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Myeloid Blastic Transformation of Myeloproliferative Neoplasms – A Review of 112 Cases

Syed J Noor¹, Wei Tan², Gregory E Wilding², Laurie A Ford¹, Maurice Barcos³, Sheila N J Sait⁴, AnneMarie W Block⁴, James E Thompson¹, Eunice S Wang¹, and Meir Wetzler¹

¹ Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA

² Department of Biostatistics, Roswell Park Cancer Institute, Buffalo, NY, USA

³ Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY, USA

⁴ Clinical Cytogenetics Laboratory, Roswell Park Cancer Institute, Buffalo, NY, USA

Abstract

Blastic transformation of myeloproliferative neoplasms (MPN) is still poorly understood. We describe a cohort of 23 Roswell Park Cancer Institute (RPCI) patients and 89 additional cases from the English literature for whom biologic features were described. We initially compared our 23 patients to the 89 cases from the literature. Our population had significantly less patients with prior history of polycythemia vera (PV), shorter time from MPN diagnosis to blastic transformation, <3 prior therapies, more frequent use of hydroxyurea and erythropoietin and less frequent use of alkylating agents. Interestingly, the overall survival of the two cohorts from the time of blastic transformation was similar. We therefore looked at the outcome of the entire cohort (n=112). Patients with prior history of essential thrombocythemia survived longer than patients with prior history of myelofibrosis or PV. Further, patients with <3 prior therapies, those who lacked complex karyotype and those <60 year old at MPN diagnosis had significantly longer survival. Among the RPCI population, 20/23 patients underwent induction treatment with cytarabine and an anthracycline containing regimens; 12 achieved remission and their overall survival was significantly longer than those who did not. Three patients underwent an allogeneic transplantation and their survival was significantly longer than those who did not. Patients with <3 prior therapies, those who lack complex karyotype and those <60 at MPN diagnosis have longer survival following blastic transformation. Finally, allogeneic transplantation represents the only chance for long-term survival in these patients.

Corresponding Author: Meir Wetzler, MD, Leukemia Section, Department of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY, 14263, USA, Tel: 716-845-8447, Fax: 716-845-2343, meir.wetzler@roswellpark.org.

Authors Contributions

SJN reviewed the literature and all the cases and wrote the manuscript; WT and GEW performed the statistical analyses; LAF constructed the database; MB reviewed the pathology specimens; SNJS and AWB reviewed all the karyotype analyses; JET and ESW contributed to the care of the patients and MW oversaw the conduct of the study, contributed to the care of the patients and to the manuscript preparation. All authors reviewed the final manuscript and approved it.

Conflict of Interest

The authors have no conflict of interest to report.

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Keywords

Myeloproliferative neoplasms; acute myeloid leukemia; Blastic transformation

Introduction

Myeloproliferative neoplasms (MPNs) represent clonal hematologic diseases characterized by excess production of one or more lineages of mature blood cells, a predisposition to bleeding and thrombotic complications, extramedullary hemopoiesis and a variable progression to leukemia [1]. They constitute of polycythemia vera (PV), characterized by an expansion in red blood cell production; essential thrombocythemia (ET), characterized by an isolated elevation in the platelet count; and myelofibrosis (MF), distinguished by a fibrotic bone marrow and peripheral cytopenia and accompanied by higher risk of leukemic transformation. Myelofibrosis can arise *de novo*, as primary MF (PMF) or can evolve out of PV or ET as those diseases progress (so called post-PV MF and Post-ET MF or secondary MF, SMF). MPNs are known to transform into acute leukemia in approximately 4–6% of the patients [2–4]. Such a transformation is associated with very poor outcome.

A major breakthrough in our understanding of the pathophysiology of MPNs occurred when four groups described a recurrent somatic mutation in the Janus Activated Kinase 2 (*JAK2*) in the majority of MPN patients [5–8]. The point mutation in *JAK2* encodes a valine to phenylalanine change at position 617 (*JAK2*^{V617F}) and confers constitutive tyrosine kinase activity. Introducing the mutation into the bone marrow of mouse models recapitulates the PV phenotype [9,10] and *JAK2* inhibitors attenuate the growth of cell lines bearing the mutation *in vitro* and *in vivo* [11], suggesting that *JAK2*^{V617F} is a pathophysiologically relevant target. It is estimated that 95% of PV cases carry the *JAK2*^{V617F}, while 50–60% of ET and MF cases are *JAK2*^{V617F} positive [5–8]. Recently, several groups [12–16] have shown that approximately half of the cases with secondary acute leukemia following *JAK2*-positive MPN continue to carry the *JAK2* mutation. It suggests that in some of the cases, acute leukemia arose from another clone. In that regard, *JAK2*^{T875N} was recently described as a novel mutation that results in MPN with features of megakaryoblastic leukemia in murine bone marrow model [17], and *MPL*^{W515L/K} was found as novel somatic activating mutation in some MF cases [18]. However, the pathogenesis of the blastic transformation in MPNs remains poorly understood [4].

