



ORIGINAL RESEARCH



Blast Crisis in Chronic Myeloid Leukemia: An Immunophenotypic Analysis



Authors' Contribution:
A – Study design;
B – Data collection;
C – Statistical analysis;
D – Data interpretation;
E – Manuscript preparation;
F – Literature search;
G – Funds collection

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**Background and
Aim of Study:**

Abstract

There are two different phases of untreated chronic myeloid leukemia – chronic phase, and blast crisis – according to the World Health Organization classification of Hematolymphoid tumors. The blast cells in the chronic myeloid leukemia blast crisis can express myeloid, lymphoid, bi-phenotypic, monocytic, megakaryocytic, and erythroid phenotypes. The immunophenotype of blast population determines how chronic myeloid leukemia – blast crisis patients respond to treatment, hence flowcytometric examination is required.

The aim of the study: to assess immunophenotyping outcomes of flowcytometry performed on the chronic myeloid leukemia – blast crisis.

Material and Methods:

A five-year retrospective descriptive analysis was carried out in Pathology Department at King George's Medical University Lucknow, India (2017-2021). The patient's peripheral blood and bone marrow aspirate samples were analyzed. Clinical, hematological, and immunophenotypic data were retrieved. The flow cytometry samples were prepared using the standardized "lyse-stain-wash" method.

Results:

A total of 43 cases of chronic myeloid leukemia – blast crisis were retrieved from the departmental archive in 5 years. The mean age of study population was 39.62±14.86 years. There were 24 males and 19 females. 27 patients were diagnosed with myeloid blast crisis, 14 cases of B-lymphoid blast crisis and 2 cases of mixed phenotypic acute leukemia.

Conclusions:

Identification of the blast lineage of patients with chronic myeloid leukemia – blast crisis is crucial since the existence of atypical blast phenotypes influences the disease treatment and prognosis.

Keywords:

immunophenotyping, flowcytometry, chronic myeloid leukemia, lymphoid blast, myeloid blast, mixed phenotypic acute leukemia

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Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm that is characterized by a balanced translocation between chromosome t (9;22) (q34; q11), leading to the formation of the Philadelphia (Ph) chromosome (Narang et al., 2016). It mainly affects older persons and seldom happens in youngsters, but can occur at any age. There is an increased number of granulocytes and their immature precursors, including occasional blast cells, seen in the peripheral blood smear. CML accounts about 20% of all adult leukemias (Pandey & Pal, 2021).

According to the latest updated fifth edition of the World Health Organization (WHO), there are two different phases of untreated CML: Chronic phase (CP), and Blast crisis (BC). Blast crisis of CML according to the WHO is defined by: 1) presence of $\geq 20\%$ myeloid blasts in the peripheral blood or bone marrow; 2) presence of extramedullary blasts proliferation; or 3) presence of increased number of lymphoblasts in bone marrow or peripheral blood. The significance of low-level B-lymphoblasts or optimal cut-off for lymphoblasts remain unclear (Khoury et al., 2022). The blasts in the CML blast phase (CML-BP) can express myeloid, lymphoid, bi-phenotypic, monocytic, megakaryocytic, and very infrequently erythroid phenotypes (Khemka et al., 2019; Rahnemoon, 2022).

BC develops as a result of persistent BCR-ABL activation, which causes genomic instability and an accumulation of further chromosomal abnormalities. Acute leukemia symptoms could be seen in patients with blast transformation (e.g., bleeding diathesis, bone pain, night sweats, weight loss, and fatigue). Complete blood counts, an extensive metabolic panel, a bone marrow aspiration, and a biopsy should be performed all during the initial assessment of BC patients. Flow cytometry, immunohistochemistry, and cytogenetics should be requested for the latter. The immunophenotype of the blast population determines how CML-BP patients respond to treatment; hence, flowcytometric examination is required in every case of blast crisis (Hehlmann et al., 2016). Almost all CML-CP patients will develop BC in 3-5 years without treatment, although in the tyrosine kinase inhibitor (TKI) era, this dreaded transition is now extremely uncommon. Most CML-BC cases are myeloid, but up to one-third of them have the potential to become lymphoid BC. The B-cell lineage is more prevalent, and lymphoid blast crisis makes up about 30% of CML-BC. T-cell BC is a very infrequent presentation for patients (Yohannam & George, 2022).

