Clinical spectrum and treatment response in patient of chronic myeloid leukemia in correlation with ABO blood group

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ABSTRACT

Background: Several studies have been conducted to evaluate and investigate the molecular mechanisms underlying alterations in ABO blood group antigens in oncogenesis. We observed that no study has been reported yet that correlate cytological, molecular and haematological responses of Imatinib therapy in chronic myeloid leukemia (CML) patients with different types of blood groups.

Objective: To determine the distribution of CML in the ABO blood group, clinical spectrum of CML in different blood groups, and treatment response of CML patients in correlation with ABO and Rh blood groups.

Material and Methods: All the patients included in the study were diagnosed on the basis of clinical features, peripheral smears and bone marrow aspiration findings. Real-time reverse transcriptase polymerase chain reaction (PCR) and cytogenetic analysis were done in all patients at the time of initiation of therapy. Blood grouping and Rh typing of each patient were done at the initiation of therapy.

Results: Out of 100 included patients, 58 were male and 42 were female patients. It was observed that 45 (45%) patients were having a B+ blood group; 33% patients were having O+ blood group, followed by A+ (10%), AB+ (8%), A− (2%), B− (1%) and AB− (1%). Around 43.64% study subjects with O+ blood groups showed complete cytogenetic response, followed by B+ (41.82%), A+ (10.91), A− (1.82) and AB+ (1.82). An equal number of patients (40% each) with O+ and B+ blood groups, followed by A+ (20%) showed undetectable Abelson-breakpoint cluster region (BCR-ABL)/ratio (%). About 75% of patients showed complete haematological response (CHR) and 25% showed PHR. Patients with B+ and O+ blood groups (41.33%) showed a CHR. It was observed that a maximum number of patients were suffering from symptoms of an abdominal mass (37%), 43.24% of patients with B+ blood group showed an abdominal mass, followed by O+ (35.13%), A+ and AB+ (8.11% each), B− and AB− (2.70% each).

Conclusion: This study revealed that study subjects with B+ and O+ blood groups showed better cytogenetic, molecular and haematological responses as compared with patients with other blood groups at 6 and 12 months of treatment with Imatinib.

Keywords: ABO blood group, CML, Imatinib

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative malignancy defined by the uncontrolled proliferation or growth of mature and pre-mature myeloid cells. It is a type of malignancy that starts in the hematopoietic cells of the bone marrow and circulates in the peripheral blood. CML is caused by a genetic...
translocation, t(9;22), also known as the Philadelphia (Ph) chromosome. The product of this fusion gene is a constitutively active tyrosine kinase called BCR-ABL1, which induces a cytokine-independent proliferation of CML cells. Depending on the type of the A and B antigen, the ABO blood group system have four types: A, B, AB and O. The genes of these antigens are located on long arm of chromosome 9. The BCR-ABL translocation in CML also happens on chromosome 9. A number of studies have shown the association of the ABO blood group with many malignant disorders. Therefore, the ABO blood group antigens on the surface of malignant cells can be used as a prognostic marker in different types of human malignancies including CML. The red cell antigens are very important for blood component transfusion, but the relationship between the development of cancer and alterations in blood group antigens is poorly understood. This is known that the cancerous or oncogenic transformation in all type of human cancer is associated with multiple changes in cell surface membranes including the cell surface carbohydrate structures. The D antigen of the Rh blood grouping system is also a very important RBC antigen because D-negative persons are easily anti-D immunized. D-positive persons harbouring a partial D antigen may produce an allo-anti-D because individuals with partial-D antigen have altered RhD proteins that differ from normal RhD to allow allo-anti-D production. A number of studies have described the involvement of the ABO blood group in the pathogenesis of many human diseases, including different types of malignancies and cardiovascular disease, so that its clinical importance rises now beyond the restrictions of transfusion medicine. However, data for an association with CML are inconsistent. We observed that no study has been reported yet that correlate cytological, molecular and haematological responses of Imatinib therapy in CML patients with different types of blood groups.

