Retrospective Analysis of 111 Cases with Chronic Myeloproliferative Disorders: Clinical Features and Survival

Kronik Miyeloproliferatif Hastalığı Olan 111 Olgunun Retrospektif Analizi: Klinik Özellikler ve Sürvi

Olga Meltem AKAY, MD,[a]
Nazife Şule YAŞAR, MD,[a]
Hava ÜSKÜDAR TEKE, MD,[a]
Fezan ŞAHİN MUTLU, MD,[b]
Zafer GÜLBAŞ, MD[a]

Departments of [a]Hematology, [b]Biostatistics Eskişehir Osmangazi University Faculty of Medicine, Eskişehir

Geliş Tarihi/*Received:* 18.05.2008
Kabul Tarihi/*Accepted:* 21.10.2008

Yazışma Adresi/*Correspondence:*
Zafer GÜLBAŞ, MD
Eskişehir Osmangazi University Faculty of Medicine,
Department of Hematology, Eskişehir, TÜRKİYE/TURKEY
zgulbas@superonline.com

ABSTRACT Objective: In this retrospective study, the clinical features, treatment modalities and survival durations of 111 patients with chronic myeloproliferative disorders (MPDs) were analyzed. **Material and Methods:** The medical records of 111 MPD patients including 58 patients with polycythemia vera (PV), 32 with essential thrombocythemia (ET), and 21 with idiopathic myelofibrosis (IMF) who presented to our center between 1987-2006 were evaluated. **Results:** Among all of the patients, 57 were female and 54 were male (female/male ratio, 1.1). The median age at the time of diagnosis was 61 years (range, 28-81 years). Thrombotic events were more common than bleeding in patients with PV (thrombotic/hemorrhagic events: 34/16) and ET (thrombotic/hemorrhagic events: 21/11) whereas bleeding was slightly more common than thrombotic events in patients with IMF (thrombotic/hemorrhagic events: 4/5). Arterial thrombotic events predominated over venous events and involved primarily cerebral and coronary arteries. The majority of bleeding manifestations affected the skin, mucous membranes, and the gastrointestinal system. Kaplan-Meier curves showed that mean survival time was 21.3 ± 3.6 years (1-29) in PV patients and 12.7 ± 0.3 years (1-13) in ET patients while IMF patients had a mean survival time of 7.4 ± 1.5 years (0.5-12). Survival was shortened with advanced age ($p < 0.05$), anemia ($p < 0.05$) and male gender ($p > 0.05$). **Conclusion:** MPDs share many overlapping clinical and laboratory features but exhibit different survival rates being highest for PV and lowest for IMF. The relatively high frequency of thromboembolic complications in this study cohort emphasizes the importance of using an antithrombotic preventive strategy in MPD patients.

Key Words: Polycythemia vera; thrombocythemia, essential

ÖZET Amaç: Bu retrospektif çalışmada, kronik miyeloproliferatif hastalığı (MPH) olan 111 olgunun klinik özellikleri, tedavi şekilleri ve yaşam süreleri incelendi. **Gereç ve Yöntemler:** 1987-2006 yılları arasında merkezimize başvuran 58 polistemia vera (PV), 32 esansiyel trombositoz (ET) ve 21 idiyopatik miyelofibrozis (IMF) olgusunu içeren 111 MPH hastasının tıbbi kayıtları değerlendirildi. **Bulgular:** Olguların 57'si kadın, 54'ü erkek (kadın/erkek oranı, 1.1) idi. Tanı sırasında hastaların ortanca yaşları 61 (28-81 yaş aralığı) idi. PV ve ET'li olgularda trombotik olaylar, hemorajik olaylardan daha sık gelişirken (trombotik/hemorajik olay oranları PV ve ET alt gruplarında sırasıyla 34/16 ve 21/11), IMF'li olgularda hemorajik olaylar, trombotik olaylardan hafifçe daha yüksek oranda bulunmuştur (trombotik/hemorajik olay oranı 4/5). Arteriyel trombotik olaylar venöz olaylardan daha sık olup başlıca serebral ve koroner arterlerde gelişmiştir. Hemorajik olaylar çoğunlukla cilt, mukoz membranlar ve gastrointestinal sistemi etkilemiştir. Kaplan-Meier eğrisine göre ortalama sağkalım süresi PV'li olgularda 21.3 ± 3.6 yıl (1-29 yıl), ET'li olgularda 12.7 ± 0.3 yıl (1-13 yıl) iken IMF'li olgularda 7.4 ± 1.5 yıl (0.5-12 yıl) olarak gösterildi. İleri yaşta ($p < 0.05$), anemisi olan olgularda ($p < 0.05$) ve erkek cinsiyette ($p > 0.05$) sağkalım daha kısa bulundu. **Sonuç:** MPH'ler birçok örtüşen klinik ve laboratuvar özellikleri paylaşırken; PV'de en yüksek ve IMF'de en düşük olmak üzere farklı sağkalım oranları göstermektedir. Çalışma grubumuzdaki oldukça yüksek tromboembolik komplikasyon oranı, MPH'li olgularda antitrombotik profilaktik tedavi kullanımının önemini vurgulamaktadır.

