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Research Article

Epidemiological, Clinical, Biological and Therapeutic Characteristics of Myeloproliferative Neoplasms in Eastern Morocco

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Keywords
- Chronic myeloid leukemia
- Primary myelofibrosis
- Polycythemia vera
- Essential thrombocythemia
- Morocco

Abstract

Background: Myeloproliferative neoplasms (MPN) are the most common myeloid neoplasms in Eastern Morocco. The aim of this study is to determine the epidemiological, clinical, biological and therapeutic characteristics of MPN in this region.

Methods: Retrospective descriptive study of patients diagnosed with MPN between January 2008 and December 2012 in two centres in Eastern Morocco. The diagnosis was based mainly on clinical features, blood counts, peripheral blood films and morphology review of bone marrow aspirate and biopsy. Genetic analyses were included whenever available.

Results: Among the 84 cases of MPN registered in Eastern Morocco, chronic myeloid leukemia (CML) was the most frequent accounting for 78.6% of all MPN, followed respectively by primary myelofibrosis (PMF) with 8.3%, polycythemia vera (PV) with 7.1%, essential thrombocythemia (ET) with 4.8% and chronic eosinophilic leukemia (CEL) with 1.2%. Unlike Western countries, CML in Eastern Morocco affects younger populations, and a higher percentage of patients were diagnosed at late stages (12% with accelerated phase and 32% with blast phase). Moreover, to confirm the diagnosis of CML, the detection of the Philadelphia chromosome and the *BCR-ABL1* fusion gene were carried out in only a minority of patients (33% and 6% of cases respectively). Only 23% of patients received treatment with the tyrosine kinase inhibitor (TKI) Imatinib. In addition, none of the patients in our series received the second or third generation TKIs treatment or hematopoietic stem cell transplantation. Analysis of the most commonly recognized mutation in *BCR-ABL1* negative MPN (*JAK2* V617F) was carried out in only 16.7%, 25% and 42.9% of cases of PV, ET and PMF, respectively.

Conclusions: For the majority of patients with MPN, the disease is diagnosed at an advanced stage. In addition, the diagnostic resources are insufficient and need to be developed, particularly cytogenetic and gene mutations analysis. Our results justify the need to establish an effective program aiming at the control of the various subtypes of MPN amongst Eastern Moroccan population.

ABBREVIATIONS

MPN: Myeloproliferative Neoplasms; CML: Chronic Myeloid Leukemia; PMF: Primary Myelofibrosis; PV: Polycythemia Vera; ET: Essential Thrombocythemia; CEL: Chronic Eosinophilic Leukemia; TKI: Tyrosine Kinase Inhibitor

INTRODUCTION

Chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) share similar biological and clinical features, and therefore they were grouped in 1951 by William Dameshek in an entity called "myeloproliferative disorders" [1,2]. Myeloproliferative disorders are hematological malignancies with diverse phenotypes, which originate at the progenitor or stem cell level, and are characterized by abnormal proliferation of more than one cell lineage [3,4]. The 4th edition of the WHO classification of 2008 adopted a new classification of hematological malignancies in which the nomenclature for "myeloproliferative disorders" was changed to myeloproliferative neoplasms (MPN) [5-7]. A revised version of this classification has been published recently [8,9]. In this 2008 WHO classification, MPN includes eight diseases: CML BCR-ABL1 positive, chronic neutrophilic leukemia (CNL),

PV, PMF, ET, chronic eosinophilic leukemia (CEL), mastocytosis, unclassifiable MPN [5].

CML is characterized by abnormal proliferation of granulocytes which contain the Philadelphia (Ph) chromosome, t (9;22), resulting from a translocation between chromosomes 9q34 and 22q11. This translocation is responsible for the production of the *BCR-ABL1* fusion gene, which encodes an activated tyrosine kinase molecule that activates cell proliferation, causing the disease [10-12].

Most of the *BCR-ABL1* negative MPN are characterized by the presence of an activating mutation in the Janus kinase 2 gene (*JAK2* V617F), inducing a high level of proliferation. This mutation is found in more than 95% of PV, 60% of ET and 50% of PMF [13-17]. The search for this mutation has become essential in the diagnosis of Philadelphia chromosome negative MPN [16,18]. Thus, at present, molecular analysis has taken a key role in the diagnostic process and monitoring patients with these hematologic diseases.

