

Is it really the Transplant Renaissance in CML Acceleration Phase?

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Case Study

WHO 2016 guidelines regarding chronic myeloid leukemia (CML) do not contain groundbreaking changes [1]. Mainly criteria of acceleration phase (AP) identification were revised. Despite these changes, the guidelines are still not standardized and differ significantly, even when compared to guidelines of European Leukemia Net (ELN) [2], International Bone Marrow Transplant Registry (IBMTR) or M. D. Anderson Cancer Center, to give some examples (Table 1). Compared to previous editions of the WHO classification, new parameters appeared, the presence of which requires identification of acceleration phase. In this case, one should list e.g. chronic leukocytosis ($>10 \times 10^9/L$), non-responding to treatment, chronic splenomegaly non-responding to treatment, additional clonal chromosomal aberrations (the so-called "major route") in Ph+ cells on diagnosis. New provisional criteria also appeared, related to response to therapy using tyrosine kinase

inhibitors (TKI). Among the latter ones the following were distinguished: hematological TKI resistance when used as a first-line or lack of complete hematological response (CHR) during first-line treatment when using TKI; hematological, cytogenetic or molecular resistance during treatment with a subsequent second TKI; presence of two or more mutations within BCR/ABL during TKI therapy. These changes resulted in necessity to diagnose acceleration phase much more frequently, compared to e.g. ELN criteria. This presents importance, particularly for patients already treated with TKI, as it increases the percentage of patients with indications for allogeneic hematopoietic stem cell transplantation (allo-HSCT). It contrasts with everyday practice and tendency to marginalize the role of transplanting hematopoietic cells in case of this disease classification unit, in the TKI era. The thesis as such is best illustrated with an example.

Criterion	Mdacc	lbmrt	Eln	WHO 2008	WHO 2016
Blasts	PB or BM 10-29%	PB or BM $\geq 10\%$	PB or BM 15-29%	PB or BM 10-19%	PB or BM 10-19%
Blasts and promyelocytes	$\geq 30\%$	PB or BM $\geq 20\%$	$\geq 30\%$ with blasts $<30\%$	NA	NA
Basophils	PB or BM $\geq 20\%$	PB $\geq 20\%$	PB $\geq 20\%$	PB $\geq 20\%$	PB $\geq 20\%$
Platelets	$>1000 \times 10^9/L$ or $<100 \times 10^9/L$, responding to treatment or not to	Persistent thrombocytosis	Persistent thrombocytopenia ($<100 \times 10^9/L$) independent of treatment	Persistent thrombocytosis ($>1000 \times 10^9/L$) not responding to treatment; Persistent thrombocytopenia ($<100 \times 10^9/L$) independent of treatment	Persistent thrombocytosis ($>1000 \times 10^9/L$) not responding to treatment; Persistent thrombocytopenia ($<100 \times 10^9/L$) independent of treatment
Leukocytes	$>10 \times 10^9/L$	Difficult management	NA	Increasing WBC count not responding to treatment	Persistent or increasing WBC count ($>10 \times 10^9/L$) not responding to treatment
Anemia	NA	Anemia not responding to treatment	NA	NA	NA
Splenomegaly	Persistent splenomegaly, responding to treatment or not to	Increasing spleen size	NA	Increasing spleen size	Persistent or increasing splenomegaly, not responding to treatment
Cytogenetic disorders	NA	Clonal evolution	Major route type clonal chromosomal aberrations in Ph+ cells during treatment	Clonal evolution absent at the time of diagnosis	Clonal evolution absent at the time of diagnosis
Other	NA	Bone marrow fibrosis	NA	Large foci or clusters of blasts in marrow biopsy	NA

Provisional	NA	NA	NA	NA	Hematological resistance to first TKI (or lack of CHR during first-line treatment)
MDACC: M. D. Anderson Cancer Center; IBMRT: International Bloos and Marrow Transplant Registry; WHO: World Health Organization; ELN: European LeukemiaNet; NA: not applicable; WBC: white blood cells; PB: peripheral blood; BM: bone marrow.					

Table 1: Criteria of acceleration phase in chronic myeloid leukemia.

Our patient is a 68-year old at the time of diagnosis - female. Leukocytosis of $22 \times 10^9/L$ and thrombocytosis of $1252 \times 10^9/L$ found accidentally during routine screening tests were the indication to extend diagnostics. Over the course of further diagnostics significantly hypercellular bone marrow with "left shift" in granulopoiesis system were found. CML was diagnosed on 4th December 2015, based on Philadelphia chromosome (Ph) presence in cytogenetic test, presence of t(9;22)(q34;q11.2) translocation in a test using FISH technique, and presence of BCR/ABL p210 transcript in a test using RT-PCR method. The disease was in chronic phase (CP). Blasts constituted 4.3% of bone marrow nucleated cells, and basophils: 4% of nucleated cells in peripheral blood. The risk according to EUTOS scale was estimated as low.

