ACUTE PROMYELOCYTIC LEUKEMIA WITH ATYPICAL KARYOTYPE AND FLT3-ITD MUTATION IS ASSOCIATED WITH INFERIOR CLINICAL OUTCOME

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Introduction

Acute promyelocytic leukemia (APL) is an aggressive leukemia involving *PML-RARA* gene fusions, which usually respond to all-trans-retinoic acid (ATRA) plus idarubicin or arsenic trioxide (ATO) with 90-100% complete remission and overall survival of 86-97%[1-3]. A subset of APL cases reveal additional cytogenetic abnormalities beyond t(15;17)(q22;21) or variants of RARA gene rearrangements. *FLT3-ITD* mutations have been reported in some of newly diagnosed APL(15-25%) cases and are associated with early relapse, lower complete remission rate, and higher mortality during induction therapy. However, frequency of *FLT3* mutations in APL with an atypical karyotype is unclear.

Methods

Retrospective analysis (Institutional Review Board approved) of APL cases seen at Moffitt Cancer Center between 1/2009-5/2017 was performed. The patients with atypical karyotypes other than the standard reciprocal translocation and additional cytogenetic aberrations were retrieved. Clinical and laboratory investigation including bone marrow biopsy, flow cytometry, fluorescent in situ hybridization (FISH), karyotyping, molecular studies, and clinical outcomes were analyzed.

References

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NO.	AGE /SEX	KARYOTYOING	IMMUNOPHENOTYPING	TREATMENT	OS (mon)	ALIVER
1	70/M	46,XY,t(7;17;15)(q22;q21.2;q24)[15]/46,XY[5]	CD13 +, CD33+, CD34 -, CD45 dim+, CD56 -, CD117 +, HLA-DR -, MPO +, TDT -	AT +AR	7	Y
2	32/F	46,XX,t(4;17;15)(p16;q21.2;q24)[20]	CD13+, CD33+, CD34+, CD45 dim+, CD56-, CD117 subset+, HLA-DR-, MPO dim+, TDT-	AT + ID + CT	17	Y
3	40/M	46,XY,add(4)(q21),t(15;17)(q24;q21.2)[20]	CD13+, CD33+, CD34+, CD45 dim+, CD56 subset+, CD117 dim+, HLA-DR-, MPO+, TDT-	AT + AR	< 1	N
4	/51M	46,XY,t(6;17;15)(q21;q21.1;q24)[18]/46,XY[2]	CD13+, CD33+, CD34-, CD45 dim+ ,CD117+, HLA-DR-	AT + CT + DA / AT +AR	16	
5	22/F	46,XX,t(1;11)(q32;q23),der(9)t(9;15)(p24;q22)t(15;17)(q24;q21),der(15)t(9;15)t(15;17),der(17)t(15;17)[9]	CD13+, CD33+, CD34-, CD45 dim+, CD117+, HLA-DR-	AT + CT + DA + MT / AR	3	-
6	33/F	46,XX,add(2)(q37) inv(5)(p13q13),add(6)(q27),t(15;17)(q22;q21)[cp20].	CD34-, HLA-DR-, CD15-, CD14-, CD19-, CD3-, CD7-, CD11b- , CD33+, CD117+, CD38+, CD64+ and CD13+	AT + ID / AT + MI + ID / AT	65	Y
7	51/F	46,XX,?del(9)(q12q22),t(15;17)(q24;q21.1)[cp4]/ 46,XX[13].	CD33+, CD13+, CD117+, bright MPO+, HLA-DR-, CD34-, CD11b-, CD11c- and TdT-	AT + ID + PE /ME +MT + AT	74	Y
8	55/F	92,XXYY,t(15;17)(q24;q21.1)x2[cp20]	CD34dim+, HLA-DR-, CD117+, CD11b-, CD11c-, CD13+, CD33+	AT + ID / AT + ID + MI / AT	57	Y
9	73/M	46,XY,t(11;17)	CD13+, CD33+, CD34-, CD117+, HLA-DR-, CD11b subset+, CD11c-	CT + ID + GE	18	N
10	46/F	46,XX,ins(15;17)(q22;q21.1q21.3), ins(17;15)(q21.1;q22q26)[16]/46,XX[4].	CD13+,CD33+, CD117+, HLA-DR-, and CD34-	AT +AR / AT+AR	42	Y
11	51/F	46,XX,del(7)(q31q32),?t(14;15;17)(q32;q24;q21.1)[2]/46,XX[2].	CD34+, CD117+, HLA-DR-, CD11b-, Cd11c-, CD13+, CD33+	AT +AR / AT+AR	8	Y
12	59/F	46,XX,t(4;21)(p12;q11.2)?c,t(15;17)(q24;q21.1)[20]	CD34 subset +, CD117 subset +. CD13+, CD33+ and MPO+ and HLA-DR.-	AT	1	N
13	57/F	86-91,XXX,-X,inv(1)(p13q25),-2,add(4)(q21),del(4)(q21q31),del(5)(p13p15),-9,add(9)(q13),t(9;22)(q34;q11.2),del(12)(q12),t(15;17)(q22;q21)x2,der(16)t(14;16)(q12;q12),-18[cp18]/46,XX[2]*.	CD13+, CD33+, CD34+, CD117+, HLA-DR+	AT + CT + DA / AT +AR + DA / AT	57	Y
14	58/F	46,XY[20]. But FISH and PCR PML-RARA showed positive fusions, indicating cryptic translocation	CD13+, CD33+, CD34-, CD117-, HLA-DR-	AT + DA + AR + GE	Lost follow up	