**Objectives**

1. To determine the distribution of CML in ABO blood group.
2. Clinical spectrum of CML in different blood group.
3. Treatment response of CML patient in correlation with ABO and Rh blood group.

**Material and Methods**

This prospective study was conducted in the Department of General Medicine with the collaboration of Department of Pathology, at a tertiary care hospital from June 2018 to February 2020. Patients in the age group of 21 to 70 years who were diagnosed to have CML and undergoing treatment with Imatinib mesylate were enrolled. A written informed consent was taken from every patient. The study was approved by the institutional ethical committee. All the patients included in the study were diagnosed on the basis of clinical features, peripheral smears and bone marrow aspiration findings. Real-time reverse transcriptase PCR (RT-PCR) and cytogenetic analysis by karyotyping was done in all patients at the time of initiation of therapy. Blood grouping and Rh typing of each patient was done at the initiation of therapy. Inclusion criteria includes consent to participate in the study, age between 21 and 70 years and BCR-ABL positive patients who were willing to take Imatinib. Exclusion criteria includes pregnant women, patient who were not coming for follow-up and patient who discontinued treatment for more than 2 weeks. The dose of Imatinib administered was 400 mg/day orally. Patients were followed up for 6 months using the following parameters: (1) Monthly clinical examination, (2) Monthly CBC and peripheral blood smear examination and (3) RT-PCR for BCR-ABL at the end of 6 month. For the haematological, cytogenetic and molecular response the standard criteria were followed every 12 months.

**Statistical analysis**

The data obtained from the study was subjected to statistical analysis using SPSS version 20.0 for further evaluation. The data was presented as mean ± standard deviation for continuous variables and frequency for categorical variables. For categorical data, analysis of variance (ANOVA) statistical analysis was used and for continuous data, student's t test was used. One way ANOVA statistical analysis was done for intergroup comparison between cytogenetic response and blood groups after 6 months of treatment.