Anahtar Kelimeler: Polistemia vera; esansiyel trombositoz

Turkiye Klinikleri J Med Sci 2009;29(1):162-8

Myeloproliferative disorders (MPDs) are clonal hematological malignancies that arise from the transformation of a multipotent hematopoietic stem cell. MPD comprises the conditions chronic myeloid leukemia (CML), PV, ET, IMF and in the revised World Health Organization (WHO) classification also includes rare entities such as chronic neutrophilic leukemia.[1] These diseases in the past have been poorly understood except for CML, which is genetically characterized by the presence of the Philadelphia (Ph) chromosome and the bcl/abl fusion gene.[2] However, the identification of a mutation in the Janus kinase 2 (JAK2) detectable in the majority of patients represented a major advance in our understanding of the molecular pathogenesis of MPDs.[1]

The distinction between subgroups is based on the presence or absence of particular clinical and laboratory features. PV is defined primarily by an elevated red cell mass, ET by high platelet counts and IMF by substantial bone marrow fibrosis and extramedullary hematopoiesis.[3] As a group, all MPDs are preleukemic and are predisposed to clonal evolution and disease transformation.[4] The propensity to transform into acute myeloid leukemia differs between subgroups, being highest for CML and lowest for ET. Another biologic complication shared among the MPDs is the thrombotic and bleeding tendency that significantly influences upon prognosis and quality of life.[1] Because of the variable risks of blastic transformation and thrombosis-associated deaths, overall survival in the MPDs ranges from a near-normal life expectancy in patients with ET to a median of less than 5 years in patients with IMF.[5]

This retrospective single-center study analyzed 111 patients with MPDs, including PV, ET, and IMF only. Here, we present data on the complications, treatment modalities and survival.

MATERIAL AND METHODS

In this study, we identified 111 patients with MPD for whom clinical data and follow-up information could be obtained from the records of the Department of Internal Medicine, Division of Hematology, Eskişehir Osmangazi University Faculty of Medicine between 1987-2006. For the diagnosis of PV, raised cell mass ≥36 mL/kg for males and ≥32 for females in the absence of hypoxemia (arterial oxygen saturation ≥92%) and in the presence of splenomegaly were used as major criteria. A diagnosis of ET was made with peripheral thrombocytosis (>600 x 10^9/L), characteristic marrow features with stainable marrow iron stores as described by Murphy et al.[3] The diagnosis of IMF was based on characteristic bone marrow histology with splenomegaly, leucoerythroblastic smear and the absence of other causes of myelofibrosis.[6]

In the analysis of thromboembolic complications, occlusive events in the arterial or venous system and in the microcirculation including erythromelalgia and Raynaud's phenomena were included. In the analysis of hemorrhagic events, major hemorrhage and prolonged mucocutaneous bleedings were recorded.

