Acute promyelocytic leukemia (APL) is an aggressive leukemia involving PML-RARA gene fusions, which usually respond to all-trans retinoic acid (ATR) plus idarubicin or arsenic trioxide (ATO) with 90-100% complete remission and overall survival of 86-97% [1,2]. A subset of APL cases reveal additional cytogenetic abnormalities beyond t(15;17)(q22;q21) 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, poor overall survival, and higher mortality during induction therapy. Therefore, 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


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;17)(1;22), t(15;17)(1;22), t(6;17)(15;22), t(11;15)(17;17), tetraploidy(92,XXX;15;17)(q22;q12.3)(11), t(11;17)(11;17), additional cytogenetic aberrations including del(9)(q), del(7)(q), 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 e-Ki 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 idarubicin-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 FLT3-ITD mutations and t(11;17). It is recommended that karyotyping with FLT3 mutation analysis be routinely performed when a diagnosis of APL has been made.