From 7th January 2016 imatinib was used at a dose of 400 mg/day. After the first month of treatment, leukocytosis of $30.05 \times 10^9/L$ was found, as well as thrombocytosis of $1052 \times 10^9/L$. After 3 months of treatment, absence of complete hematological remission (CHR) was found. As a reminder, CHR condition is characterized by: white blood cell (WBC) count $< 10 \times 10^9/L$, platelet (PLT) count $< 450 \times 10^9/L$, absence of young granulocyte line cells in peripheral blood smear, lack of splenomegaly on palpation and basophil percentage in peripheral blood $< 5\%$. In our patient, the WBC count was $56.71 \times 10^9/L$, and the PLT count was $989 \times 10^9/L$. Ph chromosome was present in karyotype test in all analyzed metaphases. Treatment failure was stated based on these results. Analysis using sequencing method did not show mutations within BCR/ABL coding domain.

The patient was qualified for second-line treatment with dasatinib (100 mg/day). CHR was achieved after 3 months of treatment. In karyotype test, Ph+ cells constituted 82% of all analyzed metaphases (14/17) which allowed to determine minimal cytogenetic response (minCyR) and constituted a warning criterion according to ELN 2013. Higher molecular response (MMoIR) was also not achieved, the amount of BCR/ABL transcript was 29.5% according to international scale (IS). After 6 months of treatment, the response was already optimal. CHR was maintained, complete cytogenetic response (CCyR) was achieved, as well as higher molecular response (BCR/ABL percentage of 0.006%, according to IS).

As we can see, the patient achieved optimal response to treatment with second generation TKI over relatively short time, and the response magnitude systematically increases. According to previous clinical practice at our facility, conversions to second-generation TKI and use of response criteria with regard to second-line treatment according to ELN guidelines is the optimal procedure.

And here is the appropriate time to ask the question: What effect on patient's future would the use of new WHO criteria regarding diagnosis of acceleration phase and diagnosing her with AP have?

AP diagnosis is related to quite radical change in the strategy of proceedings. According to ELN 2013, this strategy is different for newly diagnosed patients, and patients previously treated with TKI. In

case of patients previously treated with TKI, progression to AP or BP is related to changing TKI to any one that was not used prior to progression to AP/BP (ponatinib - only in case of T315I mutation being present). Allo-HSCT in this patient group, according to ELN 2013, is recommended FOR ALL PATIENTS, preferably after reaching chronic phase. Polychemotherapy might be necessary in order to prepare patient for transplantation.

EBMT guidelines 3 recommend HSCT in the following cases:

In patients with suboptimal response or failure of first-line therapy treatment in case of:

- a. EBMT risk score of 0-1 (recommended to include second-generation TKI and perform transplantation after obtaining optimal response)
- b. EBMT risk score of 0-4 in case of losing response to imatinib (hematological or cytogenetic one);

In patients with no hematological response to second-generation TKI, regardless of EBMT risk score (and in this case those patients may benefit from treatment with third-generation TKI, taking note of mutations within BCR/ABL coding domain and applied prior to HSCT.

In patients with imatinibem therapy failure who are known to have mutations within BCR/ABL, resistant to second-generation TKI; and their EBMT risk score is 0.

In patients with AP or BP after earlier preparation using TKI or TKI in combination with polychemotherapy. Transplantation should be performed possibly quickly after reaching second chronic phase, yet in this case reaching profound cytogenetic or molecular response is not required.

First chronic Phase	Acceleration Phase	Blast Phase	Crisis Phase
Failure of therapy using available TKI (search for donor shall be started after first-line therapy failure)	Less advanced acceleration phase at the time of diagnosis – treatment as in case of first chronic phase	Cases at the borderline of diagnosing blast phase, and patients with symptoms of transformation to acceleration phase during TKI treatment – treatment as in case of blast phase	HSCT immediately after reaching chronic phase using TKI or polychemotherapy (one should consider subsequent treatment with second-generation TKI after transplantation)

Table 2: Indications for HSCT in chronic myeloid leukemia – position of experts at Hammersmith Hospital.

It is also worth mentioning the position of experts at London Hammersmith Hospital from 2013 which presents similar, slightly more intuitive approach to the subject of qualifying patients for HSCT after first-line therapy failure (Table 2) [3,4].

According to the analysis above, it is clear that following the most important guidelines (ELN, EBMT, NCCN), in case of our patient one should strive for performing HSCT. Such proceedings were not considered, because at the time when the decision was made with regard to second-line treatment (April 2016, the number of data pieces in favor of diagnosing AP was lower than the number of ones excluding diagnosis of advanced disease phase. In our opinion, WHO guidelines of 2016 changed that situation.

It seems necessary to conduct a discussion, and perhaps plan and perform an appropriate clinical trial which would provide more data and allow optimizing the proceedings in such controversial cases.

Conflict of Interest

The authors declare no conflict of interest.

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