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Research paper

Disease characteristics and response to treatment of patients with myelofibrosis: a multicentre descriptive, retrospective study from Sri Lanka

YJ Costa, SJ Senanayake[1], HSA Williams, D Moratuwegama, B Jayaratne, V Ratnamalala, N Ranasinghe, LV Gooneratne, HWW Goonasekera, D Gunawardena, I Wijesiriwardene, C Kulatilake, A Jayawardene, JA de Silva, I Dharmasena, N Perera, NANS Mendis, PLSP Vitharana, R Jayatunga, H Gunasekera, LS Basnayake, YR Samaraweera, T Sooriyakumar, DTD Dissanayake, WDP Vidyaratne, KADS Jayaratne, H Alwis, R Wijeratne, A Attanayake, S Athawuda, R Pullaperuma, R Jayatunga, BGNT Somarathna, S Yoganathan, LS Senerath, VCP Gunawardene, BLH Balasooriya, D Epa

Key words: myelofibrosis, presentation, treatment

Abstract

Introduction and objectives: Myelofibrosis (MF) is a BCR/ABL negative, myeloproliferative neoplasm. The manifestations of MF include constitutional symptoms, splenomegaly, anaemia and other cytopenias. Most of the patients are elderly with multiple comorbidities and cannot undergo-allogeneic stem cell transplantation. Hence treatment is mainly aimed at controlling symptoms and complications. Given the varying clinical needs of these patients, and the wide array of therapeutic options available, it is challenging to choose the best therapeutic agent for each patient.

The main objective of this multicentre study, the first of this nature for MF in Sri Lanka, was to describe clinical and laboratory characteristics of patients and to assess various treatment modalities practiced in the country.

Method: Following informed written consent, data was gathered from 28 units covering 9 provinces in the country. Analysis was using SPSS software.

Results: Of the 104 patients with MF, 87 were primary, 16 post polycythaemia vera and one post essential thrombocythemia. Median age 58.9 years and male : female ratio 51:49. The main presenting features were splenomegaly 78.8%, constitutional symptoms 63.5% and anaemia 59.6%. Leukocyte count >25x10^9/L, blasts in the peripheral blood and platelets <100x10^9/L were seen in 23.1%, 18.3 and 17.3%. JAK 2 V617F mutation was checked only in 77 patients due to lack of facilities and 61% were positive.

62 paitents required RBC transfusions, 32 patients received erythropoietin therapy, 19 thalidomide/ prednisolone and 7 received only thalidomide. Positive responses were seen in 53.1%, 52.6% and 42.9% respectively. Splenomegaly was seen in 82 patients. 67 received hydroxyurea, 13 ruxolitinib, 10 thalidomide/ prednisolone and 10 thalidomide only. Positive responses were 80.6%, 61.5%, 50% and 50% respectively. Constitutional symptoms were treated with ruxolitinib in 14 patients. 92.9% showed a positive improvement.

Conclusions: Hydroxyurea, is the most commonly used, least expensive and the most effective treatment option for splenomegaly. Thalidomide/ prednisolone and thalidomide alone have shown similar positive responses when used against splenomegaly but the patient number is small and should be further analysed with a larger study population. Out of the treatment options used for anaemia, more than 50% of positive responses were seen with erythropoietin and thalidomide/ prednisolone. Ruxolitinib though used only in 14 patients, had shown a good response in controlling constitutional symptoms and splenomegaly, but the use of the drug was limited by high cost and anaemia.

[1]*Doctoral Researcher, Queensland University of Technology, Australia. All other Researchers are Consultant Haematologists from Sri Lanka College of Haematologists.*

Correspondence: Dr. Yasintha Costa

E-mail: yasinthacosta@live.com

Introduction

Myelofibrosis (MF) is a BCR /ABL negative, myeloproliferative neoplasm. It can be primary (primary MF) or secondary to polycythaemia vera (PV) or essential thrombocythemia (ET) (post PV MF or Post ET MF respectively)[1]. Both primary or secondary MF are characterized by clonal stem cell proliferation, release of cytokines, bone marrow fibrosis, extramedullary haemopoiesis and organomegaly[2,3].