Statistical Analysis

Statistical tests were performed using SPSS for Windows 15.0 software package and Sigmastat 3.1 software package; differences with a p value below 0.05 were considered significant. The Shapiro-Wilk test was performed for testing normality. The chi-square test was used to compare categorical variables and the Kruskal Wallis test for continuous variables not normally distributed, followed by Dunn's post hoc test. Survival was assessed using the Kaplan-Meier analysis; the log-rank test was used for univariate comparisons. The effect of prognostic factors on survival was analyzed by Cox proportional hazards regression models.

RESULTS

The characteristics of 111 patients included in this study are summarized in Table 1. 54 patients were male and 57 female; their ages at diagnosis ranged from 28 to 81 years (median 61 years). 58 patients were classified as PV, 32 as ET, and 21 as IMF. Splenomegaly was present in 44 of 56 (79%), 10 of 32 (31%), and 21 of 21 (100%) patients with PV, ET and IMF, respectively ($p < 0.001$). The spleen was mildly enlarged in patients with ET and PV and massively enlarged in the IMF subgroup.

TABLE 1: Clinical and laboratory characteristics of 111 patients with MPDs.

	PV	ET	AMM	p value
Clinical Characteristics				
No. of patients (n)	58	32	21	
Female	29	14	14	
Male	29	18	7	
Age (mean ± SD)	59.7 ± 11.0	58.3 ± 14.0	63.0 ± 10.00	
Splenomegaly (%)	44/56 (79)	10/32 (31)	21/21 (100)	< 0.001
Laboratory Characteristics (Median, Range)[a]				
Hematocrit (%)	54 (20-67)	37 (21-47)	31 (11-52)	< 0.001
Leucocyte count (x 10^9/1)	15.1 (5.0-51.7)	13.2 (3.6-50.4)	9.3 (3.2-21.9)	NS
Platelet count (x 10^9/1)	609 (116-3480)	1412 (699-3100)	284 (15-942)	< 0.001
Patientsb with pseudohyperkalemia (%)	15/54 (28)	14/31 (45)	2/19 (11)	< 0.05
Patients with increased LDH (%)	36/52 (69)	21/27 (78)	16/19 (84)	NS

[a]Available before the onset of any treatment modalities.

PV: Polycythemia vera, ET: Essential thrombocythemia, IMF: Idiopathic myelofibrosis, MPDs: Myeloproliferative disorders.

TABLE 2: Treatment modalities in 111 patients with MPDs.

	PV	ET	AMM
Cytoreductive Therapy (patients, %)			
Hydoxyurea	47 (81)	29 (91)	7 (33)
Androgens	1 (2)	-	11 (52)
Alkylating agents	11 (19)	10 (31)	-
Interferon-α 2a	2 (3)	1 (3)	-
None	2 (3)	-	3 (14)
Antithrombotic Therapy (patients, %)			
Anti-aggregants[a]	28 (48)	17 (53)	-
Anticoagulants[b]	6 (10)	4 (13)	1 (5)
Phlebotomy	46 (79)	-	2 (10)
Splenoctomy (patients, %)	3 (5)	3 (9)	5 (24)

[a] Aspirin and dipyridamole, [b]Warfarin and heparin

PV: Polycythemia vera, ET: Essential thrombocythemia, IMF: Idiopathic myelofibrosis, MPDs: Myeloproliferative disorders.

At the time of diagnosis, the median hematocrit count was 54% (range 20-67) in PV patients and the median platelet count was 1412 x 10^9/L (range 699-3100) in ET patients. The hematological parameters at initial diagnosis differed significantly among MPD subgroups as shown in Table 1. Hematocrit was elevated in PV ($p< 0.001$) and platelet count was highest in ET ($p< 0.001$) while leucocyte count showed no difference between subgroups. 30% of patients had a potassium level of greater than 5.5 meq/L (range 3.5-5.5 meq/L) at diagnosis and LDH level exceeded 480 U/L (range 240-480 U/L) in 74%.