Most individuals with CML will respond very well to TKI therapy when it is administered during the chronic phase (CML-CP), which is characterized by granulocytic proliferation. The prognosis is still bad for those who advance to the blast phase, with less than 20% of patients in the modern period surviving for five years. Response to TKI therapy is the most crucial indicator of advancement. Age, spleen size, and basophil count are other variables predicting likelihood of transformation or mortality.

Sensitive detection of aberrant haematopoietic populations is made possible by flow cytometry. Flow cytometry has been thought to be of limited use at this stage of the disease since CML-CP is characterised by proliferation of mostly granulocytes and granulocytic precursors without immunophenotypic aberrancy or maturation arrest. However, there are reports of aberrant lymphoblast populations being found when flow cytometry has been used, and there is conflicting information regarding the risk of the blast phase developing as a result. mortality (Barge et al., 2022).

The initial targeted treatments for CML were tyrosine kinase inhibitors (TKIs). The first-generation TKIs were introduced as the primary therapy in 1998, and they stopped the disease's natural development. With the accomplishment of morphological, clinical, and molecular remission targets, this has allowed patients to sustain chronic phase disease. The speed and depth of molecular remission have improved after the advent of second and third generation TKIs (Hodkinson et al., 2022).

The aim of the study. To assess the immunophenotyping outcomes of flowcytometry performed on CML-BP cases at a tertiary care facility in North India.

Materials and Methods

A five-year retrospective descriptive analysis was carried out in the Pathology Department at King George's Medical University in Lucknow, North India (January 2017 – December 2021). A total of 43 cases of CML with blast crisis were retrieved from January 2017 to December 2021 and included in the final study. The cases in which flowcytometry analysis and/or BCR-ABL translocation identification were not performed, were excluded from the study. The patient's peripheral blood and bone marrow aspirate samples were analyzed. Clinical, hematological findings and immunophenotypic data were retrieved from records. For immunophenotyping of blasts, peripheral blood was used in 28 patients and bone marrow aspirate samples in 15 patients respectively. The flow cytometry samples were prepared by using the strict protocols and standardized "lyse-stain-wash" method.

For immunophenotyping of the blasts the antibody panel was comprised of CD13, cCD13, CD14, CD15, CD33, cMPO, MPO, CD64, CD14, cCD79a, CD117, CD19, CD20, CD10, CD22, cCD22, CD2, CD4, CD5, CD7, CD8, CD3, sCD3, cCD3, CD34, CD38, CD25, TdT (terminal deoxynucleotidyl transferase), and HLA-DR. In order to help with blast gating in all of the tubes, CD45PerCP was utilized as an anchor marker. 2 ml of samples (Peripheral blood or Bone marrow) were collected in Ethylene Diamine Tetraacetate (EDTA) vacutainer and analyzed using a dual laser BD FACS-Canto II, and FACS Diva software.

The single-cell basis of flow cytometry analysis makes it possible to examine multiple populations at once and detect low-level aberrant populations, particularly when a larger number of events are studied to boost sensitivity (Tembhare et al., 2020).



Results

The flowcytometry findings of total of 43 cases of CML-BP were retrieved from records. The patient's mean age included in the study was 39.62±14.86 years. There were 24 males and 19 females (M:F=1.2:1) showing male predominance. 27 patients were diagnosed with myeloid blast crisis followed by 14 patients with B-lymphoid blast crisis and 2 patients with mixed phenotypic acute leukemia (MPAL). Table 1 presents an epidemiological profile of study population.

The mean age of patients in myeloid blast crisis, lymphoid blast crisis, and mixed phenotypic acute leukemia subgroups was 41.88±14.76, 34.79±15.30, and 44.00±8.49 respectively. There was no statically significant correlation noted for age (p=0.331) and gender (p=0.194) distribution in different subgroups of blast crisis (Table 2).

The results of present study showed that B-lymphoid blast crisis had aberrant co-expression of CD13 and CD33 in four cases (28.57%) along with three case (12.50%) of myeloid blast crisis having aberrant expression of CD7 (Table 3).

