertension	X	✓	✓	✓	✓	✓	✓
	Hepatomegaly	✓	X	X	X	X	✓	X
	Splenomegaly	X	X	X	X	✓	X	X
	Others	X	X	X	X	IVC thrombosis	Plethora, DVT	X

TIA: Transient ischemic attack ✓: Present, X: Absent, IVC: Inferior vena cava, DVT: Deep vein thrombosis

Table 3: Baseline full blood count

Hematological parameters	Cases						
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
PCV (%)	35	41	56	40	49	51	39
WBC (/mm^3)	5400	12,500	12,100	6990	7400	7300	7100
PLT (/mm^3)	660,000	3,770,000	1,159,000	865,000	962,000	929,000	1,147,000

PCV: Packed cell volume, WBC: White blood cells, PLT: Platelet count

All but one of the patients were placed on cytoreductive therapy using hydroxycarbamide at a dose of 1–2 g as the first-line therapy along with antiplatelet therapy with clopidogrel. Case 1 at baseline was placed on pegylated interferon-α at 90 μg weekly and she had two doses. She subsequently commenced hydroxycarbamide at 500 mg twice daily for 5 months. Interferon-α therapy was recommenced thereafter at 90 μg weekly because of fertility concerns.

One of the patients, Case 2, with an initial platelet count of >3000 × 10^9/L, developed peripheral neuropathy on hydroxycarbamide and was converted to interferon-α. However, he developed flu-like symptoms necessitating cessation of the therapy and recommencement of hydroxycarbamide at a lower dose (500 mg twice daily). No psychiatric effects were observed in the patients while taking interferon-α.

In all, two patients had pegylated interferon-α during their treatment.

The serial full blood count of these patients was also evaluated to assess the hematological changes in the patients following therapy [Table 5 and Figure 1].

Discussion

Nigeria, a middle-income resource-limited country, is faced

Table 4: Bone marrow aspiration findings

Cases	Cellularity	Erythropoiesis	Myelopoiesis	Megakaryopoiesis		Impression
				Cellularity	Morphology	
Case 1	Hypercellular	Megaloblastic	Sequential, normal	Hyperplasia	Giant	ET
Case 2	Hypercellular	Megaloblastic	Sequential, increased	Hyperplasia	Normal	ET
Case 3	Hypercellular	Megaloblastic	Sequential, increased	Hyperplasia	Normal	MPN mainly ET
Case 4*	-	-	-	-	-	-
Case 5	Normocellular	Megaloblastic	Sequential, normal	Hyperplasia	Normal	ET
Case 6*	-	-	-	-	-	-
Case 7*	-	-	-	-	-	-

*BM trephine biopsy was not conducted. ET: Essential thrombocythemia, MPN: Myeloproliferative neoplasms, BM: Bone marrow

Table 5: Full blood count after therapy

Hematological parameters	Cases						
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
PCV (%)	38	38	37	40	44	45	40
WBC (/mm^3)	4860	4700	7800	4400	6900	2780	3400
PLT (/mm^3)	620,000	1,096,000	750,000	407,000	108,4000	465,000	124,000

PCV: Packed cell volume, WBC: White blood cells, PLT: Platelet count

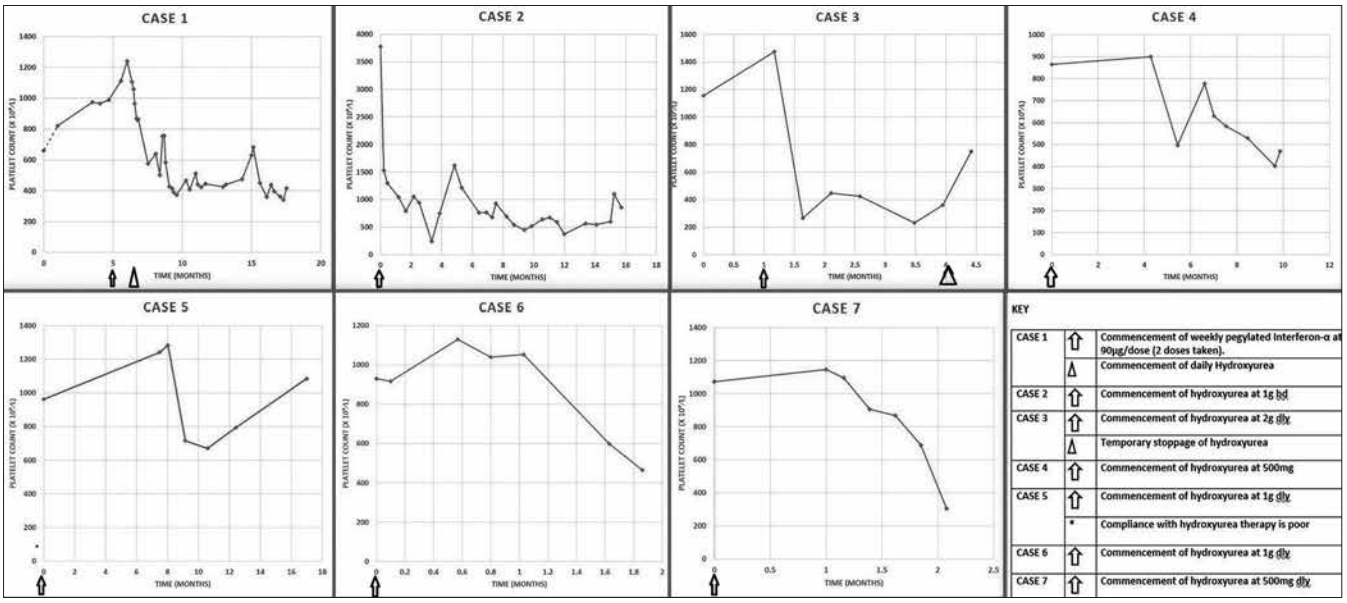

Figure 1: Baseline platelet counts and its variation during therapy

with the perennial problem of inadequate access to medical care and appropriate facilities necessary for the management of many medical conditions including hematological neoplasms. This study comprises a report of seven ET patients, their hematological changes, and clinical features through their management using available resources at our disposal.