It is known that blastic transformation can be related to the use of alkylating agents, radiation or other types of DNA damaging chemotherapy drugs used during the chronic phase in some patients [19]; those agents are now rarely used in MPN treatment. To gain more insight into the evolution, risk factors playing role in blastic transformation and treatment outcome of patients developing blastic transformation from classic MPN, we analyzed 89 case reports from the English literature along with 23 patients from Roswell Park Cancer Institute (RPCI).

Methods

Patients

We reviewed the English literature to find 89 cases with leukemic transformation from MPN on whom biologic features were described and 23 patients from RPCI. Patients were confirmed to have PV, ET, primary MF, SMF or MPN-unclassified (MPN-U) according to the World Health Organization criteria [1]. Blast phase was defined as persistent elevation in peripheral blood or bone marrow blasts of ≥20% [20]. RPCI's Scientific Review Committee and Institutional Review Board approved this study.

Therapy was classified as acute myeloid leukemia (AML) induction if the intended regimen had an expected toxicity equal to or greater than that of an anthracycline (e.g., daunorubicin at 60 mg/m²) and standard dose cytosine arabinoside (100 mg/m²) chemotherapy given in a “7+3” fashion. Three patients underwent allogeneic stem cell transplantation (SCT) in addition to chemotherapy. All other patients, including those receiving hydroxyurea for suppression of peripheral blood counts, were considered to have received supportive care only. Blast phase response was classified using the AML established criteria [21] with major response categories being complete remission (CR) and complete remission with incomplete count recovery (CRi). Patients in CR/CRi were allowed to have persistent features of MPN provided the blast percentage and peripheral blood parameters satisfied the AML CR/CRi criteria.

Polymerase Chain Reaction (PCR)

Where available, bone marrow or peripheral blood specimens were tested for *JAK2*^{V617F}, *JAK2*^{T875N} and *MPL*^{W515L/K} mutations. The primers which were utilized for genomic PCR and sequencing were: *JAK2*^{V617F}, forward, 5' TGAAGCAGCAAGTATGATGAGC3' and reverse, 5' ACCTAGCTGTGATCCTGAAACTG3'; *JAK2*^{T875N}, forward, 5' GGTAATTTTGGGAGTGTGGAGA3', AND REVERSE, 5' AGCTTACCAGCACTGTAGCACAC3'; *MPL*^{W515L/K}, forward, 5' AAGTCTGACCCTTTTGTCTCCT3', reverse, 5' GAGGTGACGTGCAGGAAGTGG3'. PCR was conducted as previously described [22].

Sequencing

Applied Biosystems BigDye Terminator v3.1 (Foster City, CA) was used for directly sequencing the PCR products by our Core Facility.

Cytogenetics

The number of cytogenetic aberrations present in each karyotype was scored according to the International Working Group on MDS Cytogenetics (IWGMC) consensus guidelines [23].

Statistical Analyses

Descriptive statistics such as frequencies and relative frequencies were computed for categorical variables. Numeric variables were summarized using simple descriptive statistics such as the mean, standard deviation, range, etc. Fisher's exact test was used to study the association between categorical variables. The Wilcoxon rank sum test was used to compare the groups in regards to numeric variables. Estimation of the overall survival distributions was done using the Kaplan-Meier method. Using this distributed estimate, summary descriptive statistics such as the median survival were obtained. Statistical assessment of observed differences in the survival distributions of different groups of interest was done using the log-rank test. Cox proportional hazards model was used to assess the effect of study variables on survival for multivariate analyses. A 0.05 nominal significance level was used in all testing. All statistical analyses were done using SAS (version 9.1).

Results

We describe a cohort of 23 patients from RPCI and discuss 89 additional cases [24–50] from the English literature for whom biologic features were described. We initially compared our 23 patients to the 89 cases from the literature (Table 1). Our population had significantly less patients with prior history of PV, shorter time from MPN diagnosis to blastic transformation, <3 prior therapies, more frequent use of hydroxyurea, less frequent use of

alkylating agents and more frequent use of erythropoietin. Also, detection of normal karyotype at the time of blastic transformation was more common in the RPCI population. The two populations did not differ in regards to age at diagnosis of MPN or blastic transformation, gender, prior use of interferon or karyotype aberrations. Interestingly, the overall survival of the two cohorts from the time of blastic transformation was similar and poor (Figure 1A). We therefore looked at the outcome of the entire cohort (n=112) (Table 2). Patients with prior history of ET survived longer than patients with prior history of MF or PV. Further, patients with <3 prior therapies had significantly longer survival (Figure 1B). Finally, patients with complex karyotype had significantly shorter survival (Figure 1C) and patients ≥60 years of age at the time of MPN diagnosis had significantly shorter survival (Figure 1D). None maintained their significance in multivariate analyses. No difference in survival was detected based on time from MPN diagnosis to blastic transformation, prior hydroxyurea treatment, prior alkylating agents, erythropoietin, or interferon, or presence of non-complex karyotype aberrations.

