Leukemia

Song et al., J Leuk (Los Angel) 2015, 2:5
http://dx.doi.org/10.4172/2329-6917.1000167

Case Report Open Access

The Challenge of t (6;9) and FLT3-Positive Acute Myelogenous Leukemia in a Young Adult

Yeohan Song[1,4], **Dale Bixby**[2], **Diane Roulston**[3], **John Magenau**[2] **and Sung Won Choi**[4*]

[1]*University of Michigan Medical School, University of Michigan, Ann Arbor, MI, USA*

[2]*Department of Internal Medicine, Division of Hematology-Oncology, University of Michigan, Ann Arbor, MI, USA*

[3]*Department of Pathology, University of Michigan, Ann Arbor, MI, USA*

[4]*Department of Pediatrics, Division of Pediatric Hematology-Oncology, University of Michigan, Ann Arbor, MI, USA*

[*]**Corresponding author:** Sung Won Choi, M.D., M.S., Department of Pediatrics, Division of Hematology-Oncology, University of Michigan, 1522 Simpson Road East, Medical Professional Building, D4118Ann Arbor, MI, 48109, USA, Tel: 734-615-5707; Fax: 734-936-8688; E-mail: sungchoi@umich.edu

Rec date: October 6, 2014, **Acc date:** November 13, 2014; **Pub date:** November 20, 2014

Abstract

Translocation t(6;9) is a rare cytogenetic abnormality found in fewer than 5% of pediatric and adult cases of acute myelogenous leukemia (AML). The outcomes of t(6;9) AML are generally poor, with low five-year overall survival and increased risk for relapse. Furthermore, FLT3-ITD is one of the most common molecular abnormalities found in AML that is associated with increased risk of treatment failure and mortality. Allogeneic hematopoietic cell transplantation (HCT) with the best available donor is a standard treatment option for these cases once remission is achieved.

We report a challenging case of t(6;9) and FLT3-positive AML in a young adult male. After failing multiple standard induction regimens, morphologic remission was eventually achieved with a FLT3 inhibitor (sorafenib) and a hypomethylating agent (azacytidine). However, despite allogeneic HCT and re-initiation of sorafenib in the post-HCT setting, he experienced early relapse with the original [FLT3-ITD and t(6;9)] and new (FLT3-D835 and +8) molecular and cytogenetic markers, respectively. This case highlights the need for improved strategies in the post-HCT setting for high-risk AML.

Keywords: Acute myelogenous leukemia; Translocation t(6;9); FLT3; Sorafenib; Trisomy 8

Abbreviations:

AML: Acute Myelogenous Leukemia; ITD: Internal Tandem Duplication; HCT: Hematopoietic Cell Transplantation

Background

Disease relapse after allogeneic hematopoietic cell transplantation (HCT) for acute myelogenous leukemia (AML) is the most frequent cause of post-transplantation treatment failure and mortality [1]. Management of relapse, particularly in the early post-transplantation setting, remains a significant challenge. While improved understanding of molecular and cytogenetic markers has led to the use of novel non-cytotoxic agents, there is no consensus on an optimal approach to post-transplantation maintenance therapy to improve outcomes of relapsed patients. Herein, we describe a case of highly refractory AML with recurrent cytogenetic abnormality t(6;9) and the FMS-like tyrosine kinase 3 gene (FLT3) internal tandem duplication (ITD) mutation and highlight the need for improved strategies to harness the immunotherapeutic benefits of HCT in conjunction with targetable agents.

Case Presentation

A 23-year-old Caucasian male presented to his primary care physician with fever, night sweats, and bilateral lower extremity rash. Laboratory testing revealed white blood cells (WBC) $8.5\times10^3/\mu L$ (normal 4.0-10.0x10^3), hemoglobin (Hgb) 10.4 g/dL (normal 13.5-17.0 g/dL), and platelets $41.0\times10^3/\mu L$ (normal 150-400$\times10^3$), with a manual differential count showing 66% blasts, 10% neutrophils, 1% myelocytes, 1% bands, and 18% lymphocytes. Bone marrow biopsy was significant for 74% blasts with Auer rods admixed with rare maturing granulocytic precursors. Flow cytometry detected an abnormal immature myeloid blast population with an immunophenotype of CD13, CD33, CD38, CD117, and HLA-DR. These cells also expressed low levels of CD4 and CD45; partially expressed CD7, CD25, and CD64; and variably expressed CD34. They did not express CD2, CD14, CD15, and CD56. Cytogenetic and molecular testing confirmed a diagnosis of AML with karyotype 46,XY,t(6;9)(p23;q34), DEK/NUP214 and the presence of the FLT3-ITD mutation, respectively. A skin biopsy of one of his lower extremity skin lesions was consistent with leukemia cutis.