The clinical manifestations of MF are variable and can be mainly categorized as constitutional symptoms, symptomatic splenomegaly, anaemia and other cytopenia[4]. An increased risk of thrombosis has also been documented in patients with MF. At present there is no curative treatment for MF other than allogeneic stem cell transplant (BMT). Since most of the patients with MF are elderly, they are not fit to undergo BMT. Therefore, the treatment is mainly aimed at controlling the disease symptoms and complications.

Conventional treatment options include RBC transfusions, erythropoiesis stimulating agents androgens, steroids, immunomodulatory agents for anaemia. Hydroxyurea, JAK inhibitor (ruxolitinib), splenic irradiation and, splenectomy for massive splenomegaly[5]. Ruxolitinib for constitutional symptoms. Cytoreductive therapy and anti-platelets to minimize the risk of thrombosis[6,7,8,9,10].

Given the heterogenous clinical needs of these patients, determination of when to treat, which agent to utilize, and how best to utilize the facilities available is often a difficult decision to make. Over the past few decades haematologists in Sri Lanka have been managing patients with myelofibrosis with the available limited resources. The main objectives of this multicentric study, the first of this nature for myelofibrosis in Sri Lanka, was to describe the clinical and laboratory characteristics of the MF patients in Sri Lanka and to assess various treatment strategies practiced in this country.

2. Method

This descriptive multicentric retrospective study was carried out over a period of 18 months from May 2017 to November 2018.

Approval for the study was obtained from the Director General of Health Services of Sri Lanka and the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya.

MF patients receiving treatment from 28 haematology centres covering all provinces of the country, were recruited into this study. All MF patients in these centres both primary and secondary MF were included and those who did not meet the WHO 2016 diagnostic criteria for primary and secondary MF were excluded. Following informed written consent, the data on clinical and laboratory parameters on presentation and the therapeutic options used and the responses of the patients to treatment were collected from the patients and from the clinic records. The data were analysed using the SPSS software.

3. Results

The study had recruited 104 myelofibrosis patients, 87 (83.65 %) were primary myelofibrosis, 16 (15.38 %) were post PV and 1 (0.96%) was post ET.

The median age at diagnosis of the patients was – 58.91 years. Male: Female ratio 51:53 (49:51).

3.1 Clinical and laboratory features at presentation

The clinical and laboratory features of the patients at presentation are given in the Table 1.

Constitutional symptoms, anaemia and splenomegaly were the commonest clinical features at presentation and low Hb and leucoerythroblastic blood picture were the commonest laboratory manifestations.

The clinical and the laboratory features of our patients were compared with the study from Europe and North America by Cervantes et al. in 2009 in "New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment" involving 1054 patients and a Chinese study of 642 patients reported by Zefeng Xu et al. Unique features of primary myelofibrosis in Chinese' in 2011. Comparison is given in Table 2.

Table 1. Clinical and laboratory features of the study population

Feature	Number (N-104)	Percentage
Clinical features at presentation		
Constitutional symptoms	68	65.4
Anaemia	62	59.6
Splenomegaly	82	71.3
Thrombocytopenia	29	27.9
Infection	9	8.7
Thrombosis	6	5.8
Pruritus	17	16.3
RBC transfusion need	47	45.2
Laboratory features at presentation		
Anaemia (Hb < 10g/dL)	61	58.7
Thrombocytopenia < 150 x 10^9/L	29	27.9
Leucocyte count > 25 x 10^9/L	24	23.1
Circulating blasts > 1%	19	18.3
Leucoerythroblastosis	65	62.5

Table 2. Comparison of the clinical and laboratory criteria of the patients with similar studies on the Caucasians and the Chinese

