Leukemia Research 37 (2013) 1451–1456

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Characteristics and prognosis analysis of additional chromosome abnormalities in newly diagnosed acute promyelocytic leukemia treated with arsenic trioxide as the front-line therapy

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ARTICLE INFO

Article history:
Received 14 April 2013
Accepted 19 July 2013
Available online 16 August 2013

Keywords:
Acute promyelocytic leukemia
Additional cytogenetic abnormalities
Arsenic trioxide
Prognosis

ABSTRACT

Currently, there are few studies that address the prognostic significance of baseline additional chromosomal abnormalities (ACAs) in newly diagnosed acute promyelocytic leukemia (APL) patients treated with arsenic trioxide (ATO) as the front-line therapy. A series of 271 consecutive APL patients has been cytogenetically investigated between 2004 and 2011 in our institution. The incidence of ACAs was 27% (46/172) in APL cases with t(15;17). Trisomy 8 was the most recurrent abnormality, accounting for 30% (14/46) of patients with ACAs, followed by +21 (7%, 3/46) and −7/7q (7%, 3/46). Nine cases (14.1%) were found to have additional balanced translocation aberrations, most of them are new and non-recurrent. Treatment protocols consisted of all-trans retinoic acid (ATRA) and chemotherapy with or without the ATO therapy. Overall, patients with and without ACAs had similar complete remission (CR) rates (94% and 98%, respectively, $P = 0.344$). With a median follow-up of 41 months, univariate analysis showed that ACAs did not show any prognostic significance in relapse-free survival (RFS) and overall survival (OS). In addition, ATO treatment was an independent favorable predictor for RFS. Thus, this data provides insights into cytogenetic features of APL, and suggests that ATO-based combination therapy improved RFS in de novo APL patients, while ACAs had no impact on prognosis.

1. Introduction

Acute promyelocytic leukemia (APL) is a special subtype of acute myeloid leukemia (AML) characterized by distinctive cytogenetic, molecular and clinical features [1]. The reciprocal translocation t(15;17) which results in the fusion of the promyelocytic leukemia (PML) gene with the retinoic acid receptor alpha (RARA) gene, is considered critically important in the pathogenesis of APL [2–4]. While transgenic mouse studies have shown that PML-RARA is necessary, but not sufficient for APL development, additional genetic alterations are required for the development of a leukemic phenotype [5–7]. Interestingly, in addition to conventional t(15;17), various additional cytogenetic abnormalities (ACAs) have been found in 23–39% of APL cases [8]. The additional genetic and chromosomal alterations may cooperate with PML-RARA in the development of APL. A detailed survey of ACAs in APL may shed new light on the underlying pathogenic mechanisms of leukemia development.

Moreover, ACAs are present frequently in newly diagnosed APL yet there have been variable results in terms of the relevance to clinical outcome. Some studies found that ACAs was related to poorer prognosis [8–11]; other reports have shown that ACAs had no impact on prognosis [12–15]. In those series, the majority of patients had received treatment with a combination of all-trans retinoic acid (ATRA) and chemotherapy. The different clinical impact of ACAs could be attributed to varying treatment plans, different sample sizes and clinical follow-up times. Recently, increasing evidence indicates that the addition of arsenic trioxide (ATO) results in a significant improvement of cure rate which is becoming the new standard front-line therapy [16–21]. However, there are only limited data on addressing the prognostic implication of baseline ACAs in newly diagnosed APL treated by ATO-based regimen. Thus, a reevaluation of the role of ACAs is needed in the era of this therapeutic progress.

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http://dx.doi.org/10.1016/j.leukres.2013.07.030

In this study, we retrospectively analyzed the incidence, characterization of cytogenetic changes in addition to t(15; 17) in a series of newly diagnosed APL patients. Moreover, we investigated the influence of ACAs on the clinical efficacy of with or without ATO treatment.

2. Patients and methods

2.1. Patients and study design

We searched for APL patients from our medical record database at a single institution from January 2004 to December 2011. The diagnosis was based on morphology, immunophenotyping and subsequently confirmed by the presence of PML-RARA fusion gene. Demographics, laboratory data, clinical and follow-up data were reviewed and analyzed retrospectively. The study was approved by the Institutional Review Board and in accordance with the Declaration of Helsinki.

