

Leukaemia Section

Short Communication

t(3;21)(q26;q22)

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Abstract: Short communication on t(3;21)(q26;q22), with data on clinics, and the genes involved.

Clinics and pathology

Disease

Chronic myelogenous leukemia in blast crisis (BC-CML), myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Note

Cases of t(3;21)(q26;q22) are mostly treatment-related blast crises of CML, and treatment-related MDS/AMLs. However, the t(3;21) may also be found in rare instances of CML prior to the onset of blast crisis (Coyle and Najfeld, 1988).

In selected publications (Sacchi et al., 1994; Secker-Walker et al., 1995; Jeandidier et al., 2006; Poppe et al., 2006; Yin et al., 2006; see below), there were equal numbers of BC-CML cases and MDS/AML cases (53% and 47% respectively, out of 60 cases). A very few cases of chronic myeloproliferative disease without a t(9;22) have been documented (3,4% of the 146 cases of t(3;21) collected in the Mitelman database). Most cases of AML are M2-AML or M4-AML (+ two cases of M5b, one M6, one M7). MDS cases are mostly refractory anemia with excess of blasts (RAEB, also including RAEB-1 and RAEB-2) (+ one case of refractory anemia, one case of chronic myelomonocytic leukemia).

Cases of t(3;21) herein reviewed were selected and pooled together from the large studies (Lafage-Pochitaloff-Huvalé et al., 1989; Rubin et al., 1990; Sacchi et al., 1994; Secker-Walker et al., 1995; Jeandidier et al., 2006; Poppe et al., 2006; Lugthart

et al., 2010; Paquette et al., 2011); BC-CML cases and MDS/AML cases were separated into two distinct entities for further studies; each entity was then compared with the equivalent entities from the largest study (Yin et al., 2006), and, in the occurrence where there was no discrepancy, all the cases in each entity (BC-CML and MDS/AML) were again pooled together.

As a matter of fact, the only discrepancy was the sex ratio in MDS/AML entity: 55% male / 45% female patients in the 29 cases from the "large studies" vs 30% male / 70% female patients in the 10 cases from the "largest study".

In the review herein below, we therefore study a sample of 42 cases of BC-CML, and 39 cases of MDS/AML. In some instances, the whole sample of cases of t(3;21) harvested in the Mitelman database was taken into account (146 cases).