Hydroxyurea was the most commonly preferred agent in PV and ET subgroups while androgens were used in a significant proportion (52%) of patients with IMF. Only three patients were prescribed interferon-α. Phlebotomy was the usual initial treatment for most patients with PV to reduce the hematocrit and risk of thrombosis. Aspirin therapy and alternative antiagregating agents were used in the prevention of thrombosis whereas oral anticoagulants were administered for secondary prophylaxis after a first thrombotic event. Five patients with IMF who had excessive transfusion requirements and severe thrombocytopenia underwent splenectomy (Table 2).

Thrombohemorrhagic events and other complications are shown in Table 3. We observed 59 thrombotic and 32 hemorrhagic events in these 111 patients. Thrombotic events were more common than bleeding in patients with PV (thrombotic/he-

morrhagic events: 34/16) and ET (thrombotic/hemorrhagic events: 21/11) whereas bleeding was slightly more common than thrombotic events in patients with IMF (thrombotic/hemorrhagic events: 4/5). In general, arterial events (78%) predominated over venous events. Major arterial events included, in descending order of frequency, cerebrovascular accidents, coronary heart disease (angina pectoris or myocardial infarction) and erythromelalgia. Lower extremity deep venous thrombosis (DVT) and pulmonary embolism accounted for the majority of venous events. Less common sites of venous thrombosis were the portal, splenic and mesenteric veins. There was no significant correlation between the occurrence of thrombosis and hematologic indices such as hematocrit, leucocyte, and platelet count in PV and ET patients. 14 (36%) of patients experiencing thrombotic events, had conventional risk factors including diabetes mellitus, hyperlipidemia, hypertension, and/or smoking.

Bleeding manifestations involved primarily skin and mucous membranes (epistaxis, ecchymosis, menorrhagia and gingival hemorrhage) and gastrointestinal system. 42% of all hemorrhagic episodes were secondary to the clinically indicated use of anticoagulants or antiaggregating agents. During the follow-up, one PV and one ET patient evolved into acute leukemia, 6 years and 7 years after diagnosis, respectively. Both patients had been exposed to hydroxyurea and alkylating agents. Myelofibrosis developed in one patient with PV at 3 years after diagnosis.

The evaluation of the Kaplan-Meier curves showed that the mean survival time was 21.3 ± 3.6 years (1-29) in PV patients and 12.7 ± 0.3 years (1-13) in ET patients while IMF patients had a mean survival time of 7.4 ± 1.5 years (0.5-12) (Figure 1). Overall survival time in MPD patients was 19.9 ± 2.5 years (0.5-29). We evaluated the association between survival time and gender, age (<60 years and ≥60 years) and hemoglobin level (<10 g/dL and ≥10 g/dL) by cox regression analysis. Cox regression analysis showed that survival was shortened 5.8-fold with advanced age (p= 0.044; hazard ratio of 5.8, [95% Cl 1.1-31.6]), 2.9-fold with male gender (p= 0.230; hazard ratio of 0.3, [95% Cl 0.1-2.0]), and 10.3-fold with anemia (p= 0.018; hazard ratio of 0.1, [95% Cl 0.01-0.7]). Thrombotic and hemorrhagic events and conventional risk factors had no influence on the length of survival. We evaluated

TABLE 3: Hemostatic and other complications in 111 patients.

	PV	ET	AMM
Tromboembolic Events (Absolute Numbers)	34	21	4
Atreial	28	15	3
Cerebral	12	6	-
Cardiac	4	3	1
Extremity	1	2	-
Raynaud's phenomenon	3	-	-
Erythromelalgia	8	4	2
Venous	6	6	1
Extremity	3	3	1
Pulmonary embolism	3	-	-
Others[a]	-	3	1
Hemorrhage[b]	16	11	5
Epistaxis	6	6	4
Other mucocutaneousc	7	1	1
Gastrointestinal	3	4	-
Leukemic Transformation	1	1	-
Secondary Myelofibrosis	-	1	-

[a] Mesenteric, portal and splenic thrombosis,
[b] 42% of all events observed in anticoagulated patients,
[c] Hematoma, oral bleeding and menorrhagia.
PV: Polycythemia vera, ET: Essential thrombocythemia, IMF: Idiopathic myelofibrosis, MPDs: Myeloproliferative disorders.