Feature	Sri Lankan		White		Sig	Chinese		Sig
	Number (N-104)	%	Number (N-1054)	%		Number (N-642)	%	
Age >65 yrs	43	41.3	470	45.0	0.469	114	18.0	<0.001
Male	51	49.0	638	61.0	0.017	358	56.0	0.183
Constitutional symptoms	66	63.5	281	27.0	<0.001	134	21.0	<0.001
Splenomegaly	82	78.84	681/768	89.0		289	45.0	0.002
Anaemia (Hb< 10g/dl)	62	59.6	371	35.0	<0.001	427	67.0	0.139
Leucocyte count > 25 × 10^9/L	24	23.1	101	10.0	<0.001	94	15.0	0.037
Circulating blasts >1%	19	18.3	370/1018	37.0	0.001	115	18.0	0.941
Jak2 mutation	47/77	61.0	203/648	59.0	0.736	159/238	67.0	0.336
Platelets <100 x 10^9/L	18	17.3%	174	16.5	0.938	297	46.3	<0.001

3.2 Treatment responses

Management of anaemia

Anaemia is one of the commonest manifestations that affects the quality of life of the MF patients. 62 (59.6%) of patients had presented with anaemia. 65 patients required frequent or intermittent transfusions.

Table 3. Drug therapy for anaemia

Drug	Average dose	Number	%	Response[#]				Adverse effects
				Good	Partial	Poor	Not recorded	
Erythropoietin	20,000 iu /wk	29	27.9	06 (20.7)	13 (44.8)	10 (34.5)		Severe allergic reaction (1 patient)
Danazol	200mg bd	8	7.7	01 (17.4)	02 (28.6)	04 (57.1)	01	
Thalidomide only	100mg/day	7		0	2	2	3	
Prednisolone only	5mg/day	1				1		
Thalidomide/ prednisolone combination	Thalidomide 100mg EOD and Prednisolone 20 mg daily	19	18.3	5	6	7	1	Neutropenia, peripheral neuropathy, oedema, vertigo, rising AST/ALT

[#]Good response – if best Hb reached 10 g/dl or more or became transfusion free; Partial response – best Hb > 8-10 g/dl, intermittent transfusion need; Poor response – Hb 8d/dl or less or no response

Drug therapy for constitutional symptoms

Ruxolitinib, a JAK inhibitor was the only drug available for treating constitutional symptoms

Table 4.

Ruxolitinib therapy	number	%	Response		Adverse effects
	14		Average dose	Average duration	Anaemia, thrombocytopenia, itchy rash, dyspepsia, Bacterial and fungal infections
Ruxolitinib					
Good	5	31.25%	15 bd	10 months	
Moderate	8	50%	10 bd	10 months	
Poor	1		20 bd	3 months	

2 patients with poor response are not included. One of the patients was started on ruxolitinib after the patient was in blast crisis. The other patient had been on a sub therapeutic dose (7.5mg EOD).

Drug therapy for symptomatic splenomegaly

Massive splenomegaly is a common and a characteristic manifestation of MF.

The drugs used and the responses are summarised in the Table 5.

Table 5.

