Imatinib in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRB* in chronic or blast phase

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ABSTRACT

We evaluated clinical characteristics and outcome on imatinib of 22 patients with myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRB*. Median age was 49 years (range 20-80), 91% were male. Fifteen different *PDGFRB* fusion genes were identified. Eosinophilia was absent in 4/19 (21%) cases and only 11/19 (58%) cases had eosinophils ≥1.5x10^9/L. On imatinib, 17/17 (100%) patients in chronic phase achieved complete hematologic remission (after median 2 months, range 0-13). Complete cytogenetic remission and/or complete molecular remission by RT-PCR were achieved in 12/13 (92%) and 12/14 patients (86%) after median 10 (range, 3-34) and 19 months (range, 7-110), respectively. In patients with blast phase (myeloid, n=2; lymphoid, n=3), treatment included combinations of imatinib (n=5), intensive chemotherapy (n=3) and/or allogeneic stem cell transplantation (n=3). All 3 transplanted patients (complex karyotype, n=2) experienced early relapse. Initially, patients were treated with imatinib 400mg/day (n=15) or 100mg/day (n=7), the dose was reduced from 400mg/day to 100mg/day during follow-up in 9 patients. After a median treatment of 71 months (range, 1-135), the 5-year survival rate was 83%; 4/22 (18%) patients died (chronic phase; n=2; blast phase, n=2) due to progression (n=3) or comorbidity while in remission (n=1). Of note, 3/4 patients had a complex karyotype. In summary, the most important characteristics of myeloid/lymphoid neoplasms with rearrangement of *PDGFRB* include a) male predominance, b) frequent lack of hypereosinophilia, c) presentation in chronic or blast phase, d) rapid responses and long-term remission on low-dose imatinib and e) possible adverse prognostic impact of a complex karyotype.

Keywords: MPN; Clonal Eosinophilia; PDGFRB rearrangement; Imatinib

INTRODUCTION

Clonal eosinophilia is associated with different myeloid neoplasms which are frequently characterized by constitutive activation of protein tyrosine kinases as consequence of translocations, inversions, or insertions and creation of tyrosine kinase fusion genes. A distinct subcategory of the WHO 2016 classification of myeloid neoplasms is the group of 'myeloid/lymphoid neoplasms with eosinophilia and rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1* or *PCM1-JAK2* fusion gene.[1] The cytogenetically invisible *FIP1L1-PDGFRA* fusion gene, which can be detected by FISH or RT-PCR,[2] is by far the most frequent fusion, identified in approximately 3-10% of unselected patients with eosinophilia of unknown significance. 5q31-33 translocations, which fuse the *PDGFRB* gene with diverse partner genes are identified in less than 3% of those patients. To date, more than 30 different partner genes of *PDGFRB* have been identified; many as unique fusions in individual patients.[3-6]

The identification of patients with rearrangements of *PDGFRA/B* has important implications for treatment and prognosis. Several groups have reported on high rates (>90%) of complete hematologic (CHR) and complete molecular remissions (CMR) on imatinib in chronic but also in blast phase.[7,8] These durable responses translate into excellent progression-free and overall survival (OS). Primary and secondary resistance to imatinib is very rare. If it occurs, resistance is usually associated with point mutations in the kinase domains of *PDGFRA* (T674I, D842V)[9,10] or *PDGFRB* (D850E).[11]

Here, we report on 22 patients with myeloid/lymphoid neoplasms with eosinophilia and diverse *PDGFRB* fusion genes focussing on the heterogeneous clinical, cytogenetic and molecular characteristics at diagnosis. Moreover detailed descriptions of treatment with imatinib in regards to dosing, response and long-term remissions are given. Finally, we discuss the role of allogeneic stem cell transplantation for patients presenting in blast phase.

METHODS

Twenty-two imatinib-treated patients with a myeloid/lymphoid neoplasm and rearrangement of *PDGFRB* were analyzed. All patients were primarily enrolled within the 'German Registry for Disorders of Eosinophils and Mast cells'. Data collection was compliant with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University, Germany. All patients gave written informed consent.