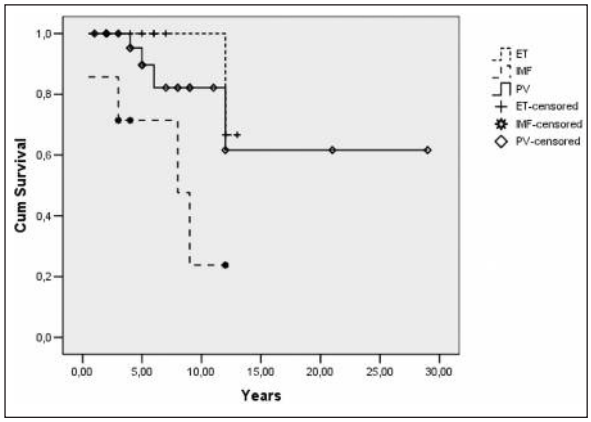

FIGURE 1: Kaplan Meier survival curves of 111 patients with myeloproliferative disorders.

the association between survival time and hemoglobin level (<10 g/dL and ≥10 g/dL) and platelet count (<100 x 10^9/L ≥) in a separate data of IMF patients and noticed that these parameters did not influence survival in patients with IMF.

DISCUSSION

This single-center retrospective study aimed to compare clinical features, treatment modalities and survival durations in a cohort of 111 patients with MPDs.

Thrombohemorrhagic events were the most frequent complications shared among the 111 MPD patients. The frequency of thrombosis was greater than that of bleeding being highest in PV patients followed by ET and IMF patients. Arterial events predominated over venous events in all subgroups occurring commonly in cerebral arteries, coronary arteries, and microcirculatory locations. The incidence of either thrombosis or hemorrhage is difficult to establish in MPDs. Published data describe a wide range of values for the relative frequency of thrombohemorrhagic episodes, probably due to factors including patient selection, definitions of events, accuracy in data reporting and the effect of therapy.[7] Regardless, the frequency of thrombosis (arterial, venous and microcirculatory) has been consistently greater than bleeding.[8] The prothrombotic effect of an elevated hematocrit is well established in the pathogenesis of thrombosis. The relationship between increased hematocrit level and decreased cerebral blood flow rate was shown in vivo.[9]

Increasing age and a history of vascular events proved to be other independent predictors of thrombosis in patients with PV.[10] Leucocytosis is also a risk factor for thrombosis in PV and ET through recently discovered mechanisms of activation and interaction with platelets and endothelial cells.[11-13] High JAK2 V617F mutation allele burden is being currently investigated for additional prognostic value in vascular events.[10] Although this data could not show any correlation between the occurrence of vascular events and hematologic indices (ie, hematocrit, leucocyte, and platelet count), our findings demonstrated the differences in the kind and localization of hemorrhagic and thromboembolic complications in MPD subtypes. The relatively high frequency of thromboembolic complications in this study cohort suggests that more stringent thromboprophylaxis may be indicated for MPD patients.[10]

Hydroxyurea was the most commonly used agent in PV and ET subgroups whereas aspirin therapy was preferred for the prevention of thrombosis. In high-risk patients for thrombosis, the benefits of myelosuppressive therapy outweigh the potential risk of toxicity.[7] Current evidence supports the use of hydroxyurea as the initial choice of cytoreductive agent because of its proven efficacy.[14,15] Aspirin further reduces thrombotic risk in PV patients whereas retrospective observations suggest that it might be similarly beneficial in ET patients.[16-19] The current data supports the therapeutic value of hydroxyurea and aspirin in patients with PV and ET.