We have recently showed that MPN are the most common myeloid neoplasms in Eastern Morocco [19]. To our knowledge the pattern of MPN has not been reported for this region so far. The objective of this study is to determine the epidemiological, clinical, biological and therapeutic characteristics of MPN in this region.

MATERIALS AND METHODS

Data collection and analysis

This retrospective study was carried out in two centers which diagnose and manage MPN cases in Eastern Morocco: Boussif Diagnostic Center and Al-Farabi Regional Hospital with its hematology and internal medicine units.

We explore all medical records, pathology records and admission records in each participating center to select patients for whom the diagnosis of a MPN was confirmed during the study period from January 2008 to December 2012. The diagnosis was based mainly on clinical features, blood counts, peripheral blood films and morphology review of bone marrow aspirate and biopsy [20]. Genetic analyses were included whenever available to fulfill the 2008 WHO classification criteria [5-7]. A form has been used for collecting information recorded on each MPN case, such as the record number, name and surname of the patient, gender, and age at diagnosis, basis of diagnosis, clinical characteristics, laboratory characteristics, cytogenetic and molecular analysis if available, and treatment characteristics. For CML, the accelerated phase (AP) and the blastic phase (BP) were defined according to the criteria of the World Health Organization [5]. In the case of targeted therapy of CML with Imatinib, we recorded information on dosage, duration of the treatment, and side effects.

Data collection was performed on Excel. Statistical analysis was performed using SPSS software version 21.0. For the qualitative variables, we calculated the percentage, and for the quantitative variables, we calculated the median, minimum and maximum.

Ethical approval and authorization for personal data processing

In this retrospective study, obtaining informed consent was not possible. So, we were granted a waiver of consent by the Ethical Review Committee, and patient records/information was anonymized and de-identified prior to analysis. The study was approved by the Ethic Committee of the Faculty of Medicine and Pharmacy of Casablanca under the number 41/14. The authorization for personal data processing was obtained from the National Commission of control of Personal Data Protection under the number A-RS-280/2014.

RESULTS

Among the 84 cases of MPN registered between January 2008 and December 2012 in the two participating centres in Eastern Morocco, CML was the most frequent accounting for 78.6% of all MPN. PMF was the second most common MPN with 8.3%, followed respectively by PV (7.1%), ET (4.8%) and finally CEL (1.2%) (Table 1).

Chronic myeloid leukemia

In this study, 66 cases of CML were registered, 39 were women and 27 were men. The median age at diagnosis of CML patients was 49.5 years (Table 1). 97% of CML cases were observed in adults and 3% in children.

As shown in Table (2), 60% of CML patients in Eastern Morocco were symptomatic. The most common symptom was asthenia in 21.2% of cases, followed by unexplained fever (15.2%), left upper quadrant pain (13.6%), mucocutaneous pallor (12.1%), vomiting (7.6%) and weight loss (4.5%). In this study, it was noticed that 60% of CML patients had splenomegaly, and 30% had both splenomegaly and hepatomegaly.

The laboratory features of CML patients at initial presentation are given in Table (2). The median white blood cell (WBC) count was 100 G/L (rang: 10.6-600). The median platelet count was 211 G/L (range: 20-2305), while the median hemoglobin level was 95g/L (range: 41-160).

The analysis of the stage of the disease at diagnosis revealed that 55% of patients were in the chronic phase, 32% were in the blast phase, and 12% were in the accelerated phase (Table 2). Bone marrow examination at diagnosis was carried out in 83% of cases. In contrast, cytogenetic testing was performed in 33% of

Table 1: Distribution pattern, male to female ratio, and median age at diagnosis of MPN subtypes in Eastern Morocco.

MPN	N	%	F	M	M/F	Median age (years)
CML	66	78.6	39	27	0.7	49.5
PV	6	7.1	6	0		75.5
ET	4	4.8	4	0		46.5
PMF	7	8.3	1	6	6	66.0
CEL	1	1.2	0	1		

Abbreviations: N: Number of Cases; %: Percentage amongst all MPN Subtypes; F: Female; M: Male; M/F: Male to Female Ratio

Table 2: Characteristics of patients affected with CML.

