Cancer Genetics 216-217 (2017) 29–36

Cancer Genetics

ORIGINAL ARTICLE

Prognostic significance of recurrent additional chromosomal abnormalities in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia

Chang Ahn Seol [a], Young-Uk Cho [a], Seongsoo Jang [a], Chan-Jeoung Park [a], Jung-Hee Lee [b], Je-Hwan Lee [b], Kyoo Hyung Lee [b], Eul-Ju Seo [a,*]

[a] *Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea;* [b] *Department of Internal Medicine, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea*

In Philadelphia (Ph) chromosome-positive acute lymphoblastic leukemia (ALL), additional chromosomal abnormalities (ACAs) are frequently observed. We investigated the cytogenetic characteristics and prognostic significance of ACAs in Ph-positive ALL. We reviewed the clinical data and bone marrow cytogenetic findings of 122 adult Ph-positive ALL patients. The ACAs were examined for partial or whole chromosomal gains or losses, and structural aberrations. The overall survival (OS) and disease-free survival (DFS) of patients who received hematopoietic cell transplantation were compared between the isolated Ph group and ACA group. ACAs were present in 73.0% of all patients. The recurrent ACAs were extra Ph (24.7%), 9/9p loss (20.2%), and 7/7p loss (19.1%). Complex karyotype was found in 28.1% of patients in the ACA group. Younger patients (19–30 years) in the ACA group showed the highest frequency of extra Ph (54%) compared to other age groups. The OS in the ACA group was significantly shorter than in the isolated Ph group. The presence of an extra Ph chromosome or 9/9p loss was significantly associated with shorter OS and DFS, whereas 7/7p loss and complex karyotype were not associated with poorer prognosis. We suggest that subclassification of ACAs could be applied to prognostic investigation of Ph-positive ALL.

Keywords Acute lymphoblastic leukemia, Philadelphia chromosome-positive, additional chromosomal abnormality, prognosis

Introduction

The Philadelphia (Ph) chromosome is the most common chromosomal aberration in adult acute lymphoblastic leukemia (ALL) and is associated with an unfavorable prognosis. The Ph chromosome is observed in 15–30% of adult ALL patients, compared to 2–4% of children with ALL; the frequency of the Ph chromosome can approach 50% in 40–50-year-old ALL patients (1–6). Additional chromosomal abnormalities (ACAs) are frequently observed in Ph-positive ALL patients, compared to chronic myelogenous leukemia patients in the chronic phase (7,8). In previous studies, the frequency of ACAs in Ph-positive adult ALL patients was 42–71% (1,9–13). However, the prognostic impact of ACAs has not been established and controversies regarding the impact of ACAs remain. In several reports, ACAs in Ph-positive ALL patients were not associated with a worse prognosis compared to those in isolated Ph-positive ALL patients (1,10,13). In other studies, Ph-positive ALL patients with ACAs showed a worse prognosis compared to the isolated Ph-positive ALL patients (9,11,12,14,15). Whether recurrent ACAs such as 7/7p loss are associated with poor prognosis is debatable (9,12). Studies on ACAs in Ph-positive ALL patients, especially in the post tyrosine kinase inhibitor (TKI) era, are lacking (9,14). In this study, we retrospectively investigated the frequency and

Received March 7, 2017; received in revised form May 19, 2017; accepted June 7, 2017.

* Corresponding author.
E-mail address: ejseo@amc.seoul.kr

2210-7762/$ - see front matter © 2017 Published by Elsevier Inc.
https://doi.org/10.1016/j.cancergen.2017.06.001

prognostic impact of ACAs in Ph-positive adult ALL patients from a single institute. The investigation was focused on the analysis of recurrent abnormalities in the ACAs and the prognostic significance of the recurrent ACAs in the patients who received hematopoietic cell transplantation (HCT).

Materials and methods

Patients

The subjects of this study comprised 122 patients diagnosed with Ph chromosome-positive ALL between 2000 and 2015 at the Asan Medical Center, Seoul, Korea. The diagnosis of Ph-positive ALL was performed according to the WHO classification of tumors of hematopoietic and lymphoid tissues (16). Subjects were required to be 19 years of age or older at the time of diagnosis for inclusion in the study. The median age of the subjects was 49.5 years (19–80). We retrospectively reviewed the clinical data, laboratory findings, and cytogenetic findings of the bone marrow (BM) aspirate from the medical records of each subject. The clinical and laboratory findings included age, sex, complete blood cell counts and blast percentage in peripheral blood (PB), serum lactate dehydrogenase (LDH) level, results of immunophenotypic analysis, major or minor BCR-ABL1 fusion transcript, and treatment modalities such as chemotherapy and HCT. The subjects were assigned to the isolated Ph group or the ACA group. The clinical and laboratory findings were compared between the 2 groups. This study was approved by the Institutional Review Board of the Asan Medical Center, Seoul, Korea.