Table 1
 Epidemiological Profile of Study Population

Parameters	Age range	Patients	
		number (n)	percentage (%)
Age (n=43)	1-10 years	2	4.65
	11-20 years	3	6.98
	21-30 years	6	13.95
	31-40 years	14	32.56
	41-50 years	8	18.60
	51-60 years	7	16.28
	>60 years	3	6.98
	Total	43	100.00
Gender (n=43)	Male	24	55.81
	Female	19	44.19
	Total	43	100.00

Table 2

Age and Gender Distribution in Different Subgroups of Myeloid, Lymphoid and Mixed Phenotypic Acute Leukemia – Blast Crisis

Parameters	Myeloid blast crisis (n=27)		Lymphoid blast crisis (n=14)		Mixed phenotypic blasts (n=2)		p-value
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	41.88	14.76	34.79	15.30	44.00	8.49	0.331
Gender:							
Male	17	62.96	7	50.00	0	0.00	0.194
Female	10	37.04	7	50.00	2	100.00	

Table 3

Immunophenotypic Profiles in Cases of CML-Blast Phase

Parameters	Myeloid blast crisis (n=27)		Lymphoid blast crisis (B-lineage) (n=14)		Mixed phenotypic blasts (n=2)		p-value
	Positive		Positive		Positive		
	n	%	n	%	n	%	
CD13	24	92.31	4	28.57	2	100.0	<0.001*
CD33	26	100.0	6	42.86	2	100.0	<0.001*
cMPO	27	100.0	0	0.00	2	100.0	<0.001*
CD64	2	22.22	0	0.00	0	0.0	0.523
cCD79a	0	0.00	0	-	1	100.0	0.025*
CD117	16	76.19	1	10.00	1	100.0	0.002*
CD19	2	8.70	11	91.67	1	100.0	<0.001*
CD20	0	0.00	11	84.62	0	0.0	<0.001*
CD10	2	8.00	13	100.00	1	100.0	<0.001*
cCD22	0	0.00	2	100.00	1	100.0	0.821
CD5	0	0.00	0	0.00	1	100.0	0.002*
CD7	3	12.50	0	0.00	1	50.0	0.080
cCD3	0	0.00	0	0.00	1	50.0	<0.001*
CD34	26	100.00	10	76.92	2	100.0	0.031*
CD38	5	50.00	5	71.43	0	-	0.598
CD25	1	11.11	1	16.67	1	50.0	0.462
TdT	2	10.00	9	81.82	2	100.0	<0.001*
HLA-DR	24	100.00	11	100.00	1	100.0	-

Note. *Significant (p<0.05)



Discussion

CML is a disease that results from the reciprocal translation of genes on chromosomes 9 and 22 (Asif et al., 2016). The fused BCR-ABL protein has altered tyrosine kinase activity (Rajkumar et al., 2016).

The prognosis for CML patients depends on the disease stage at presentation, although even for people diagnosed in CP, survival rates might vary significantly. Patients with chronic phase CML have myeloid cells at all stages of maturity (CP). Contrary to acute myeloid leukaemia (AML), the flow cytometry (FC) approach enables the detection of aberrant cell surface markers. FC is a straightforward diagnostic tool for (CP-CML) since it is used to estimate the proportions of immature cells (Blast) in the late stages of the disease. This is a disease in adults and extremely rare in childhood. This retrospective study analyzed 43 cases of chronic myeloid leukemia – blast crisis over a period of 5 years. In the present study on flowcytometric analysis, the most common blast phenotype in the blast crisis was myeloid (62.7%) followed by B-lymphoid blast crisis (32.5%) and mixed phenotypic acute leukemia (4.7%). Out of two cases, of MPAL, one case was of T-Myeloid and the other was of B-Myeloid phenotypic blast crisis. A study conducted earlier also showed similar results (Narang et al., 2016). Their study was comprised of 15 cases, which showed 14 cases of myeloid blast crisis and a single case of lymphoid (B-lineage) blast crisis. The evolution of CML into blast crisis is common in myeloid type followed by lymphoid type (Shi et al., 2015). A previous study also showed blast crises in CML are of myeloid phenotype in the majority of cases and lymphoid phenotype in 30% of cases (Bonifacio et al., 2019).

Chronic immunological dysfunction and T-cell fatigue are brought on by CML, a disease that primarily results from long-term immune cell activation in an immunosuppressive milieu.