We then evaluated the treatment response among the PRCI patients (n=23) (Table 3). A total of 20/23 patients underwent induction treatment with cytarabine and an anthracycline containing regimens; 12 achieved remission and eight did not. The overall survival of those achieving remission was significantly longer than those who did not. Three patients underwent an allogeneic SCT and their survival was significantly longer than those who did not.

Samples were available for eight of the patients at disease transformation; *JAK2*^{V617F} was detected in two and none had *JAK2*^{T875N} or *MPL*^{515L/K}. In summary, patients with <3 prior therapies, those who lacked of complex karyotype and those <60 at time of MPN diagnosis, had longer survival following blastic transformation. Finally, allogeneic SCT represents the only chance for long-term survival in these patients.

Discussion

The overall survival of the two cohorts (both RPCI and data from the literature) was poor (4.6 and 3 months). These results are similar to four other [2–4,16] single institution studies encompassing 13, 23, 74 and 91 patients. However, in our population, survival from blastic transformation differed significantly based on the type of primary MPN diagnosis, the number of therapies for MPN disease and the presence of complex karyotype while in one series only the type of primary MPN affected survival [3] and in the other [16] only karyotype affected survival. Reasons for the heterogeneity could be differing criteria for MPN diagnosis over the years, variety in the yield of successful karyotype analysis and incorporating these results into prognostic models.

It is not clear why patients with prior history of ET survived longer than patients with prior history of PMF or PV. Possible explanation would be prior cytotoxic therapy; for example, in the PVSG-01 study, PV patients who were treated with phlebotomy only had a lower risk of leukemic transformation (1.5%) compared to patients treated with ³²P (9.6%) or chlorambucil (13.5%) [51]. Interestingly, leukemic transformation seemed more common in ET patients carrying the *JAK2*^{V617F} mutation by one group [52] but not the another [53]. Only the availability of a large database crossing many institutes will enable us to answer this question.

The controversy whether blastic transformation is a sequela of therapy, natural progression of the disease or a combination of the two [54] continues. However, two recent prognostic models [55,56] to predict death in patients with PMF did not include prior therapies suggesting that blastic transformation, most probably, represents natural disease progression.

Similar to our study, chemo-sensitivity at the blastic phase, resulting in improved survival, was described by one additional study [16] but not in two others [2,4]. This difference may be related to the type of chemotherapy used. Further, superior survival with allogeneic SCT was noted in one study [16] as was noted in our series. However, even after SCT, the outcome of these patients is suboptimal and therefore SCT should be offered before the disease progresses to the blastic phase, based on the prognostic models mentioned above.

The role of *JAK2* and *MPL* mutations in disease progression is unclear. In the other series [16] and our work, some patients kept their *JAK2* and *MPL* mutations, others gained those while some lost these previously detected mutations, to suggest a minimal role in disease progression. Other mutations detected in blastic transformation include *TET2*, *ASXL1* and *IDH1* [57]. Their role in the pathogenesis and leukemic transformation needs to be further clarified.

Despite the unclear role of *JAK2* mutation in the leukemic transformation, it is of interest that the selective JAK1 and JAK2 inhibitor, INCB018424, demonstrated some single agent activity in relapsed/refractory patients with leukemic transformation of myelofibrosis [58]. This suggests that inhibiting JAK2 may result in down-regulation of downstream key proteins such as signal transducer and activator of transcription 3 and 5, both important in leukemogenesis [59].

Karyotype aberrations are the most important pretreatment prognostic markers in AML. Specific aberrations are more commonly associated with MPN and its blastic transformation. The most frequent changes are del(20q), del(13q), trisomy 8 and 9 and abnormalities of chromosome 1 [60], including 1q21→1q32 and 1p11→13 [61]. Our analysis revealed that only complex karyotype affected outcome. The occurrence of complex karyotype in this population may be related to prior use of chemotherapy [60].

In conclusion, patients with <3 prior therapies, those who lack complex karyotype and those <60 year old at time of MPN diagnosis have longer survival following blastic transformation. However, the outcome of patients following MPN transformation is poor and attempts should concentrate on early identification of patients at risk for disease progression. If the patients' disease undergoes transformation, allogeneic SCT for the eligible patient should be considered while searching for novel therapeutic agents, alone or in combination, continues.