Another biologic complication shared among our patients was disease transformation. Transformation into a myelofibrotic stage develops in approximately 12% of PV patients, but rarely occurs in ET patients. The propensity to transform into acute leukemia differs among the subgroups, being highest for IMF and least for ET.[20] Radioactive phosphorus (^{32}P) and cytoreductive agents such as busulfan and hydroxyurea are thought to play a causative role in the pathogenesis of leukemic transformation.[21] One PV and one ET patient

transformed to acute leukemia after receiving hydroxyurea and an alkylating agent, which is also mentioned in leukemic transformation of ET.[22,23]

We observed that survival was highest in PV and lowest in IMF. Survival of patients in this cohort was favorably comparable with previous reports. PV has a survival rate between 10 and 20 years, while IMF has the worst prognosis with a median survival of 3.5 to 5.5 years among MPDs.[24,25] The survival rate for MPDs varies, depending on the type of disorder and the kind of symptoms experienced by each individual. Prognosis is highly dependent on the occurrence of thrombohemorrhagic complications.[26] The other factors associated with shorter survival include age (>60), sex (male), splenomegaly, anemia, leucocytosis or leucocytopenia, thrombocytopenia, increased blasts in the peripheral blood and the presence of symptoms.[27-29] It is notable that several prognostic scoring systems have been established and widely used for survival in IMF patients.[30-33] In the current study, we demonstrated an unfavorable prognostic impact of male gender, age, and anemia, supporting the predictive value of clinical and laboratory variables for defining survival in MPD patients.

Being a retrospective study, the main limitation of our study was that diagnostic criteria for PV, ET, and IMF were based on clinical and morphologic findings. Recent discoveries of myeloproliferative disease specific molecular markers, including JAK2 mutation have opened a new era in our understanding of these diseases and furthermore the diagnostic criteria for MPDs have been revised by incorporating JAK2 mutation screening.[34,35]

In conclusion, MPDs share many overlapping clinical and laboratory features but exhibit different survival rates being highest for PV and lowest for IMF. The relatively high occurrence of thromboembolic complications suggests a rationale for the use of an antithrombotic preventive strategy in patients with MPD. The current study supports the use of prognostic markers to aid further both physicians and patients in treatment recommendations and informed decisions making, respectively. Finally, much larger group of patients is required to establish new international prognostic models for MPD.

REFERENCES

1. Vainchenker W, Constantinescu SN. A unique activating mutation in JAK2 (V617F) is at the origin of polycythemia vera and allows a new classification of myeloproliferative diseases. Hematology Am Soc Hematol Educ Program 2005:195-200.
2. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. J Natl Cancer Inst 1960;25:85-109.
3. Murphy S, Peterson P, Iland H, Laszlo J. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol 1997;34(1):29-39.
4. Gaidano G, Guerrasio A, Serra A, Rege-Cambrin G, Saglio G. Molecular mechanisms of tumor progression in chronic myeloproliferative disorders. Leukemia 1994;8(Suppl 1):S27-9.
5. Rozman C, Giralt M, Feliu E, Rubio D, Cortés MT. Life expectancy of patients with chronic nonleukemic myeloproliferative disorders. Cancer 1991;67(10):2658-63.
6. Silverstein MN. Agnogenic myeloid metaplasia. In: Williams WJ, Beutler E, Erslev AJ Lichtman MA, eds. Williams Hematology. 3rd ed. New York: McGraw-Hill; 1983. p.214.
7. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 2005; 128(3):275-90.
8. Landolfi R, Rocca B, Patrono C. Bleeding and thrombosis in myeloproliferative disorders: mechanisms and treatment. Crit Rev Oncol Hematol 1995;20(3):203-22.
9. Kassum D, Thomas EJ. Morbidity and mortality of incidental splenectomy. Can J Surg 1977;20(3):209-14.
10. Finazzi G, Barbui T. How I treat patients with polycythemia vera. Blood 2007;109(12):5104-11.
11. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 2007;109(6):2446-52.
12. Carobbio A, Finazzi G, Guerini V, Spinelli O, Delaini F, Marchioli R, et al. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: interaction with treatment, standard risk factors, and Jak2 mutation status. Blood 2007;109(6):2310-3.
13. Gangat N, Strand J, Li CY, Wu W, Pardanani A, Tefferi A. Leucocytosis in polycythaemia vera predicts both inferior survival and leukaemic transformation. Br J Haematol 2007;138 (3):354-8.
14. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol 1986;23(2):132-43.
15. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995;332(17):1132-6.
16. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004;350(2):114-24.