Cytogenetic analysis and fluorescence in situ hybridization (FISH) were performed on bone marrow (BM) cells according to standard procedures. Fusion gene specific nested RT-PCR was performed for detection of residual disease.[3,12-14]

Eosinophilic organ involvement was diagnosed by positive histopathology of organs biopsies or cytology of pleural effusions. Indicative signs of organ involvement were findings surveyed by imaging (e.g. ultrasound, echocardiography, computer tomography, magnetic resonance imaging).

Statistical analyses considered clinical, laboratory or molecular parameters obtained at the time of diagnosis, start of treatment and at multiple time points during treatment. OS analysis was considered from the date of start of treatment to date of death or last contact. OS was estimated with the Kaplan-Meier method. *P*-values <0.05 (two-sided) were considered significant. SPSS version 22.0.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

RESULTS

Patients´ characteristics

At diagnosis, the median age was 49 years (range 20-80) with a striking male predominance (20/22, 91%). Seventeen of 22 (77%) patients were diagnosed in chronic phase (Table 1). Five patients (23%; *ETV6-PDGFRB*, n=3; *SART3-PDGFRB*, n=1; *DIAPH1-PDGFRB*, n=1)

presented in blast phase. Four patients (chronic phase, n=2; blast phase, n=2) had a complex karyotype at diagnosis. However, three patients in blast phase (patient #1, #4 an #5) and eight patients in chronic phase have been previously published separately.[3-4,11-14]

In peripheral blood (PB), significant eosinophilia ≥0.5x10^9/L was absent in 4/19 (21%) and ≥1.5x10^9/L in 8/19 (42%) patients, respectively (Table 1). All patients in blast phase had a short history of persistent eosinophilia (median 4 months, range 1-9). The median monocyte count was 0.5x10^9/L (range 0-9) and 5/15 (33%) patients had significant monocytosis >1.0x10^9/L. If available (14/17), initial histopathological diagnoses in chronic phase included myeloproliferative neoplasm with eosinophilia [MPN-eo], n=7, myelodysplastic syndrome [MDS]/MPN unclassified [MPN-U] (n=3), atypical chronic myeloid leukemia (aCML, n=1), chronic myelomonocytic leukemia (CMML, n=1) or systemic mastocytosis with eosinophilia (SM-eo, n=2). A significant increase of mast cells was described in 5/14 (36%) cases but no case tested positive for *KIT* D816V. The most common organ involvement in chronic phase included splenomegaly (10/12, 83%) and pleura (n=1), liver (n=1) and skin (n=1), as proven by cytology or biopsy, or endo-/myocard (n=1), as indicated by MRI. In blast phase, the morphological phenotypes included B-cell acute lymphoblastic leukemia (ALL, n=1), T-cell lymphoblastic lymphoma (n=1), angioimmunoblastic T-cell lymphoma (n=1), myeloid blast phase/myeloid sarcoma of the central nervous system and pleura (n=1), and myeloid blast phase/secondary acute myeloid leukemia (AML, n=1). The 2 patients with T-cell lymphoma and the patient with the myeloid sarcoma were diagnosed with a concomitant MDS/MPN-eo in BM. The patient with B-ALL also had significant eosinophilia in BM.

PDGFRB fusion genes

Overall, rearrangements of 5q31-33 (*PDGFRB*) were detected by conventional cytogenetics and/or FISH in 21 of 22 patients. In one patient, a new cryptic fusion gene was identified using RNAseq. Fifteen different partner genes of *PDGFRB* were identified, the vast majority in individual patients. Only *ETV6* and *CCDC88C* were involved recurrently: *ETV6*, n=5;

CCDC88C, n=3; *DIAPH1*, n=1; *DTD1*, n=1; *CPSF6*, n=1; *GIT2*, n=1; *GOLGB1*, n=1; *GPIAP1*, n=1; *H4*, n=1, *MYO18A*, n=1; *PRKG2*, n=1; *SART3*, n=1; *SPECC1*, n=1; *TP53BP1*, n=1; *WDR48*, n=1. Known fusion genes were amplified by RT-PCR analysis based on the karyotype. New partner genes were identified by RACE-PCR (*SART3*, *GIT2*, *GPIAP1*, *CCDC88C*)[4,13,14], LDI-PCR (*DTD1*, *GOLGB1*, *MYO18A*, *PRKG2*)[3,4,12,13] and RNAseq (*DIAPH1*, Jawhar *et al*., submitted). In one case, the partner gene remains unknown despite a *PDGFRB* rearrangement by FISH analysis. Figure 1 shows all *PDGFRB* fusion partners with corresponding translocations.