Characteristics of the patients	(n) %
Circumstance of revelation	
Incidental	(26) 40
Symptomatic	(40) 60
Type of symptoms	
Asthenia	(14) 21.2
Unexplained fever	(10) 15.2
Left upper quadrant pain	(9) 13.6
Mucocutaneous pallor	(8) 12.1
Vomiting	(5) 7.6
Weight loss	(3) 4.5
Organomegaly at diagnosis	
Splenomegaly	(40) 60
Splenomegaly and hepatomegaly	(20) 30
Complete blood counts at diagnosis	
White blood cells (G/L, median, (min-max))	100 (10.6-600)
Eosinophils (% median)	2
Basophils (% median)	4
Blasts (% median)	4
Myelemy (% median)	38
Platelets (G/L, median, (min-max))	211 (20-2305)
Hemoglobin (g/L, median (min-max))	95 (41-160)
Stage of CML at diagnosis	
Chronic phase	(36) 55
Accelerated phase	(8) 12
Blastic phase	(21) 32
Treatment	
Hydroxyurea	(51) 77
Hydroxyurea + Imatinib	(9) 13
Imatinib	(6) 10
Imatinib dose (mg/day; median (min-max))	400 (100-800)
Duration of Imatinib treatment (months median (Min-max))	13.5 (1-36)

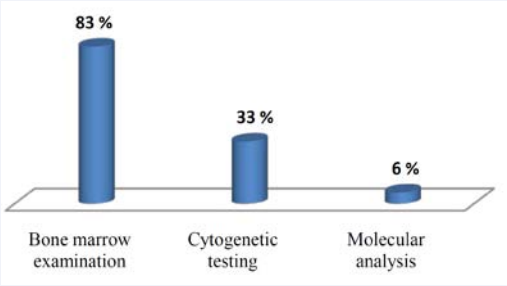

Figure 1 Percentage of CML patients who underwent bone marrow examination or for whom cytogenetic testing or molecular analysis was performed to confirm the diagnosis of CML in Eastern Morocco, 2008-2012.

cases. While, molecular testing for detecting the *BCR-ABL1* fusion gene was used in 6% of cases (Figure 1).

77% of CML patients were treated with Hydroxyurea (HU) alone, 10 % received treatment with the tyrosine kinase inhibitor (TKI) Imatinib alone, and 13% were treated with HU before starting treatment with Imatinib. The patients received a median daily dose of 400 mg (rang: 100-800) of Imatinib. The median duration of Imatinib treatment was 13.5 (range: 1-36) months. Amongst patients treated with Imatinib, the most frequent non-hematological adverse reactions were edema, diarrhea, nausea, fatigue and vomiting. While hematologic side effects were represented by thrombocytopenia, neutropenia and leukopenia. None of the patients in our series received a second or third generation TKI treatment or hematopoietic stem cell transplantation. At the end of the study and data collection period, 21% of the patients were deceased and 79% were still alive. Amongst the deaths, 18% were treated with HU, and 3% received Imatinib as targeted therapy.

Polycythemia vera

In our series, six cases of PV were registered and all were female (Table 1). The median age of PV patients at diagnosis was 75.5 years. The age distribution of PV shows that the majority of PV cases were observed in patients aged 60 years and over. As shown in Table (3), four cases of PV patients were symptomatic. The symptoms present at diagnosis were asthenia, plethora together with aquagenic pruritus, and headache together with dizziness. Splenomegaly was diagnosed in three cases. The median hematocrit percentage was 56.1 (range: 51-85), while the median hemoglobin level was 184 g/L (range: 165-245). The median platelet count was 543 G/L (range: 282-836), while the median white blood cell (WBC) count was 16.8 G/L (range: 7.3-41). Analysis of the most commonly recognized mutation in PV (JAK2 V617F) was carried out in one case and was positive. Three cases of PV patients were treated with phlebotomy alone, two cases with HU associated with phlebotomy, and one case with HU alone (Table 3).

Essential thrombocythemia

In this study, four cases of ET were registered and all were female (Table 1). The median age of ET patients at diagnosis was 46.5 years. The age distribution of ET shows that two cases of ET were observed in young adults (20-39 years), and two patients aged 60 years and over.

As shown in Table (3), two cases of ET were symptomatic. The symptoms present at diagnosis were asthenia, thrombosis and splenic infarction. None of our patients showed splenomegaly. Thrombocytosis has been well observed with a median platelet count of 1023.5 G/L (range: 884-16110). The median hemoglobin level was 115 g/L (range: 86-136). Analysis for mutated *JAK2* (*JAK2* V617F) was carried out in one case of ET and was positive. In our series, all ET cases for which data on treatment were available, were treated with HU.