Thrombotic complications have been widely documented as a major source of morbidity and mortality in ET. In our report, all the patients presented with varying thrombotic complications which were consistent with previously documented studies and cases.[1,7]

Patients may present at any age, although ET is largely a disorder of later years with a peak incidence between the ages of 50 and 70 years. The median age at diagnosis of the patients in this cohort (62 years) is similar to previously reported findings.[1,7] This highlights the age-associated preponderance of the diagnosis of ET in older patients. In addition, 3 (42.86%) of the 7 patients studied were below 60 years of age which further underscores the possibility of presentation at any age.[7]

In our report, there appears to be a slight male preponderance compared to the female-reported cases. This finding is, however, different from previously documented reports of a higher prevalence of ET in females,[7] and this could be ascribed to the small number of cases considered in this study.

Aside the preponderance of thrombotic events affecting the nervous and cardiovascular system, there have also been reports of the involvement of unusual sites such as hepatic, portal, or mesenteric veins and may precede the onset of clinically overt ET.[1,8] In our report, one of the patients studied presented with a history suggestive of an IVC thrombosis and one had a transient ischemic attack before the diagnosis of ET. The patient with DVT also had a history of a recent myomectomy for fibroids and primary infertility, which could have also complicated the clinical course of the disease in her. Headache, dizziness, fainting spells, and TIA documented as common neurologic findings in ET are similar to other reports. These are ascribed to the microvascular occlusion that occurs in ET.[1,8]

Two cases with hepatomegaly were reported in this study, while one had mild splenomegaly. These findings in our study are consistent with the report of variable prevalence of mild hepatomegaly and splenomegaly as important clinical features associated with ET.[3,9-11] The relatively small sample size and the occurrence of IVC thrombosis in one of our patients may have accounted for the prominence of hepatomegaly in our cohort.

A recurring clinical sign was hypertension which had found in 6 (85.7%) out of 7 patients and was managed along with the ET treatment. This finding is consistent with the documented presentation of hypertension as a major complication in the MPNs and ET. Hypertension as a complication also plays an important role as a predisposing risk factor responsible for the thrombotic cardiovascular events associated with ET.[8,9,11] Other studies have also reported the combined role of ET and hypertension as an associated factor responsible for renal vascular stenosis.[5]

Apart from the management practice in this report, another major consideration is the availability of resources and appropriate facilities in the management of these cases. This is exemplified by the unavailability of cytogenetics and molecular assay facilities for MPN-associated mutations (such as MPL, TET, and CALR). These tests would have been crucial in further characterizing the MPN clinical entity. The significant role of the patients' socioeconomic status was also a major consideration in their inability to finance some of the recommended tests, while just one patient was able to perform the BCR-ABL 1 mutation test (for CML exclusion) conducted in a medical facility outside the country. This highlights the impact of patients' socioeconomic status and resources on their treatment and compliance to the recommended management practices. This is worsened by the overreliance of the Nigerian health-care system on out-of-pocket payment system and the poor enrolment of Nigerians in the National Health Insurance Scheme.[12,13] This has been reported to further worsen the level of poverty and health inequalities among the different social classes consequent on managing a resource-intensive condition like ET.[13]

In this study, 5 (83.3%) of 6 patients tested positive for the JAK2 mutation, while 1 tested negative. This finding is similar to the reported delineation of ET into JAK2-positive and JAK2-negative cases although it highlights a higher prevalence of the JAK2-positive cases than the 50%–65% traditionally reported in literature.[3,6]

The bone marrow studies in these cases showed an increase in hyperlobulated and giant megakaryocytes in all four patients. This is consistent with the previously documented reports of proliferation and enlargement of megakaryocytes with hyperlobulated nuclei associated with the documented ET cases.[1,6,10]

All other patients had a good response to hydroxycarbamide apart from one patient who did not fully comply with treatment modalities. Antiplatelet drugs (low-dose aspirin and clopidogrel) were also routinely prescribed for all patients with thrombotic events and complications. This is important as the prevention of thrombotic events is one of the primary goals for ET therapy. Consequently, response to therapy is usually evaluated by the decrease in platelet count and resolution of clinical features.[14] In addition, patients who develop hydroxycarbamide adverse effects and resistance will benefit from novel therapies such as JAK2 inhibitors.[15,16]

Recommendations

With the recent increase in the body of knowledge on the molecular basis of ET and other MPNs, there is a need for the availability of modern diagnostic facilities to ensure evaluation of other molecular markers apart from JAK2. This would also help reduce the underreporting of ET cases as the

diagnosis of many cases could be missed due to poor access to full complement of the necessary test facilities. More so, the incorporation of other adjunct diagnostic procedures such as bone marrow studies for iron stain, marrow fibrosis, and cytogenetic analysis will be crucial for appropriate prognostication and risk stratification of cases. This would be essential in providing more robust information that will help in treating and monitoring these patients. While the practicality of having a full complement of the diagnostic test facilities available in health-care facilities might not be possible in resource-limited areas, the use of the diagnostic criteria in case ascertainment would however result in ease of case identification and early institution of appropriate management.

Furthermore, the availability of novel therapy with JAK2 inhibitors may confer a better prognosis while also limiting the adverse effects associated with hydroxycarbamide therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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