Treatment

The induction chemotherapy comprised vincristine, daunorubicin, TKI (imatinib or dasatinib), and steroid treatment (prednisolone, methyl prednisolone, or dexamethasone). Consolidation chemotherapy comprised cyclophosphamide, cytosine arabinoside, high-dose methotrexate, TKI, and steroid treatment. Central nervous system prophylaxis was performed by intrathecal methotrexate injection. For the patients who received HCT after chemotherapy including TKI (n = 74), the conditioning regimen comprised busulfan, fludarabine, methotrexate, and antithymocyte immunoglobulin. The study subjects included the patients who received only chemotherapy including TKI (n = 34), the patients who received only chemotherapy without TKI (n = 7), and the patients who did not receive chemotherapy (n = 7). Complete remission (CR) was defined according to the ALL response criteria of the National Comprehensive Cancer Network (17). Relapse was defined as reappearance of lymphoblasts accounting for more than 5% of the nucleated cells in BM, or appearance of extramedullary leukemia, after CR.

Cytogenetic analysis

BM cells were cultured with RPMI-1640 working medium and fetal bovine serum for 24 and 48 hours in a 37 °C 5% CO_2 incubator. Using colcemid and 0.075 M potassium chloride solution, the metaphase cells were harvested. The metaphase cells were stained by GTL-banding technique. At least 20 metaphase cells were analyzed in each patient. The results of chromosomal analysis were described according to the International System for Human Cytogenetic Nomenclature (18). The ACAs from the karyotype descriptions were examined for partial or whole chromosomal gains or losses, and structural aberrations. A complex karyotype was defined as having equal to or more than 4 independent chromosomal aberrations. The type and frequency of recurrent ACAs were investigated in the patients in the ACA group. The patients were divided into 5 age groups (19–30 years, 31–40 years, 41–50 years, 51–60 years and >60 years group) and the frequencies of ACAs were also investigated in each age group.

Statistical analysis

The quantitative data were presented as medians (ranges). The comparison of the clinical and laboratory data between the ACA group and the isolated Ph group was performed by Mann Whitney U-test or Pearson's Chi-square test. The comparisons of the frequencies of recurrent ACAs in the age groups were performed by Pearson's Chi-square test or Fisher's exact test. Overall survival (OS) was defined as time from date of diagnosis to time of death for any reason. The disease-free survival (DFS) was defined as time from date of CR to date of relapse or death for any reason. The 5-year survival rate was presented as an estimated rate ± standard error and the median survival was presented as an estimated survival ± standard error. The OS and DFS in the patients who received HCT were analyzed by the Kaplan-Meier method, and the outcomes were compared between the ACA group and the isolated Ph group by the log-rank test. The OS and DFS in the patients who received only chemotherapy including TKI were also compared between the ACA group and the isolated Ph group. Cox proportional hazard models for multivariate analysis were used to investigate hazard ratios of recurrent ACAs for the total patients. SPSS 19.0 (IBM, Chicago, USA) was used for the statistical analysis and a p-value of <0.05 was considered statistically significant.

Results

Clinical and laboratory data

The clinical and laboratory findings are summarized in Table 1. ACAs were present in 73.0% of total patients with Ph-chromosome positive ALL. The incidence of patients with ACAs was not significantly different by sex or age. The median age and male proportion were 53 years and 45.5% in the isolated Ph group, compared to 49 years and 51.7% in the ACA group. The complete blood cell counts were not significantly different between the isolated Ph group and the ACA group. The blast counts in PB, serum LDH level, the immunophenotype of BM flow cytometry, and the proportion of major and minor BCR-ABL1 transcripts in the ACA group were compared with the results in the isolated Ph group; no statistically significant difference was found. The proportion of patients who received HCT after chemotherapy including TKI in the isolated Ph group and in the ACA group was 57.6% and 61.8%, respectively ($p = 0.682$).