Primary myelofibrosis

In this study, seven cases of PMF were registered, one was female and six were male. The median age at diagnosis of PMF patients was 66 years (Table 1). As shown in Table (3), two cases of PMF were symptomatic. The symptoms present at diagnosis were asthenia and portal hypertension. Splenomegaly was diagnosed in four cases, while hepatosplenomegaly was observed in two cases of PMF. The laboratory characteristics at diagnosis of PMF are shown in Table (3). The median hemoglobin level was 59 g/L (range: 57-106), while the median hematocrit percentage was 20.6% (range: 14.5-36.9). The median platelet count was 99

Table 3: Characteristics of the patients affected with BCR-ABL1 negative MPN subtypes.

Characteristics of the patients	PV (N= 6)	ET (N= 4)	PMF (N= 7)
Circumstance of revelation			
Incidental	2	2	2
Symptomatic	4	2	2
Not available	-	-	3
Type of symptoms			
Asthenia	2	1	1
Plethora and aquagenic pruritus	1	-	-
Headache and Dizziness	1	-	-
Thrombosis and splenic infarction	-	1	-
Portal Hypertension	-	-	1
Organomegaly at diagnosis			
Splenomegaly	3	0	2
Splenomegaly and hepatomegaly	0	0	2
Complete blood counts at diagnosis			
Hemoglobin (g/L, median (min-max))	184 (165-245)	115 (86-136)	59 (57-106)
Hematocrit (%; median (min-max))	56.1 (51-85)	36 (28.3-42)	20.6 (14.5-36.9)
White blood cells (G/L, median, (min-max))	16.8 (7.3-41)	10.1 (6.4-21.7)	7.4 (3.5-40)
Platelets (G/L, median, (min-max))	543 (282-836)	1023.5 (884-16110)	99 (26-698)
Molecular analysis for Mutated *JAK2*			
Not performed	5	3	4
Present	1	1	2
Absent	0	0	1
Treatment			
Phlebotomy alone	3	-	-
Phlebotomy + Hydroxyurea	2	-	-
Hydroxyurea	1	3	2
Danazol	-	-	1
Danazol and Corticotherapy	-	-	1
Thalidomide	-	-	1
Not available	-	1	2

G/L (range: 26-698), while the median white blood cell (WBC) count was 7.4 G/L (rang: 3.5-40). The analysis for mutated *JAK2* (*JAK2 V617F*) was carried out in three cases of PMF, and amongst these two cases were positive. For PMF treatment, two cases of PMF patients were treated with HU, one case with Danazol alone, one case with Danazol associated with corticotherapy, and one case with Thalidomide.

Chronic eosinophilic leukemia

In this study, one case of CEL, a male patient aged 29 years, was recorded. The patient presented with pallor and hepatosplenomegaly. The laboratory features at initial presentation were as follow: the hemoglobin level was 100 g/L, the hematocrit percentage was 32%, the platelet count was 59 G/L, and the white blood cell (WBC) count was 19 G/L. The basophil percentage was 1.2%, and the eosinophil count was 5.7 G/L, while the myelemy percentage was 13%. Treatment evaluation could not be performed due to lack of available data in this case.

DISCUSSION

In a previous work, we have shown that MPN are the most common myeloid neoplasms in Eastern Morocco [19]. Here we show the detailed investigation of the various subtypes of MPN. To our knowledge, this is the first study on MPN in Eastern Morocco. We found that CML was the most frequent accounting for 78.6% of all MPN, followed respectively by PMF, PV, ET, and finally CEL.

Chronic myeloid leukemia

Median age at diagnosis of CML in Eastern Morocco: Our study revealed that the median age at diagnosis of CML patients in Eastern Morocco was 49.5 years. However, in Western countries, CML generally affects older people. For example, in the United Kingdom the median age at diagnosis of CML was 59 years [21]. Similarly, in Turkey, the median age at diagnosis was 71 years [22]. However, in Asia and Africa, CML generally affects people who are much younger [23]. For example, in Bangladesh the median age at diagnosis was 40 years [24]. Thus, the median age at diagnosis of CML in Eastern Morocco is lower than that found in Western countries.