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References

1. Anastasi J. The myeloproliferative neoplasms: insights into molecular pathogenesis and changes in WHO classification and criteria for diagnosis. *Hematol Oncol Clin North Am.* 2009; 23:693–708. [PubMed: 19577165]
2. Passamonti F, Rumi E, Arcaini L, Castagnola C, Lunghi M, Bernasconi P, et al. Leukemic transformation of polycythemia vera: a single center study of 23 patients. *Cancer.* 2005; 104:1032–6. [PubMed: 16047334]
3. Cervantes F, Tassies D, Salgado C, Rovira M, Pereira A, Rozman C. Acute transformation in nonleukemic chronic myeloproliferative disorders: actuarial probability and main characteristics in a series of 218 patients. *Acta Haematol.* 1991; 85:124–7. [PubMed: 2042444]

4. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. *Blood*. 2005; 105:973–7. [PubMed: 15388582]
5. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005; 365:1054–61. [PubMed: 15781101]
6. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005; 434:1144–8. [PubMed: 15793561]
7. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med*. 2005; 352:1779–90. [PubMed: 15858187]
8. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005; 7:387–97. [PubMed: 15837627]
9. Lacout C, Pisani DF, Tulliez M, Gachelin FM, Vainchenker W, Villeval JL. JAK2V617F expression in murine hematopoietic cells leads to MPD mimicking human PV with secondary myelofibrosis. *Blood*. 2006; 108:1652–60. [PubMed: 16670266]
10. Wernig G, Mercher T, Okabe R, Levine RL, Lee BH, Gilliland DG. Expression of Jak2V617F causes a polycythemia vera-like disease with associated myelofibrosis in a murine bone marrow transplant model. *Blood*. 2006; 107:4274–81. [PubMed: 16478879]
11. Garber K. JAK2 inhibitors: not the next imatinib but researchers see other possibilities. *J Natl Cancer Inst*. 2009; 101:980–2. [PubMed: 19584324]
12. Jelinek J, Oki Y, Gharibyan V, Bueso-Ramos C, Prchal JT, Verstovsek S, et al. JAK2 mutation 1849G>T is rare in acute leukemias but can be found in CMML, Philadelphia chromosome-negative CML, and megakaryocytic leukemia. *Blood*. 2005; 106:3370–3. [PubMed: 16037387]
13. Campbell PJ, Baxter EJ, Beer PA, Scott LM, Bench AJ, Huntly BJ, et al. Mutation of JAK2 in the myeloproliferative disorders: timing, clonality studies, cytogenetic associations, and role in leukemic transformation. *Blood*. 2006; 108:3548–55. [PubMed: 16873677]
14. Schnittger S, Bacher U, Kern W, Haferlach T, Haferlach C. JAK2V617F as progression marker in CMPD and as cooperative mutation in AML with trisomy 8 and t(8;21): a comparative study on 1103 CMPD and 269 AML cases. *Leukemia*. 2007; 21:1843–5. [PubMed: 17443220]
15. Hsiao HH, Yang WC, Liu YC, Lee CP, Lin SF. Disappearance of JAK2 V617F mutation in a rapid leukemic transformed essential thrombocythemia patient. *Leuk Res*. 2008; 32:1323–4. [PubMed: 18078991]
16. Tam CS, Nussenzweig RM, Popat U, Bueso-Ramos CE, Thomas DA, Cortes JA, et al. The natural history and treatment outcome of blast phase BCR-ABL-myeloproliferative neoplasms. *Blood*. 2008; 112:1628–37. [PubMed: 18566326]
17. Mercher T, Wernig G, Moore SA, Levine RL, Gu TL, Frohling S, et al. JAK2T875N is a novel activating mutation that results in myeloproliferative disease with features of megakaryoblastic leukemia in a murine bone marrow transplantation model. *Blood*. 2006; 108:2770–9. [PubMed: 16804112]
18. Pikman Y, Lee BH, Mercher T, McDowell E, Ebert BL, Gozo M, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006; 3:e270. [PubMed: 16834459]
19. Finazzi G, Caruso V, Marchioli R, Capnist G, Chisesi T, Finelli C, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood*. 2005; 105:2664–70. [PubMed: 15585653]
20. Mesa RA, Verstovsek S, Cervantes F, Barosi G, Reilly JT, Dupriez B, et al. Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leuk Res*. 2007; 31:737–40. [PubMed: 17210175]

21. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003; 21:4642–9. [PubMed: 14673054]
22. Drake AS, Brady MT, Wang XH, Sait SJ, Earp JC, Ghoshal Gupta S, et al. Targeting 11q23 positive acute leukemia cells with high molecular weight-melanoma associated antigen-specific monoclonal antibodies. *Cancer Immunol Immunother*. 2009; 58:415–27. [PubMed: 18677475]
23. Chun K, Hagemeijer A, Iqbal A, Slovak ML. Implementation of standardized international karyotype scoring practices is needed to provide uniform and systematic evaluation for patients with myelodysplastic syndrome using IPSS criteria: An International Working Group on MDS Cytogenetics Study. *Leuk Res*. 2010; 34:160–5. [PubMed: 19665225]
24. Berger R, Bernheim A, Flandrin G, Dresch C, Najean Y. Cytogenetic studies on acute nonlymphocytic leukemias following polycythemia vera. *Cancer Genet Cytogenet*. 1984; 11:441–51. [PubMed: 6704942]
25. Swolin B, Weinfeld A, Westin J. Trisomy 1q in polycythemia vera and its relation to disease transition. *Am J Hematol*. 1986; 22:155–67. [PubMed: 3706291]
26. Akahoshi M, Oshimi K, Mizoguchi H, Okada M, Enomoto Y, Watanabe Y. Myeloproliferative disorders terminating in acute megakaryoblastic leukemia with chromosome 3q26 abnormality. *Cancer*. 1987; 60:2654–61. [PubMed: 3479228]
27. Nakamura H, Sadamori N, Yamada Y, Yao E, Tagawa M, Nishino K, et al. Isochromosome 17q in a case of myelofibrosis with myeloid metaplasia terminating in blastic transformation. *Cancer Genet Cytogenet*. 1987; 24:221–4. [PubMed: 3791175]
28. Przeciorka D, Bryant E, Kidd P. Idiopathic myelofibrosis in blast transformation with 4;12 and 5;12 translocations and a 7q deletion. *Cancer Genet Cytogenet*. 1988; 30:139–44. [PubMed: 3422039]
29. Kimura A, Fujimoto T, Inada T, Imamura N, Oguma N, Kajihara H, et al. Blastic transformation in essential thrombocythemia. In vitro differentiation of blast cells into granulocytic, erythroid, and megakaryocytic lineages. *Cancer*. 1990; 65:1538–44. [PubMed: 2311065]
30. Wang JK, Lin DT, Hsieh HC, Chuu WM, Wang CH, Lin KS. Primary myelofibrosis in children: report of 4 cases. *J Formos Med Assoc*. 1990; 89:719–23. [PubMed: 1981237]
31. Miyoshi Y, Okada S, Takizawa Y, Hagiwara S, Mori H, Niikura H, et al. [Acute megakaryoblastic leukemia developing 11 years after diagnosis of essential thrombocythemia]. *Rinsho Ketsueki*. 1991; 32:868–73. [PubMed: 1942527]
32. Emilia G, Sacchi S, Temperani P, Longo R, Vecchi A. Progression of essential thrombocythemia to blastic crisis via idiopathic myelofibrosis. *Leuk Lymphoma*. 1993; 9:423–6. [PubMed: 8348078]
33. Tasaka T, Nagai M, Murao S, Yamaguchi M, Kitanaka A, Sasaki K, et al. CD7, CD34-positive stem cell leukemia arising in agnogenic myeloid metaplasia. *Am J Hematol*. 1993; 44:53–7. [PubMed: 7688180]
34. Shibata K, Shimamoto Y, Suga K, Sano M, Matsuzaki M, Yamaguchi M. Essential thrombocythemia terminating in acute leukemia with minimal myeloid differentiation--a brief review of recent literature. *Acta Haematol*. 1994; 91:84–8. [PubMed: 8023650]
35. Ferrara F, Vicari L, Festa B, Di Noto R, Pane F, Sebastio L, et al. Trisomy 13 in a case of myelofibrosis with myeloid metaplasia with early blastic transformation. *Haematologica*. 1995; 80:434–6. [PubMed: 8566885]
36. Kimura A, Kawaishi K, Nakata Y, Hyodo H, Kuramoto A, Satow Y. Leukemic transformation of primary myelofibrosis: immunophenotype, genotype and growth characteristics of blast cells. *Leuk Lymphoma*. 1995; 19:493–8. [PubMed: 8590852]
37. Uesugi Y, Toba K, Nikkuni K, Fuse I, Koike T, Shibata A. [Essential thrombocythemia in transformation to smouldering megakaryoblastic leukemia with myelofibrosis]. *Rinsho Ketsueki*. 1995; 36:1210–6. [PubMed: 8531333]
38. Kumar S, Mow BM, Kaufmann SH. Hypercalcemia complicating leukemic transformation of agnogenic myeloid metaplasia-myelofibrosis. *Mayo Clin Proc*. 1999; 74:1233–7. [PubMed: 10593353]