In the present study, we found four cases of B-lymphoid blast crisis with aberrant co-expression of CD13 and CD33 along with one case of myeloid blast crisis with aberrant expression of CD7. Another study conducted by Hegde et al. (2020) on chronic myeloid leukemia showed two cases displaying mixed phenotypic features comprising each one of myeloid and megakaryocytic differentiation. The treatment of CML-BP patients depends on the immunophenotype of the blast population hence it is mandatory to do flowcytometric analysis in each and every case of blast crisis (Assi & Short, 2020; Wang et al., 2021). Atypical lymphoblast populations in CML are listed as a potential sign of an aggressive disease course in the WHO classification of myeloid neoplasms (Arber et al., 2016; Chen et al., 2020). There are some study limitations, including the fact that it was conducted at just one hospital and there was no patient follow-up. Newly diagnosed cases of CML-BC are treated with first-generation TKIs, according to European Leukemia Net (ELN) 2018 data (imatinib, nilotinib, dasatinib and bosutinib). Third or fourth generation TKIs should be used to treat patients who do not react to first generation TKIs. For patients with the BCR-ABL coding domain T315I mutation, ponatinib is the TKI of

preference. Additionally, polychemotherapy is advised for these patients. Patients who have had TKI treatment before and go on to develop AP or BC are regarded as receiving TKI treatment that has not previously been given. Allogenic stem cell transplantation is the best treatment choice for CML-CP patients who have grown resistant to at least two TKIs (Hegde et al., 2020).

After a BC diagnosis, the average survival time is thought to be 2-4 months. There are noticeable differences in the proliferation, differentiation, adhesion, and apoptosis of malignant cells during the blast crisis compared to those during the chronic phase, which is well recognised. New, non-random molecular or genetic alterations are thought to be the cause of the blast transformation. Trisomy 8, trisomy 19, isochromosome 17, and mutations in the p53, RB, or RAS pathways are the reported most frequent genetic anomalies. In myeloid BC, inactivating mutations of the genes p53 and RUNX1 are present, whereas inactivating mutations of the genes CDKN2A/B have been found in lymphoid blast crisis. Response rates to normal induction therapy are less than 20–30% for CML-BC with an unique blast phenotype. Similar to other cases of CML with BC, patients with the erythroid or megakaryocytic blast phenotype get the same care. Cases with lymphoblastic differentiation, on the other hand, are managed as acute lymphoblastic leukaemia (Hegde et al., 2020).

It is suggested that molecular or genetic changes, such as trisomy 8, trisomy 19, isochromosome 17, t(3;21), mutations in p53, RB gene, RAS pathway, or p16/ARF pathway, are responsible for the blast transformation of CML. T-cell acute lymphoblastic leukaemia (T-ALL) and BCR-ABL1-positive bilineage leukaemia might be difficult to distinguish from CML blast crisis of T-cell lineage. De novo BCR-ABL1-positive T-cell ALL has several characteristics, such as bone marrow involvement, small BCR breakpoint mutations, TCR gene rearrangement mutations, children or teenage age group, and no prior history of CML. Clonal T-cell gene rearrangement (TCR) is not usually present in early immature T-cell neoplasms (like T-ALL), therefore its absence does not always rule out a T-cell blast catastrophe. A diagnosis of CML in a T-cell blast crisis would be supported by BCR-ABL1 positive in both myeloid and lymphoid cells, as opposed to just the lymphoid component as it was found in our case.

5–10% of CML patients eventually progress to advanced phase while on therapy, despite the ground-breaking results TKI in CP-CML achieved. Most of the processes underlying TKI failure, the development of illness, and cytogenetic changes are yet unclear. TKI failure is caused by BCR-ABL1 dependent mechanisms, including mutations in the ABL1 kinase domain, amplification of the BCR-ABL1 oncogene, and high levels of BCR-ABL1 mRNA expression. When the anaplastic threshold is achieved and additional oncogenes eventually cause progression in a BCR-ABL1-independent manner, unchecked BCR-ABL1 signalling causes genomic instability and a more chaotic state. The increased aggressive behaviour of CML clones expressing high amounts of BCR-ABL1 can be explained by both



quantitative and qualitative factors (Bonifacio et al., 2019).