Treatment

The median time from diagnosis to the start of imatinib was 2 months (range, 0-63). Prior cytoreductive treatment in 13/22 patients included hydroxyurea (n=8, 36%), high-dose intensive chemotherapy (n=2, 9%) or interferon alpha (n=2, 9%). The median time on imatinib was 71 months (range 1-135, Table 1).

Chronic phase. All patients (n=17) were treated with imatinib (400 mg/day, n=12, 71%; 100 mg/day, n=5, 29%) and achieved CHR within median 2 months (range, 0-13); no primary resistance was observed. Complete cytogenetic remission (CCR) and/or CMR (undetectable fusion transcripts by nested RT-PCR) were achieved in 12/13 (92%) and 12/14 patients (86%) after median 10 months (range 3-34) and 19 months (range 8-110), respectively. Imatinib was reduced during follow-up from 400 mg/day to 100 mg/day (after a median time of 39 months, range 8-133) in 8/12 (67%) patients and from 100 mg/day to 3x100 mg/week in 2/8 (25%) patients. All patients remained in remission (Table 1 and 2). Of interest, one patient in chronic phase with a complex karyotype and a *TP53BP-PDGFRB* fusion gene achieved a CHR for 13 months (but no CCR or CMR) and died because of progressive disease (possibly secondary resistance or therapy non-compliance but material was not available for further investigations). He received therapy with a second-generation tyrosine kinase inhibitor (TKI, nilotinib) for 4 weeks but did not achieve any response. A second

patient in chronic phase died in association with a cardiac comorbidity (cardiac involvement by disease was excluded) 27 months after start of imatinib while in CHR.

Blast phase. In 5/22 patients (23%), blast phase (myeloid, n=2; lymphoid, n=3) was diagnosed. Overall, 3/5 patients (#1, #2, #3) received an allogeneic stem cell transplantation (SCT) after intensive chemotherapy or after treatment with imatinib (median 3 months after diagnosis, range 1-7).

Patient #1 (41-year-old, male) was initially diagnosed with a MPN-eo. Initially, no cytogenetic/molecular analyses and treatment were performed. Myeloid blast phase/secondary AML emerged after eleven months and the patient received intensive chemotherapy with idarubicin, cytarabine and etoposide. Cytogenetic and molecular analyses meanwhile revealed a complex karyotype with an *ETV6-PDGFRB* fusion gene. He received imatinib 400 mg/day and achieved CHR and CCR after 6 weeks. Because of presentation in blast phase and a complex karyotype, allogeneic hematopoietic SCT from a HLA-matched related donor was performed. Four weeks after allogeneic SCT, leptomeningeal involvement was diagnosed. Despite stop of immunosuppression, donor lymphocyte infusions, radiation and re-initiation of imatinib 400 mg/day, leptomeningeal involvement relapse occured after 7 months. There was no response on dasatinib 140 mg/day and the patient died 9 months after allogeneic SCT while on CHR and CCR in BM (Figure 2).

Patient #2 (33-year-old, male) was diagnosed with B-cell ALL and an *ETV6-PDGFRB* fusion gene. On imatinib 400 mg/day, he achieved CHR after 3 months but rapidly progressed in month 4 (50% blasts in PB). After two cycles of intensive chemotherapy (according to GMALL 07/03 protocol), allogeneic hematopoietic SCT from a HLA-matched unrelated donor was performed in CHR. Seven months after allogeneic SCT, the patient was recommenced on imatinib 100 mg/day because of persisting *ETV6-PDGFRB* fusion transcripts. The patient

is still alive 48 months after allogeneic SCT while in CHR and CMR. He is free of relevant GvHD and has an excellent quality of life.