2.2. Cytogenetic analysis

Conventional cytogenetic studies were performed on bone marrow cells from direct and/or 24-h unstimulated cultures following standard procedures. The metaphase chromosomes were stained by R-banding and karyotypic annotation was designated according to the International System for Human Cytogenetic Nomenclature 2005. Cytogenetic analysis was considered successful if a clonal chromosomal abnormality (two metaphases with the same additional chromosome or the same structural abnormality and three metaphases missing the same chromosome) was detected or a minimum of 20 metaphases were analyzed. Rearrangements were described as balanced when no apparent gain or loss of genetic material was recorded. According to cytogenetic data, patients were grouped into two categories: those with classical t(15;17) as the sole cytogenetic change and those with t(15;17) and ACAs. For the purposes of this study, patients without classical karyotyping t(15;17), but with the PML-RARA fusion demonstrated by either reverse transcriptase-polymerase chain reaction (RT-PCR) or fluorescence in situ hybridization (FISH), were excluded in treatment response analysis.

2.3. Treatment procedure

Patients were separated into two groups based on the treatment strategy (without ATO group, and ATO group). For the group that did not receive ATO, patients followed the ATRA-based induction therapy and those patients who achieved CR received only sequentially ATRA and chemotherapy as post-remission therapy [22]. For the ATO-treated group, the modified Shanghai protocol was adopted [23]. Details of treatment schedule have been described previously [20]. Briefly, remission induction therapy consisted of ATRA plus ATO and chemotherapy with dose and duration determined by the leukocyte count until complete remission (CR). For the patients in CR, after receiving three courses of consolidation chemotherapy, patients negative for PML-RARA were allocated to receive ATRA and ATO maintenance therapy. A small group of patients received ATRA-based regimen for remission induction, but ATO was added for consolidation and maintenance therapy. Those patients were classified into the ATO group. The standard supportive therapy for coagulopathy, infection as well as management of the APL differentiation syndrome was performed according to international standards [23,24].

2.4. Statistical analyses

Hematologic CR and relapse were defined according to International Working Group criteria [25]. Molecular relapse was defined as the reappearance of two positive RT-PCR results for the PML-RARA fusion gene, at least two weeks apart each other. Relapse-free survival (RFS) was defined as the time interval from the achievement of CR to relapse or death or censoring of the data. Overall survival (OS) was calculated from the date of the initial diagnosis until death from any cause or censoring of the data. The date of the last follow-up was December 2012. Early death was defined as death within 30 days from commencement of ATRA induction. Baseline clinical parameters were compared between two groups by chi-square test or the Fischer's exact test for categorical variables and the Mann–Whitney test for continuous variables. Times to outcomes, including RFS and OS were estimated by the Kaplan–Meier method and then compared by the log-rank test. The logistic regression model using backward LR method was applied for the prediction of CR rate. Univariate and multivariate survival analyses were performed by using Cox proportional hazards model. All statistical analyses were performed with IBM SPSS Statistics 20.0 or GraphPad Prism 5.0. All tests were two-sided and used 0.05 as the significance level.

3. Results

3.1. Overall patient characteristics

A total of 271 consecutive newly diagnosed APL patients with PML-RARA positive have been cytogenetically investigated within the study period. There were 141 males and 130 females, with a median age of 39.6 years (range, 13–80 years). Cytogenetic data showed abnormal karyotype with t(15;17) ($n = 172$), abnormal karyotype without t(15;17) ($n = 2$), normal karyotype ($n = 56$), and failed ($n = 41$). Failures in cytogenetic analysis were due to the insufficient number of metaphases. One hundred twenty-six patients (73%) out of 172 patients showed the presence of classic t(15;17) as the sole karyotype abnormality, 46 (27%) out of 172 patients showed t(15;17) with ACAs.

3.2. Distributions of ACAs in newly diagnosed APL

As shown in the Table 1, 31 patients (67%) had one additional abnormity and 15 patients (33%) had two or more abnormities. Chromosome numerical aberrations were the most frequent; with 21 patients (46%) gaining additional chromosomes and 8 patients (17%) losing at least one of their normal chromosomes. Eight cases (17%) were found to have variant balance translocations. Specific to certain chromosomes, trisomy 8 was the most frequently observed and detected in 14/46 (30%) of ACA cases. Abnormalities of chromosome 7 were seen in 6 cases (13%), 3 cases had a monosomy 7 or del(7q), 2 had der(7q), 1 had a t(7;11)(q31;q13). Trisomy 21 was seen in 3 cases. Monosomy 18 was detected in 2 patients.

3.3. Response to therapy

As shown in Table 2, there were no significant differences in terms of sex, age, risk stratification, initial white blood cell (WBC) count, hemoglobin level and platelet count between the groups with or without ACAs. Overall, 123 out of 126 patients (97%) with the t(15;17) alone and 43 out of 46 patients (94%) with ACAs achieved CR. The difference was not statistically significant ($P = 0.344$) (Table 2). The remaining 6 patients were failure to reach CR due to early death, 3 patients in the ACAs group, and 3 patients in the without ACAs group. Five deaths were attributable