Acute biphenotypic leukaemia (ABL) is uncommon and predominantly affects children. ABL has no predetermined diagnostic standards (Ivanov et al., 2020). The BCR-ABL1 inhibitor has no effect on the various leukaemia cells (mainly cells of the granular chain) in CP-CML, whereas TKIs are mostly focused at the progenitor cell group. It is very predictive to use CD34 expression. The expression of CD34 might fluctuate from time to time, and this variation may be caused by the sensitivity of the monoclonal antibodies used, as well as by technical considerations (such as the sensitivity of the flow cytometry method) and the standards used to obtain a positive result.

CML blast crisis (CML-BC), despite recent advancements in the treatment of early-stage illness, continues to provide a therapeutic challenge. Less than 30% of patients with CML-BC respond to normal induction chemotherapy, making it highly resistant to the condition. When compared to de novo acute leukaemia, conventional chemotherapy has been substantially less effective in treating this illness, with non-responders having a mean survival time of only 2 to 4 months following diagnosis of blast crisis. In CML-BC, numerous chemotherapy regimens have been explored, with varying degrees of effectiveness. Although imatinib was studied in individuals with CML-BC, the majority of CML-BC instances currently occur in patients who are already receiving imatinib-based therapy and going through the blastic phase as a result. As a result, there is no established standard of care for CML-BC patients. The future course of new treatment modalities will be decided by further research into the molecular transformation processes of chronic-phase CML-BC and strategies to address these molecular abnormalities. Despite significant efforts, the prognosis for CML in the blast catastrophe remains depressing. Currently, extending the chronic phase and postponing the start of the blast crisis is the most effective way to increase survival in CML (Esfahani et al., 2006).

A TKI treatment was recommended before allogeneic SCT for all patients in advanced phase in earlier ELN treatment guidelines. Especially for AP patients, most recent guidelines recognised the value of frontline TKI treatment without the necessity for a future transplant. Both ELN and NCCN advise treating newly diagnosed AP patients with TKI alone; transplantation is only considered as a last resort for those who do not respond to treatment as expected. Only imatinib 600 mg daily has a market authorisation in the European Union for frontline use in newly diagnosed patients in advanced phase, although this drug's efficacy is constrained by the emergence of BCR-ABL1 kinase domain mutations, which are more common in this situation than in CP. Both retrospective and prospective trials have shown the high efficacy of frontline treatment with nilotinib or dasatinib, as well as the impressive DMR rates. Intriguingly, in the randomised prospective studies on CP patients, the amount of benefit from 2nd generation TKIs over imatinib was more pronounced in high-risk patients,

underscoring the limitations of imatinib in treating a more aggressive disease.

Numerous initial variables at the time of CML diagnosis have been linked to various probabilities of progression. Current prognostic models identify high-risk patients who are more likely to develop AP-CML or BP-CML. The EUTOS long-term survival (ELTS) score, in instance, indicates three risk categories with significantly varying risks of death from progression in advanced phase.

The kinetics of response to treatment is the most important indicator of progression. Numerous studies have shown that failure to diminish BCR-ABL1 by 10% after three months is associated with a higher risk of progression to the advanced phase and worse survival when using frontline imatinib and 2nd generation TKIs. During the first several months of treatment, measuring the BCR-ABL1 transcript halving time may help to improve the sensitivity and specificity of response measurement.

Finally, patients who receive consistent, standardised monitoring are at a decreased risk of progression than those who receive less frequent monitoring. Despite proper monitoring and an apparent satisfactory response to TKI, abrupt onset of BP may occasionally happen. We believe that all newly diagnosed CPCML patients should preferably receive frontline treatment based on the ELTS scoring system, and non-low-risk patients should be given consideration for 2nd generation TKIs or closely monitored for an early molecular response when imatinib is chosen as the treatment of choice (Bonifacio et al., 2019).

Conclusions

Identification of the blast lineage of patients with CML – blast crisis is crucial since the existence of atypical blast phenotypes influences the treatment strategy. Flow cytometry with an extended panel of antibodies is utilized to assist in blast lineage determination and detection of aberrant antigen expression in CML – blast crisis.

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Ethical Approval

This study had been approved by the Institutional Ethics Committee, King George's Medical University, Lucknow, India (No. 461/Ethics/2022 from 06.06.2022).

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