39. Tabata M, Imagawa S, Tarumoto T, Ohmine K, Hatake K, Miura Y, et al. Essential thrombocythemia transformed to acute myelogenous leukemia with t(3;17)(p24; q12), del(5)(q13q34) after treatment with carboquone and hydroxyurea. *Jpn J Clin Oncol.* 2000; 30:310–2.
40. Andrieux J, Demory JL, Morel P, Plantier I, Dupriez B, Caulier MT, et al. Frequency of structural abnormalities of the long arm of chromosome 12 in myelofibrosis with myeloid metaplasia. *Cancer Genet Cytogenet.* 2002; 137:68–71. [PubMed: 12377417]
41. Hirose Y, Masaki Y, Sugai S. Leukemic transformation with trisomy 8 in essential thrombocythemia: a report of four cases. *Eur J Haematol.* 2002; 68:112–6. [PubMed: 12061320]
42. Paolini R, Bonaldi L, Bianchini E, Ramazzina E, Cella G. Spontaneous evolution of essential thrombocythaemia into acute megakaryoblastic leukaemia with trisomy 8, trisomy 21 and cutaneous involvement. *Eur J Haematol.* 2003; 71:466–9. [PubMed: 14703699]
43. Kreft A, Burg J, Fischer T, Kirkpatrick CJ. Essential thrombocythemia terminating in pure erythroleukemia. *Am J Hematol.* 2004; 77:140–3. [PubMed: 15389906]
44. Chim CS, Kwong YL, Lie AK, Ma SK, Chan CC, Wong LG, et al. Long-term outcome of 231 patients with essential thrombocythemia: prognostic factors for thrombosis, bleeding, myelofibrosis, and leukemia. *Arch Intern Med.* 2005; 165:2651–8. [PubMed: 16344424]
45. Hsiao HH, Ito Y, Sashida G, Ohyashiki JH, Ohyashiki K. De novo appearance of der(1;7)(q10;p10) is associated with leukemic transformation and unfavorable prognosis in essential thrombocythemia. *Leukemia Res.* 2005; 29:1247–52. [PubMed: 16164981]
46. Toubai T, Tanaka J, Higa T, Ota S, Ibata M, Shono Y, et al. Long-term follow-up of a patient with idiopathic myelofibrosis associated with chromosome 11 and 13 abnormalities. *American J Hematol.* 2005; 78:67–70.
47. Pasqualucci L, Li S, Meloni G, Schnittger S, Gattenlohner S, Liso A, et al. NPM1-mutated acute myeloid leukaemia occurring in JAK2-V617F+ primary myelofibrosis: de-novo origin? *Leukemia.* 2008; 22:1459–63. [PubMed: 18200037]
48. Swolin B, Rodger S, Westin J. Therapy-related patterns of cytogenetic abnormalities in acute myeloid leukemia and myelodysplastic syndrome post polycythemia vera: single center experience and review of literature. *Ann Hematol.* 2008; 87:467–74. [PubMed: 18351338]
49. Villalon C, Talavera M, Sordo MT, Garcia-Sagredo JM, Lopez J, San Roman C, et al. Association of inv(3)(q21q26) with essential thrombocythemia in transformation. *Cancer Genet Cytogenet.* 2008; 184:122–3. [PubMed: 18617063]
50. Wu YY, Hung HM, Chen TS, Chao TY, Ho CL. Decreased JAK2 V617F allele burden level in a myelofibrosis with myeloid metaplasia patient with leukemic transformation. *Leukemia Res.* 2008; 32:1783–6. [PubMed: 18455791]
51. Berk PD, Goldberg JD, Silverstein MN, Weinfeld A, Donovan PB, Ellis JT, et al. Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *N Engl J Med.* 1981; 304:441–7. [PubMed: 7005681]
52. Fabris F, Randi ML. Essential thrombocythemia: past and present. *Intern Emerg Med.* 2009; 4:381–8. [PubMed: 19636672]
53. Gangat N, Wolanskyj AP, McClure RF, Li CY, Schwager S, Wu W, et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. *Leukemia.* 2007; 21:270–6. [PubMed: 17170720]
54. Barbui T. The leukemia controversy in myeloproliferative disorders: is it a natural progression of disease, a secondary sequela of therapy, or a combination of both? *Semin Hematol.* 2004; 41:15–7. [PubMed: 15190518]
55. Tam CS, Kantarjian H, Cortes J, Lynn A, Pierce S, Zhou L, et al. Dynamic Model for Predicting Death Within 12 Months in Patients With Primary or Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis. *J Clin Oncol.* 2009; 27:5587–93. [PubMed: 19786661]
56. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood.* 2010; 115:1703–8. [PubMed: 20008785]