Patient #3 (55-year-old, female) was diagnosed with an extramedullary myeloid blast phase/sarcoma (pleura, central nervous system). Cytogenetic and molecular analyses revealed a complex karyotype with an *ETV6-PDGFRB* fusion gene. After 4 weeks on imatinib 400 mg/day, an allogeneic hematopoietic SCT from a HLA-matched unrelated donor was performed due to the high risk genetic profile (complex karyotype and *RUNX1* mutation). Two, 6 and 9 months after allogeneic SCT, she developed skin, oral mucosa and severe liver GvHD, respectively. Twelve months after allogeneic SCT, the patient relapsed with the extramedullary myeloid sarcoma (positive histopathology of pleura biopsy). The patient is currently off treatment because of severe GvHD.

Patient #4 (37-year-old, male) was diagnosed with a MPN-eo in BM histology and a contemporaneous T-cell lymphoblastic lymphoma in a lymph node biopsy. The karyotype was normal. The patient received intensive chemotherapy (according to GMALL 07/03 protocol) and achieved CHR and disappearance of lymphadenopathy. Two weeks later, the patient developed leukocytosis (119×10^9/L) with significant eosinophilia (21×10^9/L), hepatosplenomegaly but without recurrence of lymphadenopathy. Consolidation chemotherapy treatment was started without response. Molecular analyses revealed an overexpression of *PDGDRB* and a *DIAPH1-PDGFRB* fusion by RNAseq (Jawhar *et al.*, submitted for publication). He received imatinib 100 mg/day and achieved a complete clinical and CHR within 4 weeks. The patient died due to a rapidly progressive neurodegenerative disorder at month 27 in CHR and without evidence of disease relapse in BM and cerebrospinal fluid.

Patient #5 (42-year-old, male) was diagnosed with a MPN-eo (leukocytosis, 25% eosinophils, splenomegaly, hypercellular BM with eosinophilia and fibrosis) and an angioimmunoblastic T-

cell lymphoma (stage III) in a lymph node biopsy. Cytogenetic analysis was non-informative (normal karyotype in 4 of 4 metaphases) but molecular analyses revealed an overexpression of *PDGDRB.*[14] Chemotherapy was postponed because of potential blast phase of T-cell phenotype and imatinib was initiated. The patient achieved rapid complete clinical remission and CHR within 4 months. The lymphadenopathy resolved completely after 6 months. Meanwhile a *SART3-PDGFRB* fusion gene was identified by RACE-PCR.[14] The patient is alive and well on imatinib 100 mg/day 97 months after diagnosis (CMR not analysed).

Overall survival in chronic and blast phase

Four of 22 patients (18%) died (chronic phase, n=2; blast phase, n=2) due to comorbidity while in remission (n=2) or progressive disease (n=2). Of note, 3/4 patients had an additional complex karyotype at diagnosis. Patients in blast phase (n=5) had a more unfavourable outcome than patients in chronic phase (n=17, p=0.04, 5-year OS 50% vs. 92%, Figure 3). Overall 18/22 patients (82%) are currently alive disease-free with an estimated 5-year OS of 83%.

DISCUSSION

This is a comprehensive report on several new aspects regarding the clinical and molecular characteristics of patients with myeloid/lymphoid neoplasms and associated *PDGFRB* fusion genes, which present more heterogeneously than patients with *FIP1L1-PDGFRA* fusion genes. Most relevant is the absence of (marked) eosinophilia in a significant proportion of patients, which is in stark contrast to the almost 100% presence of eosinophilia in *FIP1L1-PDGFRA* positive myeloid neoplasms.[15] The overall clinical, morphological and laboratory features mimic more frequently the various phenotypes of myeloid neoplasms, such as CMML, atypical CML, MDS/MPN-U, chronic eosinophilial leukemia (CEL), MPN-U and SM. There is accumulating evidence that the disparate partner genes of *PDGFRB* confer a significant impact on the clinical phenotype including lack of eosinophilia. The clinical