The patient consented to Children's Oncology Group (COG) protocol AAML1031 treatment arm C, which included sorafenib, but was moved to treatment arm B, as sorafenib was on a temporary hold for toxicity observation (Figure 1). The induction treatment regimen consisted of 70 mg cytarabine (Ara-C) intrathecal (IT) on day 1; cytarabine 100 mg/m^2 intravenous (IV) days 1-10; daunorubicin 50 mg/m2 days 1, 3, and 5; etoposide 100 mg/m^2 days 1-5; and bortezomib 1.3 mg/m^2 IV days 1, 4, and 8. Repeat bone marrow biopsy

on day 25 of Induction I demonstrated 2% myeloblasts by morphology, consistent with the pre-treatment leukemia phenotype. A separate sample evaluated by the COG revealed the presence of 2.8% minimal residual disease (MRD), and fluorescence in situ hybridization (FISH) assay performed at Mayo Medical Laboratories (Rochester, MN) was positive for t(6;9) in 1.6% of nuclei.

The patient proceeded with Induction II, which included Ara-C 70 mg IT on day 5; cytarabine 1000 mg/m^2 IV days 1-4; mitoxantrone 12 mg/m^2 days 3-6; and bortezomib 1.3 mg/m2 IV days 1, 4, and 8. His course was complicated by febrile neutropenia, *Klebsiella* and *Escherichia coli* bacteremia, pericardial effusion, cellulitis, and a left upper extremity deep venous thrombosis. Repeat bone marrow biopsy on day 31 of Induction II demonstrated trilineage hematopoiesis with no morphologic, flow cytometric, or cytogenetic evidence of leukemia. FISH analysis was also negative for t(6;9), thus indicating first complete remission (CR1).

The patient started Intensification I two months after his initial diagnosis with Ara-C 70 mg IT on day 1; cytarabine 1000 mg/m^2 IV days 1-5; etoposide 150 mg/m^2 days 1-5; and bortezomib 1.3 mg/m2 IV days 1, 4, and 8. He was then referred to our Blood and Marrow Transplantation Team for consultation, and allogeneic HCT with the best possible donor was recommended.

