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Clonal chromosomal aberrations in Philadelphia negative cells such as monosomy 7 and trisomy 8 may persist for years with no impact on the long term outcome in patients with chronic myeloid leukemia

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The appearance of clonal chromosomal aberrations in Philadelphia negative cells (CCA/Ph–) during the treatment of chronic myeloid leukemia (CML) was recently confirmed. Importance of these findings has not been clearly defined. We present data on the time of appearance, persistence, size of the CCA/Ph– clone in terms of drugs used and hematological, cytogenetic and molecular response rates. The focus was on the peripheral blood cytopenias and myelodysplastic changes in the bone marrow microscopic evaluation. In 5 out of 155 (3,2%) CML patients, the persistent presence (up to nine years) of CCA/Ph– was found (monosomy 7 and trisomy 8 in unrelated clones in two patients treated with tyrosine kinase inhibitors; trisomy 8 in two patients on imatinib; trisomy 21 in one patient on interferon alfa treatment). Aberrations were present in median 24% Ph– cells in 3–15 subsequent analyses at different cytogenetic and molecular response time points. No evident myelodysplastic changes nor transformation to MDS/AML occurred in patients with CCA/Ph–. All the patients achieved major molecular response (MMR). It seems that CCA/Ph– presence does not affect the long term outcome in patients with chronic myeloid leukemia. Further complex monitoring of the CML patients with CCA/Ph– is still needed.

Keywords Chronic myeloid leukemia (CML), chromosomal abnormalities in Philadelphia negative cells, monosomy 7, trisomy 8, TKI treatment

Introduction

Cytogenetic monitoring of patients with chronic myeloid leukemia (CML) during the treatment with tyrosine kinase inhibitors (TKI) revealed a small subset of patients with clonal chromosomal abnormalities in Philadelphia negative cells (CCA/Ph–). The incidence of CCA/Ph– in various treatment groups is estimated as 2–17% (1–3). The CCA/Ph– are usually not random, the most common being trisomy 8, monosomy 7 and the loss of chromosome Y (1–5). They can occur as sole chromosome abnormalities or with other clones as either transient or persisting findings (6–8). The presence of CCA/Ph– does not usually affect the course of the disease, but in some cases it may predict the transformation to the myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (2,3,6,9–16). The follow-up of the presence of CCA/Ph– is too short to draw unambiguous conclusion, however, the transformation to MDS/

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AML in CML patients with monosomy 7 in the Ph negative clone has been reported (1–3,9,13–15).

Some studies have analyzed the influence of CCA/Ph– on the clinical course of CML, but there is still a need for long-term observations of these patients (6,17).

Here we report observations of five patients with CML who had various CCA/Ph– during the treatment, especially monosomy of chromosome 7 and trisomy of chromosome 8 persisting for nearly nine years in one patient. We present data on the time of appearance of CCAs/Ph– and follow up data, as well as information about the drugs used, coexistence of cytopenias and myelodysplastic changes, hematologic (HR), cytogenetic (CyR) and molecular (MolR) response rates.

Materials and methods

Patient selection

Of 155 CML patients treated in the Department of Hematology at the Medical University of Bialystok, 23 had chromosome abnormalities in Ph negative cells (14,8%). In 10, the CCA/Ph– of autosomes were transient and they were observed only once in a small number of cells during the TKI treatment. The loss or gain of chromosome Y during the treatment with imatinib (IM) was found in eight other patients. In the remaining five, CCA/Ph– of autosomes were seen several times after a longer period of treatment. These patients are included for further detailed evaluation.

Patient characteristic

All five patients were diagnosed with the chronic phase of CML. There were four females and one male with their age ranging at the point of diagnosis from 54 to 67 years (median 60,4 years). At the time of the diagnosis, standard t(9;22)(q34;q11.2) was detected in the cytogenetic analysis of these patients.

The patients were mostly treated with tyrosine kinase inhibitors (TKI) (IM, nilotinib, dasatinib), except for one treated only with interferon-alpha (IFN). All were evaluated regularly according to ELN (European Leukemia Net) recommendations (18,19). The types of CCA/Ph–; time of the first appearance during treatment; size (%) of CCA/Ph– clones at the different time points, and a follow up of CCA/Ph– were evaluated. HR, CyR, MolR response rates were checked, when the CCA/Ph– clone was detected. The response criteria were according to the ELN recommendations (18). We paid special attention to the appearance of cytopenias during the course of the disease which may suggest myelodysplastic changes. We performed bone marrow aspiration in all the patients and biopsy in those who developed cytopenias.

This research is a part of projects approved by the Ethics Committee of the Białystok Medical University.

Methods

Cytogenetic

Cytogenetic studies were carried out on GTG banded chromosomes obtained after short-term (24, 48 h), unstimulated bone marrow cultures at regular intervals, following ELN recommendations. Patients had from a few to several karyotype analyses performed depending on the time of observation. On average, 30 cells in a metaphase were analyzed.

Molecular

The levels of BCR-ABL transcripts were evaluated by reverse transcription quantitative polymerase chain reaction (RQ-PCR) from peripheral blood, according to the ELN protocol (20–22).

Results

Cytogenetic characteristic

Cytogenetic analysis revealed 5 out of 155 patients (3,2%) with 7 numerical aberrations of autosomes persistent in more than one analysis. These were: monosomy 7 and trisomy 8 in unrelated clones in two patients (Patients 1 and 2); trisomy 8 as a sole abnormality in two patients (Patients 3 and 4); and one sole monosomy 21 (Patient 5) (Table 1).

The median time of the first appearance of persistent CCA/Ph– during the treatment with a TKI (for all aberrations after a TKI) was 17.5 months (range 6–27 months), for monosomy 7 it was 6 months during the 2nd line treatment (dasatinib or nilotinib), i.e. 24 months after starting the treatment with a TKI, for trisomy 8 it was 9.7 months (range 6–12 months) during the IM treatment and in one patient (patient 2), 9 months during the 2nd line treatment (nilotinib), i.e. 27 months after starting a TKI.

The median clone size at the first appearance of monosomy 7 was 34% (range 28–40%), for trisomy 8 it was 24% (range 6–68%). Monosomy 21 was found after 84 months of the IFN treatment and the clone size was 15% (range 10–15% in subsequent analyses). For all CCA/Ph–, the median clone size was 24% (range 6–68%).

The clone of monosomy 7 persisted for over 8 years in patient 1 and is still present, and for 6 months in patient 2 until bone marrow transplantation (BMT). Trisomy 8 was seen for nearly 9 years in patient 1 in subsequent analyses (15 karyotype examinations) and was still present at the end of the study; in two other patients (patients 3 and 4) for 1.5 years and 3 years and is still present. Monosomy 21 was detected in 3 subsequent analyses performed every 6 months over a 1.5 year period and then not present in the next studies (patient 5).

Response, outcome

Hematological response

All the patients with persistent CCA/Ph– were in complete hematological remission when the clones with chromosomal abnormalities were detected. Patient 1 developed severe cytopenias due to the TKI. The cytopenias were dealt with by stopping the drug and continuing with a reduced dosage. At the time of the first appearance of CCA/Ph– (trisomy 8) detected after 12 months of the IM treatment, the patient had neutropenia: neutrophil count (ANC) 0,93 G/l and thrombocytopenia: platelets (PLT) 87 G/l, his bone marrow aspirate was hypocellular without any dysplastic changes or