17. van Genderen PJ, Mulder PG, Waleboer M, van de Moesdijk D, Michiels JJ. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. Br J Haematol 1997;97(1):179-84.
18. Randi ML, Rossi C, Fabris F, Menapace L, Girolami A. Aspirin seems as effective as myelosuppressive agents in the prevention of rethrombosis in essential thrombocythemia. Clin Appl Thromb Hemost 1999;5(2):131-5.
19. Jensen MK, de Nully Brown P, Nielsen OJ, Hasselbalch HC. Incidence, clinical features and outcome of essential thrombocythaemia in a well defined geographical area. Eur J Haematol 2000;65(2):132-9.
20. Brodmann S, Passweg JR, Gratwohl A, Tichelli A, Skoda RC. Myeloproliferative disorders: complications, survival and causes of death. Ann Hematol 2000;79(6):312-8.
21. Sedlacek SM, Curtis JL, Weintraub J, Levin J. Essential thrombocythemia and leukemic transformation. Medicine (Baltimore) 1986;65 (6):353-64.
22. Yonekura S, Nagao T, Arimori S. Essential thrombocythemia developing into refractory anemia and complicated by acute myeloid leukemia. Intern Med 1992;31(10):1224-7.
23. Higuchi T, Okada S, Mori H, Niikura H, Omine M, Terada H. Leukemic transformation of polycythemia vera and essential thrombocythemia possibly associated with an alkylating agent. Cancer 1995;75(2):471-7.
24. Talarico L. Myeloproliferative disorders: a practical review. Patient Care 1998;30:37-57.
25. Tefferi A. Myelofibrosis with myeloid metaplasia. N Engl J Med 2000;342(17):1255-65.
26. Schafer AI. Molecular basis of the diagnosis and treatment of polycythemia vera and essential thrombocythemia. Blood 2006;107(11): 4214-22.
27. Okamura T, Kinukawa N, Niho Y, Mizoguchi H. Primary chronic myelofibrosis: clinical and prognostic evaluation in 336 Japanese patients. Int J Hematol 2001;73(2):194-8.
28. Wolanskyj AP, Schwager SM, McClure RF, Larson DR, Tefferi A. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. Mayo Clin Proc 2006;81(2): 159-66.
29. Rupoli S, Da Lio L, Sisti S, Campanati G, Salvi A, Brianzoni MF, et al. Primary myelofibrosis: a detailed statistical analysis of the clinicopathological variables influencing survival. Ann Hematol 1994;68(4):205-12.
30. Tefferi A. Essential thrombocythemia, polycythemia vera, and myelofibrosis: current management and the prospect of targeted therapy. Am J Hematol 2008;83(6):491-7.
31. Elliott MA, Verstovsek S, Dingli D, Schwager SM, Mesa RA, Li CY, et al. Monocytosis is an adverse prognostic factor for survival in younger patients with primary myelofibrosis. Leuk Res 2007;31(11):1503-9.
32. Huang J, Li CY, Mesa RA, Wu W, Hanson CA, Pardanani A, et al. Risk factors for leukemic transformation in patients with primary myelofibrosis. Cancer 2008;112(12):2726-32.
33. Tefferi A, Huang J, Schwager S, Li CY, Wu W, Pardanani A, et al. Validation and comparison of contemporary prognostic models in primary myelofibrosis: analysis based on 334 patients from a single institution. Cancer 2007;109 (10):2083-8.
34. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 2008;22(1):14-22.
35. Tefferi A. Essential thrombocythemia: scientific advances and current practice. Turkiye Klinikleri J Int Med Sci 2006;2(36):48-56.