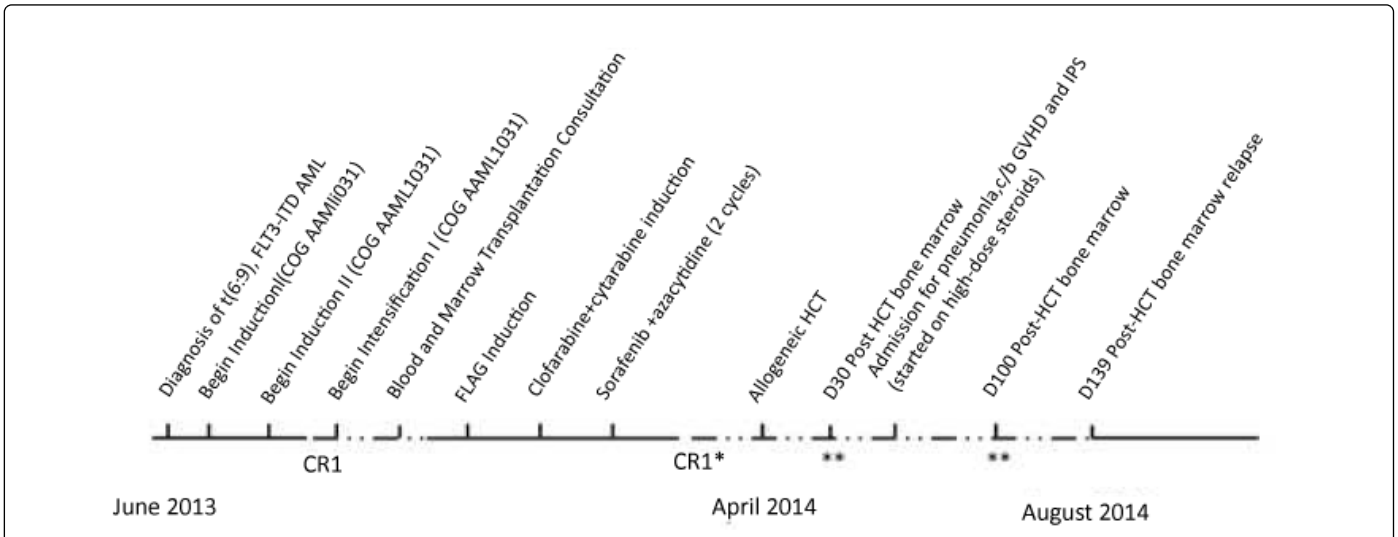

Figure 1: Diagram of patient's treatment course. FLT3: FMS-Like Tyrosine Kinase 3 Gene; ITD: Internal Tandem Duplication; AML: Acute Myelogenous Leukemia; COG: Children's Oncology Group; FLAG: Fludarabine, Cytarabine, Filgrastim; HCT: Hematopoietic Cell Transplantation; D: Day; GVHD: Graft-Versus-Host Disease; IPS: Idiopathic Pulmonary Syndrome; C/B: Complicated By Solid Line: Persistent or Recurrent Acute Myelogenous Leukemia (AML). Dotted Line: AML In Remission. *Morphologic remission, with persistent t(6;9) and FLT3-ITD. **Morphologic, flow cytometric, and molecular remission.

Given the concerns of slow count recovery following Intensification I, repeat bone marrow biopsy was performed, which revealed 12% blasts. He was reinduced with fludarabine 30 mg/m^2 IV days 1-5, cytarabine 2000 mg/m^2 IV days 1-5, and filgrastim 5 mcg/kg starting day 1 (FLAG). Repeat bone marrow biopsy two weeks later revealed persistent AML with 25% blasts and t(6;9), with WBC 0.9×10^3/μL, Hgb 9.6 g/dL, and platelets 23×10^3/μL. Another reinduction regimen of clofarabine 40 mg/m2 IV days 2-6 and cytarabine 1000 mg/m^2 IV days 1-5 was administered. However, repeat bone marrow biopsy showed persistent AML with 17% blasts, and cytogenetics confirmed karyotype 46,XY,t(6;9). The patient was referred to another hematologist to discuss alternative treatment options. Sorafenib 400 mg twice daily days 1-28 and azacytidine 75 mg/m^2 days 1-7 was recommended. After two courses, the patient achieved a morphologic remission with negative flow cytometry, but demonstrated persistent cytogenetic and molecular positivity. MRD analysis sent to Hematologics, Inc. (Seattle, WA) was inconclusive due to ANC<1000.

The patient proceeded with a 9 of 10 HLA matched (HLA-B mismatched) unrelated donor peripheral blood HCT. The conditioning regimen consisted of fludarabine 40 mg/m^2 IV and busulfan 3.2 mg/kg days -5 to -2, with the addition of thymoglobulin 2.5 mg/kg days -3 to -1 for mismatched HCT [2]. Body mass index was 31.4 kg/m^2. The patient's Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) score was 5, placing him in a high risk category. Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus 0.03 mg/kg (starting day-3) and methotrexate 5 mg/m^2 (days 1, 3, 6, 11). A cell dose of 5.6×10^6 CD34 cells/kg was administered.