Characteristics of patients affected with CML in Eastern Morocco: The majority (60%) of CML patients in Eastern Morocco were symptomatic. Such a finding is far from those reported in Western countries, where symptomatic diagnosis of CML was lower. For example, in Japan and United States the diagnosis of CML was symptomatic in about 20-50% and 30-50% of cases, respectively [25,26]. Similarly, in Belgium, CML was diagnosed symptomatically in 45.1% of cases [27]. Therefore, in comparison with the developed countries, in our population CML is diagnosed symptomatically in most cases, probably because of delayed presentation at health care centers.

It was noticed that 60% of CML patients had splenomegaly in this study. This percentage is similar than those reported in other studies (50% to 60%) [25,28] but lower than those reported in India (81% to 100%) [29,30].

Cytogenetic testing was performed in only 33% of cases. Similarly, molecular testing was used in only 6% of cases. These findings are expected because karyotyping and molecular testing are not affordable for the majority of CML patients in our population. Indeed, in our population, the majority of patients are poor and do not have health insurance. Moreover, until now there is no cytogenetic or molecular laboratory available in Eastern Morocco. Therefore, only a small percentage of patients underwent cytogenetic testing for detecting the Philadelphia chromosome or molecular testing for detecting the *BCR-ABL1* fusion gene. However, according to the WHO, detection of the Philadelphia (Ph) chromosome and/or *BCR-ABL1* fusion gene is essential to confirm the diagnosis of CML [5]. Thus, more resources are needed to facilitate access to cytogenetic and molecular diagnosis for all patients in Eastern Morocco.

We found that in our population, a high percentage of patients were diagnosed at late stages. This finding is in contrast to other studies. For example in Turkey during the first evaluation of patients, 94.9% of patients were in the chronic phase and only 1.1% were in the blastic phase [31]. Similarly, in another study in Brazil, 96% of patients were in the chronic phase of the disease and only 2% in the blastic phase [32]. This more advanced disease at diagnosis in our region may be due to the delayed presentation at health care centers and/or may be explained by little or no access to treatment.

Therapeutic characteristics of patients affected with CML in Eastern Morocco: According to the Recommendations of the European Leukemia Net, HU may be used for a short period in terms of decreasing WBC count before starting treatment of CML with TKI [33]. In our series, we observed that 13% of patients were treated with HU before starting treatment with Imatinib, which is very low compared to those reported in Belgium and Turkey, where 54.4% and 76.4% of patients had been treated with HU before starting treatment with Imatinib, respectively [27,31].

Only 23% of CML patients received treatment with TKI Imatinib. In addition, none of the patients received a second or third generation TKI treatment. These findings are expected because in our population, the majority of patients are poor and do not have health insurance and therefore cannot afford the TKI treatment. Moreover, in most cases, our patients do not have the financial ability to carry out molecular analyses, which are major diagnostic criteria according to the WHO classification to benefit from treatment with TKIs.

The median duration of Imatinib treatment was 13.5 (range: 1-36) months, which is low compared to what has been observed in other study (35.6 months) [31]. This may be explained by late diagnosis of the disease. The evaluation of the molecular and cytogenetic response has not been assessed in our retrospective study because of the lack of data in most cases.

Polycythemia vera

The median age of PV patients at diagnosis was 75.5 years. A similar median age was reported in France (71 years) [34]. However, a lower median age was reported in other studies (55-66 years) [35-39].

In our study, four cases of PV were symptomatic. Such a finding is far from those reported in other studies, where the majority of PV cases were asymptomatic and diagnosed incidentally [40,41]. The aquagenic pruritus was observed in one patient of our PV patients, and it is indeed a classical clinical feature of PV, but occurs in only a few patients [37,42].

The laboratory characteristics at initial presentation of our PV patients were similar to those reported in other studies [42]. Similarly, the thrombocytosis observed in our patients was also reported in the literature [34,36,38].

According to the WHO, detection of *JAK2* V617F mutation is one of the major criteria required for the diagnosis of PV [5,7]. Indeed, this mutation is found in over 90% of PV [42]. In Casablanca in Morocco, this mutation was detected in 89.47% of cases of PV [43]. In our series, the analysis of this mutation was carried out in only one case of PV and was positive. Therefore, diagnosis of PV in Eastern Morocco can be very challenging due to the lack of financial ability to carry out molecular analyses amongst patients.