consequences if a potential rearrangement or fusion gene of *PDGFRB* remains undetected because of misleading morphological diagnosis may be considerable.[16] The striking male predominance is almost as strong as in *FIP1L1-PDGFRA* or *PCM1-JAK2* positive myeloid/lymphoid neoplasms, yet the reasons remain to be identified. Except for splenomegaly, the incidence of organ involvement within our patient cohort is rather low. Similar to *FIP1L1-PDGFRA* positive myeloid neoplasms, special attention should certainly be paid to involvement of the heart with its potentially life-threatening complications.[10-12]

Rapid and durable complete clinical and hematological remissions on imatinib were observed in all reported chronic phase patients within median 2 months. Cytogenetic analysis for confirmation of CCR and fusion gene specific RT-PCR for confirmation of CMR was not performed in all patients. If available, CCR, CMR and CHR + CCR + CMR were observed in 92%, 86% and 82% of patients, respectively. Similar to *FIP1L1-PDGFRA* positive myeloid neoplasms, low-dose imatinib (100 mg/day) seems to be sufficient, at least as maintenance dose in patients with CR (two-thirds of our patients had low-dose imatinib from diagnosis or in due course). Consequently it may even be conceivable to stop imatinib after long-term molecular remissions as already reported for *BCR-ABL1* and *FIP1L1-PDGFRA* positive patients.[15-19] The limited number of patients with *PDGFRB* fusion genes prevents a comparison between imatinib 400 mg/day and imatinib 100 mg/day as initial dose. Unbiased data could however only be collected through worldwide registries

Similar to *PDGFRA*, *FGFR1* and *JAK2* fusion genes, major challenges remain the identification and treatment of imatinib-sensitive *PDGFRB* fusion genes in patients presenting with a primary diagnosis of *de novo* AML or ALL/lymphoblastic lymphoma.[5,20] In our series, involvement of *PDGFRB* was suggested by a cytogenetic rearrangement of 5q31-33 in 20/22 cases and in two further cases by *PDGFRB* overexpression analysis. Other potential clinical and laboratory alerts include a) eosinophilia at diagnosis or if persisting after intensive chemotherapy, b) an increase of mast cells and fibrosis in BM and/or an elevation

of serum tryptase, c) a contemporaneous diagnosis of MPN in BM and lymphoma in lymph node biopsies and d) an aberrant or complex karyotype in addition to the rearrangement of 5q31-33. However, the clinical course is not predictable in the same way as in chronic phase. Similar to blast phase CML, patients may only be offered TKI-monotherapy rather than intensive chemotherapy. The decision whether to proceed with allogeneic SCT after achievement of remission can only be made on an individual basis.[21,22] In our series, all 3 patients with an allogeneic SCT relapsed either indicated by detectable *ETV6-PDGFRB* transcripts, leptomeningeal involvement or full clinical relapse. With the limitation of our relatively small series, a complex karyotype may indicate a more aggressive clinical course possibly associated with poor prognosis. Re-emergence of *PDGFRB* fusion transcripts in the absence of evidence of clonal evolution after allogeneic SCT requires an individual decision whether to apply donor lymphocyte infusions, being associated with the risk of significant GvHD, or to recommence imatinib.

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Table 1: Clinical and treatment characteristics of 22 patients with myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRB*. Comparison between the patients reported here and by Cheah *et al*.[7]