His clinical course was complicated by coagulase negative Staphylococcus central line infection, mucositis, deep venous thrombosis, and Clostridium difficile gastrointestinal infection. He engrafted neutrophils on day 11 with an absolute neutrophil count (ANC) of 0.6×10^3/μL (>500 ANC on first of three consecutive days) and platelets on day 12 with a platelet count of 27×10^3/μL (>20×10^3/μL on first of three consecutive days). The patient was discharged on day 20. Day 30 bone marrow confirmed morphologic, flow cytometric, and molecular remission. Chimerism studies revealed 100% donor cells with CD3 and CD33, and MRD sent to Hematologics, Inc. was negative. The patient did well until day 36, when he was admitted for rhinovirus and Saccharomyces cerevisiae pneumonia and pericarditis. On day 44, he developed worsening respiratory symptoms requiring 2 L/min of supplemental oxygen, combined with progressively intense skin changes involving his hands and feet concerning for acute GVHD (not biopsy proven). The patient was initiated on prednisone 2 mg/kg/day (total dose 96 mg twice daily) for concern of idiopathic

pulmonary syndrome (IPS). His respiratory symptoms resolved, and he was subsequently discharged on day 49.

Sorafenib was initiated on day 51, with a brief hold between day 65 and day 96 due to concern for thrombocytopenia (56-81×10^3/μL). Repeat bone marrow testing on day 100 again showed no morphologic, flow cytometric, cytogenetic, or molecular evidence of AML. However, routine blood count monitoring again showed declining platelet counts (58×10^3/μL) on day 132. Sorafenib was again placed on hold, and viral studies sent to determine the etiology of his thrombocytopenia were negative. Pathology review of the peripheral blood revealed blasts consistent with his previous leukemia, and a day 139 bone marrow confirmed relapsed disease. Molecular studies revealed new FLT3-D835 mutation in addition to previously detected FLT3-ITD. Cytogenetic testing confirmed presence of the previously identified t(6;9) and demonstrated a concomitant gain of chromosome 8 in all 20 metaphases analyzed (Figure 2). Chimerism studies showed 100% donor CD3 and 45% recipient CD33. Therapy options were discussed with the patient, and he is currently undergoing treatment with crenolanib as part of a phase II clinical trial (NCT01657682) for FLT3-positive relapsed AML.

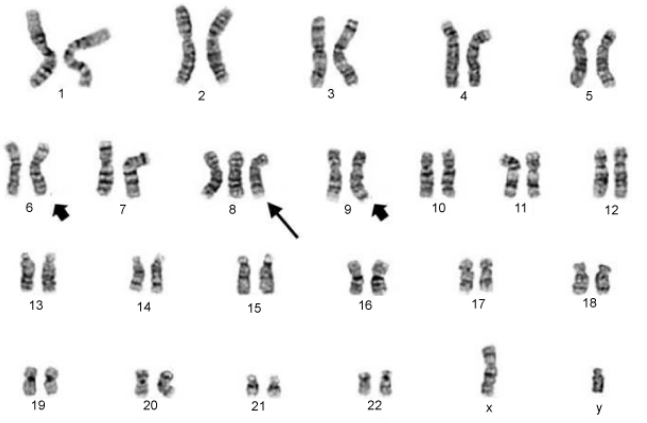

Figure 2: Post-transplantation day 139 karyogram showing 363 gain of chromosome 8 (long arrow) in addition to the previously identified t(6;9) chromosomal aberrancy (short arrows). International System for Human Cytogenetic Nomenclature (ISCN): 47,XY,t(6;9)(p23;q34),+8 [20]

Discussion

Recent efforts have been made to identify prognostic factors for relapse risk (RR) in AML to direct more intensive treatment strategies to higher risk patients through a risk- adapted therapy approach [3]. FLT3-ITD is one of the most common abnormalities in AML, detected in 15 to 25% of patients, and a high ITD allelic ratio has been associated with five-year overall survival (OS) rates <35% and RR >60% [4-6]. Furthermore, AML patients positive for FLT3-ITD have been associated with increased rates of treatment failure and death even after achieving remission [6]. The human FLT3 gene encodes a cell surface protein found predominantly on hematopoietic progenitors and dendritic cells, and its activation leads to proliferation and survival responses normally regulated by tyrosine phosphorylation and proteasomal degradation [7,8]. However, in cases of FLT3-ITD with high ITD-AR, the FLT3 receptor remains constitutively active and leads to deregulation of downstream signaling. Allogeneic HCT is the only potentially curative therapy for AML with FLT3 activating mutations [9]. The role of instituting FLT3 inhibitors, such as sorafenib, in the post-HCT setting remains to be further explored [10,11].