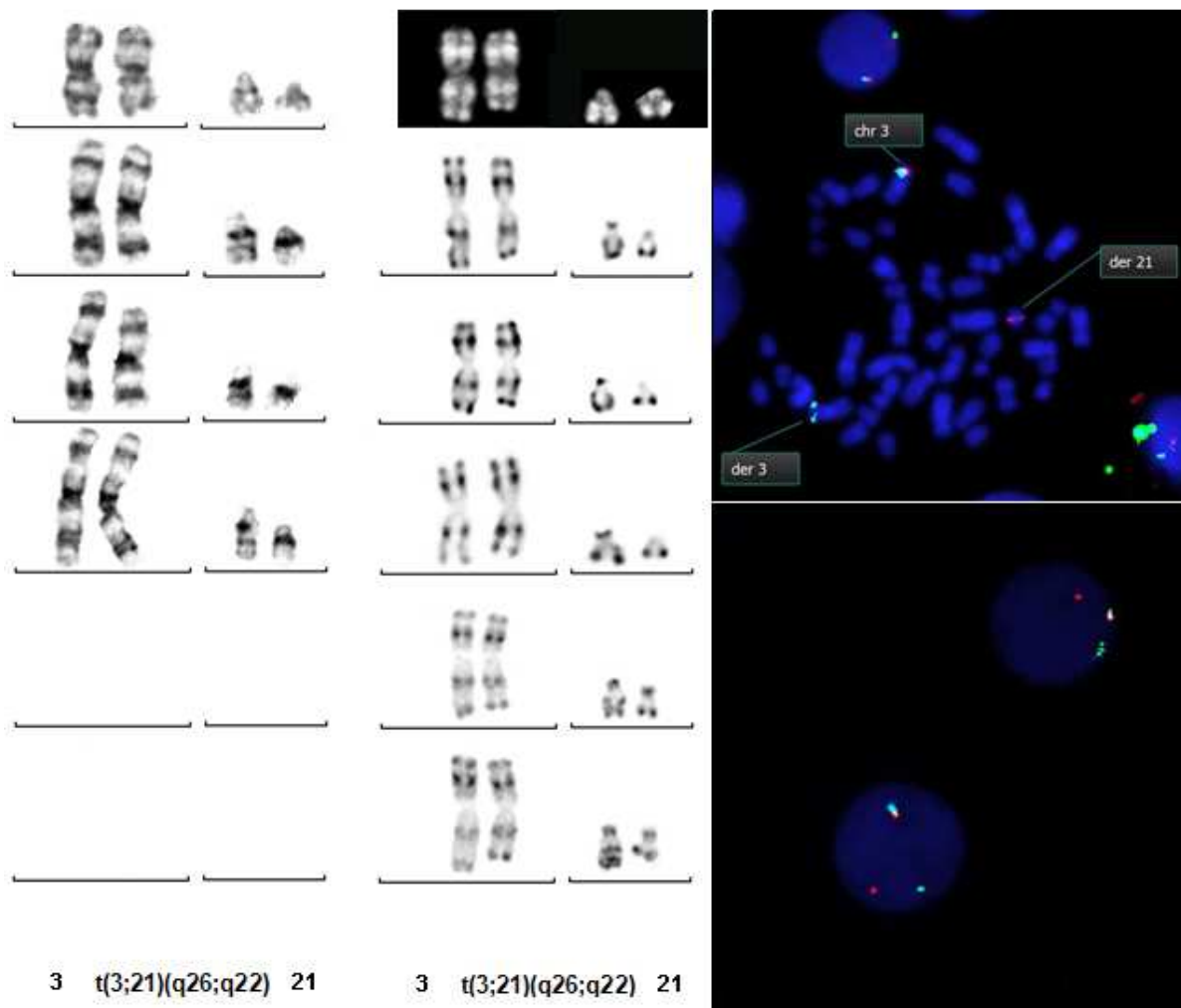
Etiology

Rubin et al., 1990 noted that t(3;21) represents 3,6% of therapy related MDS/AMLs (t-MDS/AML); they did not find one case of t(3;21) amongst 1500 de novo MDS/AMLs.

Yin et al., 2006 noted that 15 of their 16 BC-CML patients had previously been treated with hydroxyurea, before blast crisis.

The occurrence of the t(3;21) heralded blast transformation.

The authors conclude that prior treatment with hydroxyurea or other antimetabolites (fludarabine, 5-fluorouracil) are implicated in t(3;21) malignant blood diseases.



t(3;21)(q26;q22). Left: G-banding - Top - Courtesy Marian Stevens-Kroef; Middle three: Courtesy Steven Richebourg; Center: R-banding - Top: Courtesy Peter Vandenberghe; Middle three: Courtesy Olivier Theisen; Bottom two: Courtesy Christine Perot; Right: FISH with EVI1 break apart probe Courtesy Olivier Theisen.

Paquette et al., 2011, report that MECOM (also known as EVI1) translocations were seen in 12% of BC-CML before tyrosine kinase inhibitors treatments, a percentage reaching 35-40% with current treatments.

The authors note that BCR-ABL1 and MECOM collaborate in leukemogenesis in animal models. Coexistence of BCR-ABL1 and MECOM translocation is sufficient to cause evolution towards BC-CML.

The interval between the diagnosis of the initial neoplasm and the occurrence of the t(3;21) was 24 months (median, range 3-154 months) in CML-->BC-CML, and 38 months (median, range 6-144 months) for MDS/AML cases (Yin et al., 2006).

In our meta-analysis, 81% of 33 cases of BC-CML and 87% of 31 cases of MDS/AML can be considered to be secondary to previous treatment.

Results presented herein can be compared with those of a study from an International Workshop on treatment related leukemia: "t(3;21)(q26;q22) in

treatment related leukemia".

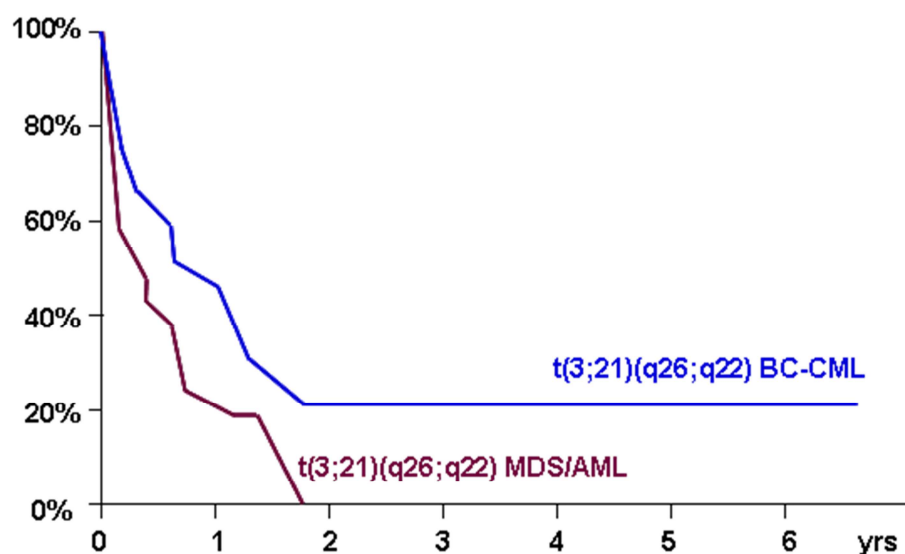
Epidemiology

Translocation t(3;21) represents 0,14% of AML cases and 3% of 3q abnormalities cases (9 cases out of 6515 AML patients) in Lugthart et al., 2010.

Median age was 58 years (range 21-77) in BC-CML (n=42), and around 65 years (range 13-76, only one child) in MDS/AML (n=39).