Variables	**Jawhar *et al.***	**Cheah *et al.***
Number of cases, n	22	26
Age at diagnosis in years; median (range)	49 (20-80)	50 (0.9-78)
Male, n (%)	20 (91%)	21 (81%)
Chronic/blast phase	17/5	25/1
Leukocytes, $x10^9$/L; median (range)	31.0 (4.5-127.6)	51 (4-138)
Eosinophils at diagnosis, $x10^9$/L; median (range)	3.9 (0.2-33.0)	3.5 (0.7-12)
Eosinophils at diagnosis <0.5 $x10^9$/L	4/19	0/21
Hemoglobin, g/dL; median (range)	11.3 (7.2-18.0)	n.a.
Platelets, $x10^9$/L; median (range)	138 (24-513)	119 (60-506)
PDGFRB partner genes, n	15	8
ETV6	5/22 (23%)	18/26 (69%)
No prior therapy	9 (41%)	8 (33%)
Time from diagnosis to imatinib, months; median (range)	2 (0-63)	8.6 (0-123)
Imatinib, starting dose		
400 mg/day	15 (68%)	22/26 (84%)
300 mg/day	-	1/26 (4%)
100 mg/day	7(32%)	3/26 (12%)
Imatinib, maintenance dose		
100 mg/day	7 (32%)	n.a.
3 x100 mg/week	2 (22%)	n.a.
Time on imatinib, years; median (range)	6.0 (0.1-11.2)	6.6 (0.1-12)

Table 2: Response and outcome of 22 patients with myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRB*. *patients with additional complex karyotype. **death in CHR (comorbidity). Abbreviations: CHR, complete hematologic remission; CCR, complete cytogenetic remission; CMR, complete molecular remission; N, evaluable.

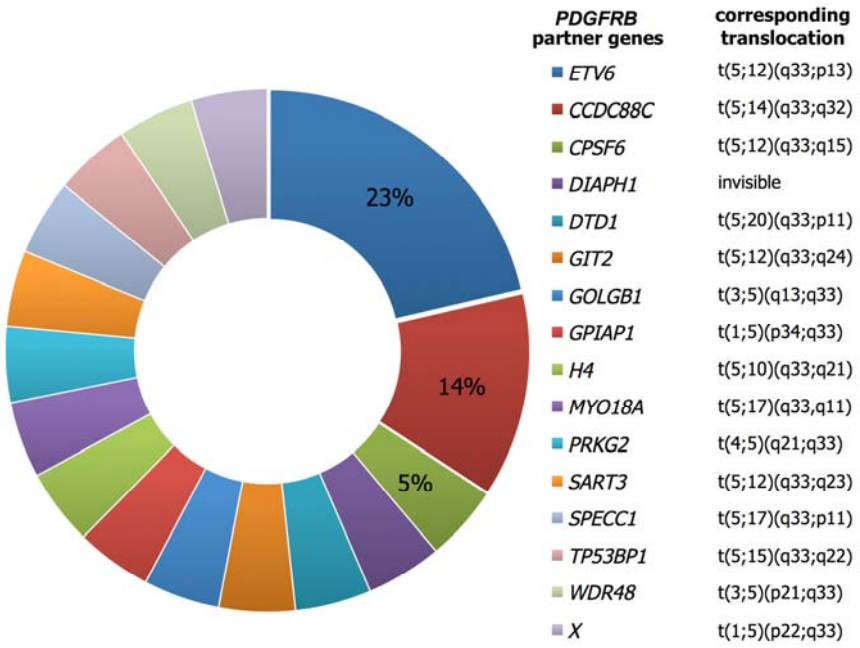
N	Variables	Results
	Imatinib	
22	Time from start ofimatinib treatment to CHR, median (range)	2 (0-13)
13	Time from start of imatinib treatment to CCR, median (range)	10 (3-34)
14	Time from start of imatinib treatment to CMR, median (range)	19 (8-110)
	Best response to imatinib	
22	CHR, n (%)	22 (100)
13	CCR, n (%)	12 (92)
14	CMR, n (%)	12 (86)
11	CHR + CCR + CMR, n (%)	9 (82)
22	**Outcome**	
	5-year OS, %	86
	Death, n (%)	4 (18)
	**Disease related, n (%)*	2 (9)
	***Non-disease related, n (%)*	2 (9)