For PV treatment, It has been previously shown that phlebotomy provides the best overall survival but it may increase the risk of thrombosis during the first 3 years [44,45]. Hydroxyurea is also used to treat PV in patients who are at high risk of thrombosis or in those who cannot tolerate phlebotomy [46]. In our study, treatment with HU was carried out in 3 PV patients aged 60 years and over. However, phlebotomy alone was used in two cases aged 80 and 82 years that died before treatment with HU. Thus, more resources are needed to facilitate access to accurate treatment for PV patients who are at high risk of thrombosis.

Essential thrombocythemia

In this study, four cases of ET were observed and all were female. This is consistent with other studies, where a female predominance was observed [35,36,47]. The median age of ET patients at diagnosis was 46.5 years. Such finding is far from those reported in other studies, where the median age at presentation for ET was higher (65-70 years) [35,36,48,49]. Although ET is primarily diagnosed in older patients, it has been also reported that there is a second peak incidence for ET around 30 years, particularly among women [50]. This is consistent with our data since the age distribution of ET in our study shows that two cases of ET were observed in young adults (20-39 years), and two in patients aged 60 years and over. However, because of the small number of ET patients in this study, further studies are needed to confirm the pattern of ET in Eastern Morocco.

Thrombocytosis, which characterizes ET has been well observed in our study with a median platelet count of 1023.5 G/L. This thrombocytosis was also reported in other studies [7,36,49]. The median hemoglobin level was 115 g/L (range: 86-136), which is lower than those reported in other studies [36,51].

Like for PV, according to the WHO, detection of *JAK2* V617F mutation is one of the major criteria required for the diagnosis of ET [5,7]. Indeed, this mutation is found in around 50% to 60% of ET [42,52]. In Casablanca in Morocco, this mutation was detected in 62.5% of cases of ET [43]. In this study, the analysis of this mutation was carried out in only one case of ET and was positive.

Primary myelofibrosis

The median age at diagnosis of PMF patients in our population was similar to those reported in other studies, where the median age at presentation was between 61-67 years [36,53-55]. The laboratory characteristics at initial presentation of our PMF patients were similar to those reported in other studies [51,56]. The analysis for mutated *JAK2* (*JAK2 V617F*) was carried out in only three cases out of the seven PMF patients. Thus, more resources are needed to facilitate access to molecular diagnosis; particularly analysis for mutated JAK2 should be included as diagnostic parameter for PMF in Eastern Morocco.

For PMF treatment, allogeneic bone marrow transplantation is currently the only therapy that has the potential to abolish bone marrow fibrosis and may achieve a cure [57]. However,

bone marrow transplantation therapy is suitable for only a minority of PMF patients [58]. In our series, none of the PMF patients received bone marrow transplantation. We found that two cases of PMF were treated with HU, one case with Danazol alone, one case with Danazol associated with corticotherapy, and one case with Thalidomide. It has been previously shown that treatment with HU is indicated in the hyperproliferative form of PMF characterized by leucocytosis, marked splenomegaly and thrombocytosis [59]. In addition, HU has been largely used despite limited data supporting its effectiveness [59,60]. Concerning Danazol which is an attenuated synthetic androgen, it is the treatment of choice in PMF patients with anemia [61]. Thalidomide is another non-transplant treatment used for palliative purposes in the case of PMF, but it is associated with adverse effects [56].

Chronic eosinophilic leukemia

Only one case of CEL, a male patient aged 29 years, was recorded in this study. The clinical and laboratory characteristics of this patient were similar to those reported in other studies for CEL patients [62,63]. It is worth noting that to make a diagnosis of CEL, other hypereosinophilic syndrome must be excluded [6]. In addition, chromosomal aberrations and gene mutation analysis are important for the classification of cases with eosinophilia [6]. In our case, data on molecular or cytogenetic analysis of CEL were not found. Similarly, treatment evaluation could not be performed due to lack of available data in this case. Therefore, much more effort is required for the diagnosis and management of CEL in our region.

CONCLUSION

This study has clarified the clinical, biological and therapeutic characteristics of MPN in Eastern Morocco. We found that in Eastern Morocco patients with MPN are young and often diagnosed late at an advanced stage of the disease, which considerably compromises the effectiveness of the treatment. In addition cytogenetic and gene mutations analysis were carried out in only a small fractions of patients with MPN. Our results justify the necessity of establishing an effective program against these hematological cancers in Eastern Morocco, particularly much more effort is needed in terms of establishment of cytogenetic and molecular laboratories required for the diagnosis and monitoring of patients with MPN.

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