From 146 cases extracted from the Mitelman database, sex ratio was 1,44 (59% male and 41% female patients). In the 42 cases of BC-CML herein selected for study, there was 71% male and 29% female patients (p<0.01).

In the 39 cases of MDS/AML, no conclusion can be drawn, owing to conflictory data between "large studies" and "the largest study" (see above); the oddity of pooling heterogenous samples would result, in the present case, in a balanced sex ratio (19M/20F), but, again this is nonsense and the issue rewards further studies.



Overall survival in 30 patients with a chronic myelogenous leukemia in blast crisis (BC-CML), and 18 patients with a myelodysplastic syndrome or an acute myeloid leukemia (MDS/AML) and a t(3;21)(q26;q22) MECOM/RUNX1, from the largest studies.

Cytology

Secker-Walker et al., 1995 noted low platelet counts, dysmyelopoiesis, decreased number of megakaryocytes, and micromegakaryocytes in MDS/AML cases; micromegakaryocytes were also seen in BC-CML cases (Yin et al., 2006).

Prognosis

Poor survival (see figure above). Median survival is 4 months (range 0-21 months, n=18) in the MDS/AML group, and 9 months (range 1-79+ months, n=30 cases, reports from 1995 to 2011) in the BC-CML group.

Median survival was 13 months in the most recent cases of BC-CML (n= 20 cases) (Yin et al., 2006; Paquette et al., 2011).

Genetics

Note

In a study of cases with 3q21 and/or 3q26 abnormalities (Lugthart et al., 2010), no mutation of FLT3-TKD (tyrosine kinase domain), NPM1, CEBPA, KIT, MLL-PTD (partial tandem duplication), K-RAS were found in the t(3;21)(q26;q22) cases; in the whole 3q26 group (inv(3)/t(3;3) excluded), there were 11% of FLT3-ITD (internal tandem duplication) and 25% of N-RAS mutation.

Cytogenetics

Cytogenetics morphological

From the 146 cases extracted from the Mitelman database, the t(3;21) was the sole anomaly in 25% of cases, accompanied with a t(9;22)(q34;q11) in 40%,

with -7/del(7q) in 15%, +8 in 11%, +12 in 5%, del(5q) in 3%, and +9, +13, or del(20q) in 1% each.

Again from these 146 cases, when the t(3;21) was the sole anomaly, the diagnosis was AML in 84% of cases, and MDS in 14%; in cases with a -7/del(7q), the diagnosis was AML in 64% of cases, MDS in 18%, and CML in 14%; in cases with a +8, the diagnosis was CML in two third of cases, and AML in 25%; in cases with a +12, the diagnosis was CML in half of the cases, and AML in the other half.

In the BC-CML series (with a t(9;22), indeed), the t(3;21) was accompanied with +8 in 16% of cases, +12 in 5%, and with -7/del(7q) or -5/del(5q) in 3% each.

The profile in MDS/AML cases is here very different: the t(3;21) was the sole anomaly in 36% of cases, accompanied with -7/del(7q) in 26%, +8 in 8%, del(5q) or del(20q) in 5% each, +12 in 3%. A complex karyotype may be present.

Genes involved and proteins

MECOM

Location

3q26

Note

MECOM is also known as EVI1 or PRDM3; MECOM symbol means: "MDS1 and EVI1 complex locus".

Protein

"EVI1" contains two domains of seven and three zinc finger motifs, respectively, a repression domain between the two sets of zinc fingers, and an acidic domain at its C-term.

Sequence specific DNA binding protein.

Interacts with transcriptional coactivators, corepressors, and other sequence specific transcription factors. MECOM ("MDS1-EVI1") also contains a PR domain from "MDS1" in N-term (Wieser, 2008).

RUNX1

Location

21q22

Note

RUNX1 has also been known as AML1 or CBFA2.

DNA/RNA

Transcription is from telomere to centromere.

Protein

Contains a Runt domain and, in the C-term, a transactivation domain, an inhibition domain, and various regulatory regions; forms heterodimers; widely expressed; nuclear localisation; transcription factor (activator) for various hematopoietic-specific genes.

Result of the chromosomal anomaly

Hybrid gene

Note

Breakpoint after exon 5 or 6 in RUNX1. Breakpoints are variable and dispersed along EVI1, MDS1 and the telomeric region of these two genes (Poppe et al., 2006).

Description

Fusion gene: on the der(3); 5' RUNX1 - 3' MECOM.

Fusion protein

Description

RUNX1/MECOM: 180 kDa. The translocation protein includes the N-term RUNX1 with the Runt domain and most of the gene MECOM, from the second untranslated exon of EVI1 to C-term, which includes the 2 zinc finger motifs, the repression domain, and the acidic domain, or also including the MDS1 PR domain followed by EVI1 domains as noted above.

Oncogenesis

Inappropriate and ectopic expression of MECOM (either as EVI1 or as MDS1-EVI1) (Poppe et al., 2006; Lugthart et al., 2010); interferes with RUNX1 functions in a dominant negative manner.

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