The translocation t(6;9)(p23;q34) represents a rare subset of AML (<5% of adult and pediatric cases [12]) that is closely associated with FLT3-ITD [13,14] and is independently associated with lower five-year OS (≤40%) and higher RR (>50%) [15,16]. Patients with t(6;9) AML demonstrate lower response rates to induction chemotherapy and higher relapse rates despite achieving remission [15]. This translocation results in the formation of chimeric fusion gene DEK-NUP214 on the der(6) chromosome, which is translated to nucleoporin fusion proteins and leads to altered nuclear transport and upregulated myeloid protein synthesis [17,18]. This chromosomal aberrancy has been identified in both de novo and treatment-related AML [16,19]. Of note, the immunophenotype of our patient's leukemic cells was consistent with that described (i.e., CD13+, CD33+, CD38+, CD45+, and HLA-DR+) [16].

This report highlights the challenge of managing AML with t(6;9) and FLT3-ITD positivity, which portend poor prognosis [4-6,15,16]. Our patient's high-risk disease left him with few available treatment options following failure of four attempts at induction with standard chemotherapy regimens. However, among ongoing studies of investigative regimens is a phase 2 clinical trial using combination therapy with sorafenib, a FLT3 inhibitor, and azacytidine, a hypomethylating agent [20]. This combination is thought to promote lower levels of FLT3-ligand compared to standard chemotherapeutics by lessening the FLT3 ligand elevation associated with chemotherapy-induced aplasia [21,22]. A recent publication describes the results of this combination therapy for high-risk AML patients with FLT3-ITD who received a median of two prior treatment regimens, reporting a response rate of 46% and a complete response rate of 16% following a median of two cycles [20]. Indeed, we observed morphologic remission following two courses, consistent with the literature [20]. In efforts to minimize the risk for relapse [23], we continued post-HCT treatment with sorafenib.

Despite this, the patient experienced early post-transplantation relapse at day 139. Although remission was documented with the absence of morphologic, cytogenetic, and molecular features as far as day 100 post-transplantation, this high-risk disease recurred with not only the originally identified genetic abnormalities, but with the further addition of FLT3-D835 and trisomy 8 (+8). This is consistent with the major modes of clonal evolution demonstrated in AML: 1) the founding clone gains mutations following induction chemotherapy and persists to become the relapse clone or 2) a subclone of the founding clone survives induction, acquires additional mutations, and expands at relapse [24]. Given the presence of both previous and new cytogenetic abnormalities in all metaphases analyzed at the time of relapse, this case likely represents the first form of clonal evolution, with clonal expansion following HCT. The importance of these mutations is manifold. The presence of the FLT3-D835 mutation may confer increased resistance to tyrosine kinase inhibitors and lower disease-free survival [25], and the presence of trisomy 8, when associated with other cytogenetic abnormalities, has been attributed with lower overall survival at lower peripheral blast counts [26].

The cytogenetic and molecular characteristics observed at relapse may reflect the accumulation of acquired treatment-related abnormalities. There is a known risk of developing therapy-related

changes leading to AML following topoisomerase-targeting chemotherapy, characterized by a shorter latency period from as little as a few months from exposure to diagnosis [27]. Additionally, treatment with tyrosine kinase inhibitors has been associated with acquired chromosomal abnormalities in chronic myelogenous leukemia, with trisomy 8 being the most commonly detected cytogenetic abnormality following treatment with imatinib [28]. Furthermore, the FLT3-D835 mutation has been observed in refractory AML maintained on sorafenib monotherapy without allogeneic HCT [29].

A recent review of the literature has found mixed results with post-transplantation use of sorafenib, and the role of this agent in treating FLT3-ITD AML remains to be determined [30]. An international survey of patients with FLT3-ITD AML refractory to a median of three chemotherapy cycles with or without prior allogeneic transplantation undergoing sorafenib monotherapy suggested that allogeneic transplantation may have a synergistic role with sorafenib in inducing allo-immune responses, but further demonstrated that over a third of these patients develop sorafenib resistance after a median treatment duration of six to seven months [31]. Recent case studies have also shown sorafenib to have a potential role in enhancing graft-versus-leukemia effects [32,33] or inducing myeloid maturation [33].