57. Abdel-Wahab O, Manshouri T, Patel J, Harris K, Yao J, Hedvat C, et al. Genetic analysis of transforming events that convert chronic myeloproliferative neoplasms to leukemias. *Cancer Res.* 2010; 70:447–52. [PubMed: 20068184]
58. Ravandi F, Verstovsek S, Estrov Z, Burger JA, George S, Bivins C, et al. Significant Activity of the JAK2 Inhibitor, INCB018424 in Patients with Secondary, Post-Myeloproliferative Disorder (MPD) Acute Myeloid Leukemia (sAML): Results of An Exploratory Phase II Study. *Blood.* 2009; 114:631.
59. Benekli M, Baumann H, Wetzler M. Targeting signal transducer and activator of transcription signaling pathway in leukemias. *J Clin Oncol.* 2009; 27:4422–32. [PubMed: 19667270]
60. Hussein K, Van Dyke DL, Tefferi A. Conventional cytogenetics in myelofibrosis: literature review and discussion. *Eur J Haematol.* 2009; 82:329–38. [PubMed: 19141119]
61. Caramazza D, Hussein K, Siragusa S, Pardanani A, Knudson RA, Ketterling RP, et al. Chromosome 1 abnormalities in myeloid malignancies: a literature survey and karyotype-phenotype associations. *Eur J Haematol.* 2010; 84:191–200. [PubMed: 20002154]

Figure 1.

Figure 1A. Overall survival of the 112 cases.

Figure 1B. Overall survival by number of prior treatments (<3 and ≥3) in the 112 cases

Figure 1C. Overall survival by presence or absence of complex karyotype in the 112 cases

Figure 1D. Overall survival by age for the 112 cases

Table 1

Comparison between RPCI dataset and other datasets from the literature

Variable	Level	Frequency (%)		P
		Other	RPCI	
Diagnosis	ET	22 (24.4)	4 (17.4)	<.0001
	PMF	20 (22.2)	6 (26.1)	
	PV	48 (53.3)	5 (21.7)	
	SMF	0 (0)	2 (8.7)	
	UN	0 (0)	6 (26.1)	
Time from MPN diagnosis to blast phase	< 5 years	34 (39.1)	15 (68.2)	0.0173
	≥ 5 years	53 (60.9)	7 (31.8)	
Age at MPN diagnosis	< 60 years	40 (44.9)	9 (40.9)	0.8132
	≥ 60 years	49 (55.1)	13 (59.1)	
Age at AML diagnosis	< 60 years	20 (23)	5 (21.7)	1.0000
	≥ 60 years	67 (77)	18 (78.3)	
Gender	F	40 (44.9)	7 (30.4)	0.2429
	M	49 (55.1)	16 (69.6)	
Less than 3 therapies	N	68 (84)	0 (0)	<.0001
	Y	13 (16)	19 (100)	
Prior hydroxyurea therapy	N	60 (73.2)	7 (36.8)	0.0057
	Y	22 (26.8)	12 (63.2)	
Prior alkylating agents	N	37 (45.1)	18 (94.7)	<.0001
	Y	45 (54.9)	1 (5.3)	
Prior erythropoietin	N	82 (100)	17 (89.5)	0.0339
	Y	0 (0)	2 (10.5)	
Prior interferon	N	81 (98.8)	18 (94.7)	0.3424
	Y	1 (1.2)	1 (5.3)	
Complex karyotype	N	44 (53.7)	14 (70)	0.2163
	Y	38 (46.3)	6 (30)	
Normal karyotype	N	76 (92.7)	13 (65)	0.0033
	Y	6 (7.3)	7 (35)	
Trisomy 1 or 1(q)	N	65 (79.3)	17 (89.5)	0.5149
	Y	17 (20.7)	2 (10.5)	
Monosomy 5 or del(5)	N	68 (82.9)	18 (94.7)	0.2914
	Y	14 (17.1)	1 (5.3)	

Variable	Level	Frequency (%)		P
		Other	RPCI	
Any abnormality of 7	N	60 (73.2)	17 (89.5)	0.2295
	Y	2 (26.8)	2 (10.5)	
Trisomy 8	N	64 (78)	18 (94.7)	0.1138
	Y	18 (22)	1 (5.3)	
Trisomy 9	N	72 (87.8)	19 (100)	0.2012
	Y	10 (12.2)	0 (0)	
Abnormality of chromosome 17	N	74(90.2)	16 (84.2)	0.4290
	Y	8 (9.8)	3 (15.8)	
del 20(q) or monosomy 20	N	73 (89)	16 (84.2)	0.6931
	Y	9 (11)	3 (15.8)	
Non complex karyotype	N	44 (53.7)	13 (65)	0.4542
	Y	38 (46.3)	7 (35)	
Overall survival		3.0 (2.0, 5.0) *	4.6 (3.1, 8.6) *	0.1758

Abbreviations: AML, acute myeloid leukemia; ET, essential thrombocythemia; F, female; M, male; MPN, myeloproliferative neoplasm; N, no; PMF, primary myelofibrosis; PV, polycythemia vera; SMF, secondary myelofibrosis; UN, unknown; Y, yes;

* Median survival time (95% Confidence Interval)