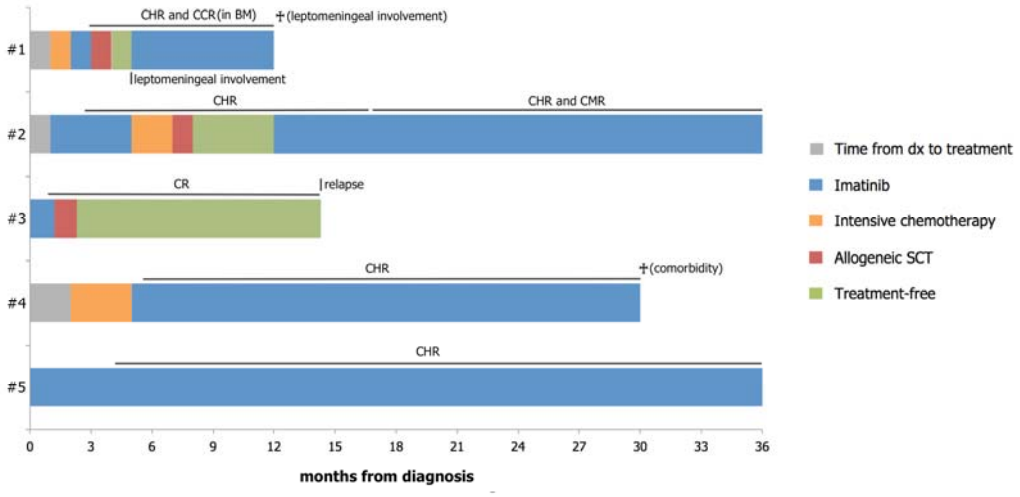
FIGURE LEGEND

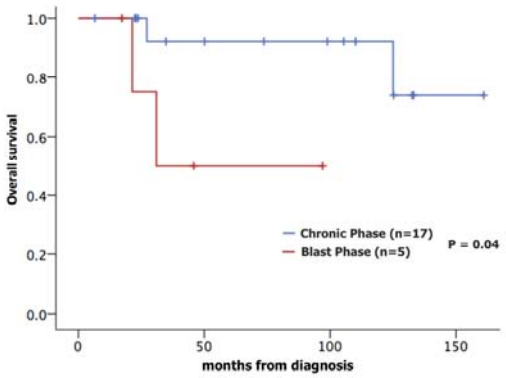
Figure 1: Fifteen different fusion genes and corresponding karyotype in 22 patients with myeloid/lymphoid neoplasms and rearrangement of *PDGFRB*.

Figure 2: Treatment of 5 patients with myeloid/lymphoid neoplasms and rearrangement of *PDGFRB* in blast phase. Abbreviations: CHR, complete hematologic remission; CCR, complete cytogenetic remission; CMR, complete molecular remission; Dx, diagnosis; Tx, transplantation.

Figure 3. Overall survival of 22 patients with myeloid/lymphoid neoplasms and rearrangement of *PDGFRB* in chronic (n=17) and blast phase (n=5) treated with imatinib (median 71 months, range 1-135; p=0.04).


23%
14%
5%
PDGFRB partner genes
corresponding translocation
ETV6 t(5;12)(q33;p13)
CCDC88C t(5;14)(q33;q32)
CPSF6 t(5;12)(q33;q15)
DIAPH1 invisible
DTD1 t(5;20)(q33;p11)
GIT2 t(5;12)(q33;q24)
GOLGB1 t(3;5)(q13;q33)
GPIAP1 t(1;5)(p34;q33)
H4 t(5;10)(q33;q21)
MYO18A t(5;17)(q33,q11)
PRKG2 t(4;5)(q21;q33)
SART3 t(5;12)(q33;q23)
SPECC1 t(5;17)(q33;p11)
TP53BP1 t(5;15)(q33;q22)
WDR48 t(3;5)(p21;q33)
X t(1;5)(p22;q33)


CHR and CCR(in BM)
+(leptomeningeal involvement)
#1
leptomeningeal involvement
CHR
CHR and CMR
#2
CR
relapse
#3
CHR
+(comorbidity)
#4
CHR
#5
0 3 6 9 12 15 18 21 24 27 30 33 36
months from diagnosis
Time from dx to treatment
Imatinib
Intensive chemotherapy
Allogeneic SCT
Treatment-free


1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
0
50
100
150
months from diagnosis
Chronic Phase (n=17)
Blast Phase (n=5)
P = 0.04