The present case highlights the high risk associated with t(6;9) independent of the FLT3-ITD status [15,16]. Moreover, the use of FLT3-targeted therapy in the post-HCT setting did not appear to prevent relapse. Further investigation into the role of DEK-NUP214 is needed, which may lead to novel strategies targeting this fusion protein.

Conclusion

Relapse remains a significant cause of mortality after allogeneic HCT for AML. While the incorporation of non-cytotoxic targeted post-transplantation maintenance agents is currently being considered, the type of drug, disease-specific characteristics, timing of initiation, dosing/schedule, and hold/re-start parameters for myelosuppression need to be better defined and studied in appropriate clinical trials to ensure uniform practices across institutions.

Acknowledgements

Sung Won Choi receives grant support by the NIH 1K23AI091623. She is an A. Alfred Taubman Institute Emerging Scholar.

References

1. Barrett AJ, Battiwalla M (2010) Relapse after allogeneic stem cell transplantation. Expert Rev Hematol 3: 429-441.
2. Choi SW, Reddy P (2014) Current and emerging strategies for the prevention of graft-versus-host disease. Nat Rev Clin Oncol 11: 536-547.
3. Estey EH (2013) Acute myeloid leukemia: 2013 update on risk-stratification and management. Am J Hematol 88: 318-327.
4. Safaian NN, Czibere A, Bruns I, Fenk R, Reinecke P, et al. (2009) Sorafenib (Nexavar) induces molecular remission and regression of extramedullary disease in a patient with FLT3-ITD+ acute myeloid leukemia. Leuk Res 33: 348-350.
5. Pratz KW, Sato T, Murphy KM, Stine A, Rajkhowa T, et al. (2010) FLT3-mutant allelic burden and clinical status are predictive of response to FLT3 inhibitors in AML. Blood 115: 1425-1432.
6. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, et al. (2001) The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood 98: 1752-1759.
7. Rosnet O, Marchetto S, deLapeyriere O, Birnbaum D (1991) Murine Flt3, a gene encoding a novel tyrosine kinase receptor of the PDGFR/CSF1R family. Oncogene 6: 1641-1650.
8. Small D, Levenstein M, Kim E, Carow C, Amin S, et al. (1994) STK-1, the human homolog of Flk-2/Flt-3, is selectively expressed in CD34+ human bone marrow cells and is involved in the proliferation of early progenitor/stem cells. Proceedings of the National Academy of Sciences of the United States of America 91: 459-463.
9. Brunet S, Martino R, Sierra J (2013) Hematopoietic transplantation for acute myeloid leukemia with internal tandem duplication of FLT3 gene (FLT3/ITD). Curr Opin Oncol 25: 195-204.
10. Fathi AT, Chabner BA (2011) FLT3 inhibition as therapy in acute myeloid leukemia: a record of trials and tribulations. Oncologist 16: 1162-1174.
11. Chang BH, Cooper TM, Gross T, Gupta S, Ho PA, et al. (2013) Sorafenib Treatment Following Hematopoietic Stem Cell Transplant In Pediatric FLT3/ITD+ AML.
12. Shearer BM, Knudson RA, Flynn HC, Ketterling RP (2005) Development of a D-FISH method to detect DEK/CAN fusion resulting from t(6;9)(p23;q34) in patients with acute myelogenous leukemia. Leukemia 19: 126-131.
13. Thiede C, Steudel C, Mohr B, Schaich M, Schäkel U, et al. (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood 99: 4326-4335.
14. Oyarzo MP, Lin P, Glassman A, Bueso-Ramos CE, Luthra R, et al. (2004) Acute myeloid leukemia with t(6;9)(p23;q34) is associated with dysplasia and a high frequency of flt3 gene mutations. Am J Clin Pathol 122: 348-358.
15. Tarlock K, Alonzo TA, Moraleda PP, Gerbing RB, Raimondi SC, et al. (2014) Acute myeloid leukaemia (AML) with t(6;9)(p23;q34) is associated with poor outcome in childhood AML regardless of FLT3-ITD status: a report from the Children's Oncology Group. Br J Haematol 166: 254-259.
16. Slovak ML, Gundacker H, Bloomfield CD, Dewald G, Appelbaum FR, et al. (2006) A retrospective study of 69 patients with t(6;9)(p23;q34) AML emphasizes the need for a prospective, multicenter initiative for rare 'poor prognosis' myeloid malignancies. Leukemia 20: 1295-1297.
17. Oancea C, Rüster B, Henschler R, Puccetti E, Ruthardt M (2010) The t(6;9) associated DEK/CAN fusion protein targets a population of long-term repopulating hematopoietic stem cells for leukemogenic transformation. Leukemia 24: 1910-1919.
18. Ageberg M, Drott K, Olofsson T, Gullberg U, Lindmark A (2008) Identification of a novel and myeloid specific role of the leukemia-associated fusion protein DEK-NUP214 leading to increased protein synthesis. Genes, chromosomes & cancer 47: 276-287.
19. Alsabeh R, Brynes RK, Slovak ML, Arber DA (1997) Acute myeloid leukemia with t(6;9) (p23;q34): association with myelodysplasia, basophilia, and initial CD34 negative immunophenotype. American journal of clinical pathology 107: 430-437.
20. Ravandi F, Alattar ML, Grunwald MR, Rudek MA, Rajkhowa T, et al. (2013) Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood 121: 4655-4662.
21. Kindler T, Lipka DB, Fischer T (2010) FLT3 as a therapeutic target in AML: still challenging after all these years. Blood 116: 5089-5102.
22. Sato T, Yang X, Knapper S, White P, Smith BD, et al. (2011) FLT3 ligand impedes the efficacy of FLT3 inhibitors in vitro and in vivo. Blood 117: 3286-3293.
23. Metzelder S, Wang Y, Wollmer E, Wanzel M, Teichler S, et al. (2009) Compassionate use of sorafenib in FLT3-ITD-positive acute myeloid