Drugs	number	%	Response		Adverse effects
			Average dose	Average duration	
1. Hydroxyurea					
Total –	67				
Good	50	74.6	500- 1000 mg	2.8 yrs	Anaemia, rash, renal insufficiency, leucopenia, gastritis.
Moderate	4	5.97	500 mg	2 yrs	
Poor	10		500-1000 mg	0.7 yrs	
Response not recorded	3				
2. Alpha interferon					
Good	-				
Moderate	2		3MU twice weekly	3 months	
Poor	1		3MU twice weekly	2 months	
3. Thalidomide and prednisolone					
Total	10				
Good	1	10	T-100mg EOD P-30 mg/day	3 months	Diabetes mellitus Weight gain GORD symptoms Rising AST/ALT Peripheral neuropathy (numbness) Vertigo Oedema
Moderate	4		T- 100mg EOD P-20 mg/day	8.5 months	
Poor	5		T-100mg EOD P-20 mg/day	3.5months	
4. Thalidomide only					
Total	10				
Good	4	40	100 mg OD	2 years	Recurrent infections Peripheral neuropathy (numbness, tremors)
Moderate	1		100 mg OD	2 years	
Poor	4		100 mg EOD	28 months	
Response not recorded	1				
5. Prednisolone only					
Total	4				
Good	-				
Moderate	1		5 mg/day	9 months	Weight gain
Poor	3		5 mg/day	6 months	
6. Ruxolitinib					
Total	19				
Good	6	30	15 bd	11 months	Anaemia, thrombocytopenia, itch rash, dyspepsia, Severe sepsis (bacterial and fungal)
Moderate	2		15 bd	12 months	
Poor	5		15 bd	7 months	
Response not recorded	5				
Sub therapeutic dose	1				

Good – splenic size reduction >10 cm. Moderate (spleen size reduction 3-10 cm). Poor – 2 cm or less than 2 cm reduction in size

4. Discussion

The comparison of the clinical and the laboratory features of our patients with the European and the North American patients reported by Cervantes et al. involving 1054 patients and 642 Chinese patients reported by Zefeng Xu et al. shows statistically significant changes (Table 2). The Sri Lankan patients had more constitutional symptoms, more anaemia, and higher WBC count than the European and the North American patients at presentation. This could be argued as late presentation of our patients due to less health care facilities as compared to Europe and North America. But even though the number of patients with a high leucocyte count (WBC > 25 x 10^9/L) was more in our patients, the presence of blasts in the peripheral blood film was statistically lower in the Sri Lankan cohort. Furthermore, lesser number of circulating blasts at diagnosis was also noted with the Chinese cohort as well. Significant differences in presentation criteria were also noted between the Sri Lankan patients and the Chinese patients. The Chinese patients were younger and had more thrombocytopenia than ours at presentation. This difference was noted between the Chinese and the Caucasian cohorts too. This highlights the differences in disease characteristics (clinical and laboratory) between different races and population categories.

Many therapeutic options have been used to manage anaemia in our patients. A good response to therapy is regarded as achieving a Hb of ≥ 10g/dL. A moderate response is achieving a Hb value of 8-10g/dL. Patients receiving erythropoietin or thalidomide/ prednisolone have shown a positive response (good and moderate responses) to therapy in more than 50 % of patients.

Treatment for splenomegaly was predominantly with hydroxyurea (HU) and 80.6% (54⁄67) patients have shown a positive response indicated by reduction of splenic size >10 cm (good response) in 50⁄67 and reduction of spleen size by 3 to 10 cm (moderate response) in 4⁄67. The other drugs have been less frequently used and show an inferior response compared to HU. Thalidomide/prednisolone and thalidomide alone have shown similar positive responses (50%) when used against splenomegaly but the patient number is small and should be further analysed with a larger study population.

16 patients have been treated with ruxolitinib for constitutional symptoms. 81.2% has responded to treatment. The average dose has varied between 10- 15mg bd.

Conclusions

Statistically significant differences in clinical and laboratory parameters were noted at presentation between the Sri Lankan myelofibrosis patients and the patient cohorts from Europe / North America and China.

Hydroxyurea is the most effective, commonly used and the least expensive treatment option for massive splenomegaly. Thalidomide/prednisolone and thalidomide alone have similar positive responses when used against splenomegaly but the patient number is small and should be further analysed with a larger study population. Out of the treatment options used for anaemia more than 50% of positive responses were seen with erythropoietin and thalidomide and prednisolone combination.

JAK inhibitor ruxolitinib, though used only in 14 patients had shown a good response in controlling constitutional symptoms and splenomegaly, but the use of the drug was limited by high cost and anaemia.

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