Table 2

Survival analysis for RPCI and the other datasets

Variable	Level	Frequency (%)	1-year Survival	Median Survival (95% CI)	P
Diagnosis	ET	26 (23)	0.3311	8.6 (4.337, 24)	0.0225
	PMF	26 (22)	0.0476	4.6 (2, 11)	
	PV	53 (47)	0.0832	3 (2, 5)	
	SMF	2 (2)	0.5000	29.6 (2.168, 57.068)	
	UN	6 (5)	0.3333	6.8 (2.924, 16.789)	
Time from MPD diagnosis to blast phase	< 5 years	49 (45)	0.1211	4.5 (3, 8.608)	0.7834
	≥5 years	60 (55)	0.1650	3 (2, 5.092)	
Age at MPN diagnosis	< 60 years	49 (44)	0.2177	5 (2.891, 11)	0.0493
	≥ 60 years	62 (56)	0.0949	3 (2.168, 5)	
Age at AML diagnosis	< 60 years	25 (23)	0.2101	3 (2, 12)	0.2590
	≥ 60 years	85 (77)	0.1256	4.3 (3, 5)	
Gender	F	47 (42)	0.0758	4 (2.037, 6)	0.1396
	M	65 (58)	0.1938	4.6 (2.924, 10.513)	
Less than 3 prior therapies	N	68 (68)	0.0979	3 (2, 5)	0.0242
	Y	32 (32)	0.2028	7.9 (4.337, 11)	
Prior hydroxyurea	n	67 (66)	0.0932	3 (2, 6)	0.3078
	Y	34 (34)	0.1999	4.5 (3, 6.834)	
Prior alkylating agents	N	55 (55)	0.1744	3.1 (2.924, 6.834)	0.2771
	Y	46 (46)	0.0793	5 (2, 8)	
Prior erythropoietin	N	99 (98)	0.1349	4.3 (3, 6)	0.6044
	Y	2 (2)	0	5 (2.168, 7.885)	
Prior interferon	N	99 (98)	0.1189	4 (2.924, 5.092)	0.1542
	Y	2 (2)	1.0000	24.6 (.,.)	
Complex karyotype	N	58 (57)	0.2146	5 (3, 10)	0.0104

Variable	Level	Frequency (%)	1-year Survival	Median Survival (95% CI)	P
	Y	44 (43)	0.0528	3 (2, 5)	
Normal karyotype	N	89 (87)	0.1008	3 (2, 5)	0.0655
	Y	13 (13)	0.3846	10 (4.337, 16.789)	
Trisomy 1 or 1(q)	N	82 (81)	0.1398	3 (2.168, 5)	0.2505
	Y	19 (19)	0.1667	5 (3, 9)	
Monosomy 5 or del(5)	N	86 (85)	0.1583	4 (2.891, 6)	0.6170
	Y	15 (15)	0.0741	5 (2, 6)	
Any abnormality of 7	N	77 (76)	0.1405	3 (2.168, 6)	0.5791
	Y	24 (24)	0.1594	5 (2, 11)	
Trisomy 8	N	82 (81)	0.1508	4.6 (2.924, 6)	0.5302
	Y	19 (19)	0.1263	3 (2, 9)	
Trisomy 9	N	91 (90)	0.1594	4.6 (2.924, 6)	0.0757
	Y	10 (10)	0	2.5 (1, 3)	
Abnormality of chromosome N 17	Y	90 (90)	0.1638	4.5 (3, 6)	0.0613
	Y	11 (11)	0	2 (1, 5.092)	
del 20(q) or monosomy 20	N	89 (88)	0.1692	4 (2.891, 6.834)	0.1056
	Y	12 (12)	0	4.4 (1, 5)	
Non complex karyotype	N	57 (56)	0.1361	4.3 (2.037, 5.092)	0.3837
	Y	45 (44)	0.1530	4 (2, 9)	

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; ET, essential thrombocythemia; F, female; M, male; MPN, myeloproliferative neoplasm; N, no; PMF, primary myelofibrosis; PV, polycythemia vera; SMF, secondary myelofibrosis; UN, unknown; Y, yes;

Table 3

Survival analysis for the RPCI dataset

Variable	Level	Frequency (%)	1-year Survival	Median Survival (95% CI)	P
Induction chemotherapy	N	1 (5)	0	1.6 (.,.)	0.0031
	Y	20 (95)	0.3000	6 (3.088, 15.047)	
Allogeneic transplantation	N	12 (80)	0	3.7 (2.924, 4.567)	0.0119
	Y	3 (20)	0.3333	10.5 (7.885, 57.068)	
Supportive care	N	20 (91)	0.3000	6 (3.088, 15.047)	0.0009
	Y	2 (9)	0	1.9 (1.61, 2.168)	
Response	N	8 (40)	0	2.9 (2.037, 4.468)	<.0001
	Y	12 (60)	0.5000	12.8 (7.885, 24.641)	

Abbreviations: CI, confidence interval; N, no; Y, yes;