**Results**

A total of 100 patients of diagnosed CML and on treatment with Imatinib mesylate were enrolled. It was observed that maximum number of patients suffered from symptom of abdominal mass (37%), followed by fatigue (26%), tiredness (17%) and pain in abdomen (11%). In B+ blood groups, 66.67% patients were asymptomatic. Maximum number of patients (46%) was having no side effects of Imatinib therapy; 23% patients suffered from edema, 12% from rashes, 9% with asthenia, 6% hyper pigmentation, 3% hypo pigmentation and 1% with pleural effusion [Tables 1 and 2]; 75% patients showed complete haematological response (CHR) and 25% showed partial haematological response. Patients with B+ and O+ blood groups (41.33%) showed maximum haematological response [Table 3]. It was observed that 45% patients were having B+ blood group, with 43.10% males and 47.62% females; 33% patients were having O+ blood group; followed by A+ (10%), AB+ (8%), A− (2%), B− (1%) and AB− (1%). No patient was observed with O− blood group. It was observed that distribution of both the genders according to blood groups was having insignificant relation (P-value > 0.05) statistically [Table 4]. After 6 months of treatment, maximum number of patients (55%) showed complete cytogenetic response (CCyR), followed by partial (19%), minimal response (19%), minor (5%) and none (2%). Around 43.64% study subjects with O+ blood groups showed CCyR, followed by B+ (41.82%), A+ (10.91), A− (1.82) and AB+ (1.82). It was found that an insignificant relation (P-value > 0.05) was observed statistically between blood groups and cytogenetic response at 6 months of treatment. On intra group analysis in patients with B+ blood group, out of 45 patients, 23 (51.11%) showed complete response,
followed by partial response in 9 (20%), minor response in 3 (6.66%) and minimal response in 10 (22.22%). Out of 33 O+ patients, 24 (72.72%) showed CCyR, followed by partial response 7 (21.21%) and minimal response (6.06%). Among 10 A+ patients, 6 (60%) showed complete response, followed by partial 1 (10%), minor 1 (10%) and minimal 2 (20%). Out of 8 AB+ patients, 1 (12.5%) showed complete response, followed by partial response in 2 (25%), minor response 1 (12.5%), minimal response 3 (37.5%) and none 1 (12.5%). Out of 2 A− patients, 1 (50%) showed complete response, followed by minimal response in 1 (50%) [Table 5]. After 12 months of treatment, maximum number of patients (64%) showed CCyR, followed by minimal response (21%), partial (9%), minor (6%) and none (0%). Around 45.31% study subjects with O+ blood group showed CCyR, followed by B+ (40.62%), A+ (10.94%), A− (1.56%) and AB+ (1.56%). It was found that a significant relation (P-value < 0.05) was observed statistically between blood groups and cytogenetic response at 12 months of treatment. On intra group analysis, out of 45 B+ patients, 26 (57.77%) showed complete response, followed by partial response in 5 (11.11%), minor response in 4 (8.88%) and minimal response in 10 (22.22%). Out of 33 O+ patients, 29 (87.87%) showed CCyR, followed by partial response 2 (6.06%) and minimal response 2 (6.06%). Among 10 A+ patients, 7 (70%) showed complete response, followed by minimal response in 2 (20%), minor response 1 (10%) and minimal response 1 (10%). Out of 8 AB+ patients, 1 (12.5%) showed complete response, followed by partial response in 1 (12.5%), minimal response 5 (62.5%). Out of 2 A− patients, 1 (50%) showed complete response, followed by partial response in 1 (50%) [Table 6]. On comparing the BCRABL/ABL ratio (%) according to blood groups after 6 months, maximum number of patients (30%) had undetectable BCR-ABL/ABL ratio (%), followed by patients with <0.1% ratio (28%), >10% (19%), 0.1% to 0.99% (12%) and 1% to 10% (11%). Equal number of patients (40% each) with O+ and B+ blood groups,
followed by A+ (20%) showed undetectable BCR/ABL ratio (%). A statistically significant (P-value < 0.05) relation was observed between blood groups and BCR/ABL ratio (%) at 6 months of the treatment. On comparing intragroup, out of 45 B+ patients, 12 (26.66%) had undetectable BCR/ABL ratio, followed by patients with >10% ratio 9 (20%), 1% to 10% (17.77%), 0.1% to 0.99% in 7 (15.55%) and <0.1% in 9 (20%). Out of 33 O+ patients, 12 (36.36%) showed undetectable BCR/ABL, followed by patients with >10% ratio 1 (3.30%), 1% to 10% in 2 (6.06%), 0.1% to 0.99% in 2 (6.06%) and <0.1 in 12 (36.36%). Among 10 A+ patients, 6 (60%) had undetectable BCR/ABL/ABL ratio, followed by >10% in 2 (20%) and 0.1% to 0.99% in 2 (20%). Out of 8 AB+ patients, 5 (62.5%) had BCR/ABL/ABL ratio >10%, followed by 1% to 10% in 1 (12.5%) and <0.1 in 2 (25%). Out of 2 A− patients, 1 (50%) had BCR/ABL/ABL ratio >10%, followed by <0.1% in 1 (50%) [Table 7].

**Discussion**

Most of the studies on blood groups and cancer risks are made in the western world, and studies on other populations are limited. Some studies also suggest that ABO blood groups can be used as an epidemiological marker or primary screening assistant to identify populations at high risk for certain haematological malignancies. Therefore, the examination of ABO blood group distributions may be useful in formulating new etiological hypotheses. In a study by Kar F et al., it was observed that the most common blood group type was A in leukemia patients and most of them were Rh+ as it was in general population.