Figure 1. Cases with Atypical Karyotype. (AT – ATRA; AR – Arsenic; CT – Cytarabine; ID – Idarubicin, DA – daunorubicin, MT – Methotrexate, MI – Mitoxantrone, PT – PETHEMA, ME – Mercaptopurine, GE- Gemtuzumab (Induction/Consolidation/Maintenance). * composite t(9;22) and t(15;17)

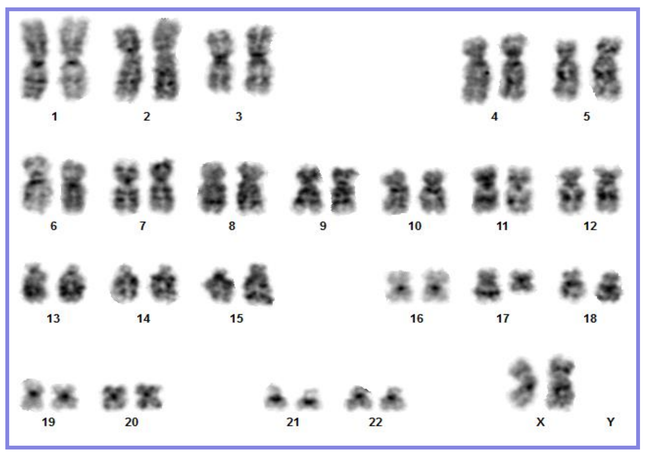

Figure 2. Karyotype: 46,XX,t(4;17;15)(p16;q21.2;q24)[20] (case No. 2)

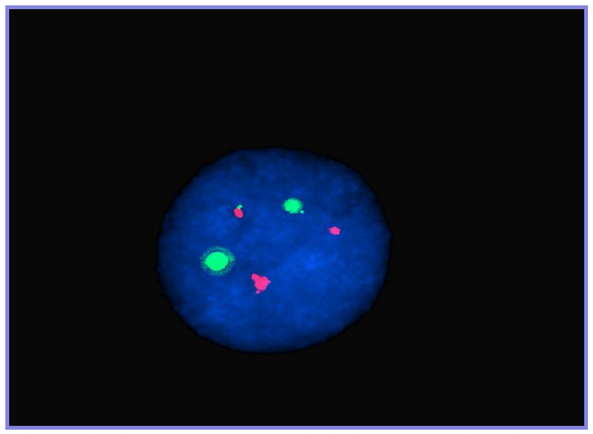

Figure 3. Fluorescence in situ hybridization: Performed using PML/RARA, dual color, dual fusion translocation probe set. Results shows a signal pattern: 2 red, 2 green, and 1 fusion signal, which support presence of a three-way translocation (Case No.2)

Results

86 patients diagnosed with APL (median age 51 years, range 22-70 years; male to female ratio of 5:9) and treated at Moffitt Cancer Center (81) and University of Florida at Jacksonville (5) were identified and confirmed by FISH and/or polymerase chain reaction (PCR).

Conventional karyotyping was performed in 80% (69/86) of the APL patients. 14 of 69 exhibited an atypical karyotype including t(7;17;15)(1), t(4;17;15)(1), t(6;17;15)(1), t(14;15;17)(1), t(1;17;15)(1), tetraploidy(92,XXYY,t(15;17))(1), ins(15;17)(q22;q21.1q21.3)(1), t(11;17)(1), additional cytogenetic aberrations including del(9q), del(7q), and t(4;21)(3), and complex cytogenetic abnormalities(3).

***FLT3* analysis was carried out in 6 of 14 patients. 3 of the 6 patients showed *FLT3-ITD* mutation, one of which had an additional *c-Kit* mutation. A subpopulation of patients demonstrated CD34 positivity(28.5%, 4/14) by flow cytometry, not frequently seen in typical APL. All 14 patients received ATRA and arsenic or iadrubicin-based chemotherapy. Two patients died during initial induction and one died due to relapse. Among the 3 patients, 1 demonstrated t(11;17)(*ZBTB16-RARA* fusion) and 2 harbored *FLT3-ITD* mutations. With median follow-up of 16.5 months (1-74 months), overall survival was 79%[1-3], which is lower than reported APL cases with typical or without defining its genetic changes.**

Conclusion

The study shows that APL patients with an atypical karyotype have inferior clinical outcome, particularly those with *FLT-3 ITD* mutations and t(11;17). It is recommended that karyotyping with *FLT-3* mutation analysis be routinely performed when a diagnosis of APL has been made.