leukemia: sustained regression before and after allogeneic stem cell transplantation. Blood 113: 6567-6571.

24. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, et al. (2012) Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 481: 506-510.
25. Whitman SP, Ruppert AS, Radmacher MD, Mrozek K, Paschka P, et al. (2008) FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. Blood 111: 1552-1559.
26. Wolman SR, Gundacker H, Appelbaum FR, Slovak ML; Southwest Oncology Group (2002) Impact of trisomy 8 (+8) on clinical presentation, treatment response, and survival in acute myeloid leukemia: a Southwest Oncology Group study. Blood 100: 29-35.
27. Allan JM, Travis LB (2005) Mechanisms of therapy-related carcinogenesis. Nat Rev Cancer 5: 943-955.
28. Medina J, Kantarjian H, Talpaz M, O'Brien S, Garcia-Manero G, et al. (2003) Chromosomal abnormalities in Philadelphia chromosome-negative metaphases appearing during imatinib mesylate therapy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. Cancer 98: 1905-1911.
29. Baker SD, Zimmerman EI, Wang YD, Orwick S, Zatechka DS, et al. (2013) Emergence of polyclonal FLT3 tyrosine kinase domain mutations during sequential therapy with sorafenib and sunitinib in FLT3-ITD-positive acute myeloid leukemia. Clinical cancer research: an official journal of the American Association for Cancer Research 19: 5758-5768.
30. Hu B, Vikas P, Mohty M, Savani BN (2014) Allogeneic stem cell transplantation and targeted therapy for FLT3/ITD+ acute myeloid leukemia: an update. Expert Rev Hematol 7: 301-315.
31. Metzelder SK, Schroeder T, Finck A, Scholl S, Fey M, et al. (2012) High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. Leukemia 26: 2353-2359.
32. Krüger WH, Hirt C, Kiefer T, Neumann T, Busemann C, et al. (2012) Molecular remission of FLT3-ITD(+) positive AML relapse after allo-SCT by acute GVHD in addition to sorafenib. Bone Marrow Transplant 47: 137-138.
33. Liegel J, Courville E, Sachs Z, Ustun C (2014) Use of Sorafenib for relapse posttransplant in FLT3/ITD+ acute myelogenous leukemia: maturation induction and cytotoxic effect. Haematologica .