A study conducted in republic of Bosnia by Sakic M et al revealed that O blood group have 40.9%, A have 37% and B have 16% leukemia patients. Another study was conducted in Iraq by Adhiah AH et al. during 2008 and 2010, and it was found that 41.8% of CML patients have blood group O while 28.8% have blood group B. Shahzad H et al conducted a study in Pakistani population and indicated that CML was more persistent in blood group B and O in male patients while persons having blood group A were less susceptible to CML. In female CML patients, blood group B is more prone to CML as in male and persons having blood group A and O were at equal risks of CML. In case of Rh blood factor, both male and female having Rh factor positive were more susceptible to CML. Our study on Indian population revealed that in patients with CML, most common blood groups observed was B+ in both males and females. Whereas, A−, B− and AB− blood groups was found to have less susceptibility for CML. A study by Jaff MS revealed that AB blood group was described as the least frequent in the majority of human populations, as observed in our study. The results obtained from our study were in contrast to the study conducted by Causil-Vargas L et al on Latin population, where distributions were reported to be A > O > B > AB. This difference can be attributed to the different sample sizes employed in the studies, in addition to the miscegenation proper to each country. Our study revealed that maximum number of patients (55% at 6 months and 64% at 12 months) showed CCyR, followed by partial (19%), minimal response (19%), minor (5%) and none (2%). Similar results were observed in study by Druker BJ et al. who observed that use of Imatinib as first-line therapy has resulted in CCyRs in 65% to 85% of patients with CML. In this study, for the first time, we observed the association of various ABO blood groups with cytogenetic response to therapy. The study showed that around 43.64% study subjects with O + blood group showed CCyR, followed by B+ (41.82%), A+ (10.91), A− (1.82) and AB+ (1.56%). In 12 months, it is observed that 45.31% study subjects with O + blood group showed CCyR, followed by B+ (40.62%), A+ (10.94%), A− (1.56%) and AB+ (1.56%). Thus, it was observed that study subjects with O + blood group showed better cytogenetic response as compared with patients with other blood groups at 6 and 12 months of treatment. It was found that a significant relation (P-value < 0.05) was observed statistically between blood groups and cytogenetic response.

| Blood groups | Complete | Partial | Minor | Minimal | None | Total |
|--------------|----------|---------|-------|---------|------|-------|
| A+           | 6 (10.91)| 1 (5.26)| 1 (20)| 2 (10.53)| 0    | 10    |
| A−           | 1 (1.82)| 0       | 0     | 1 (5.26)| 0    | 2     |
| B+           | 23 (41.82)| 9 (17.37)| 3 (60)| 10 (52.63)| 45   |       |
| B−           | 0       | 0       | 0     | 1 (50)  | 1    | 1     |
| AB+          | 1 (1.82)| 2 (10.35)| 1 (20)| 3 (15.79)| 1 (50)| 8     |
| AB−          | 0       | 0       | 0     | 1 (50)  | 1    | 1     |
| O+           | 24 (43.64)| 7 (13.74)| 0   | 2 (10.35)| 33   |       |
| O−           | 0       | 0       | 0     | 0       | 0    | 0     |
| Total        | 55      | 19      | 5     | 19      | 2    | 100   |

| Blood groups | Complete (0%) | Partial (1%‑35%) | Minimal (36‑65) | Minimal (66‑95) | None (>95) | Total |
|--------------|--------------|-----------------|-----------------|-----------------|------------|-------|
| A+           | 7 (10.94)    | 0               | 1 (16.67)       | 2 (9.52)        | 0          | 10    |
| A−           | 1 (1.56)     | 1 (11.11)       | 0               | 0               | 0          | 2     |
| B+           | 26 (40.62)   | 5 (55.56)       | 4 (66.67)       | 10 (47.62)      | 0          | 45    |
| B−           | 0            | 0               | 0               | 1 (47.6)        | 0          | 1     |
| AB+          | 1 (1.56)     | 1 (11.11)       | 1 (16.67)       | 5 (23.81)       | 0          | 8     |
| AB−          | 0            | 0               | 0               | 1 (47.6)        | 0          | 1     |
| O+           | 29 (45.31)   | 2 (22.22)       | 0               | 2 (9.52)        | 0          | 33    |
| O−           | 0            | 0               | 0               | 0               | 0          | 0     |
| Total        | 64           | 9               | 6               | 21              | 0          | 100   |

**Table 5: Cytogenetic response according to blood groups after 6 months of treatment**

**Table 6: Cytogenetic response according to blood groups after 12 months of treatment**
12 months of treatment. Thus, types of blood groups can be taken into consideration to assess the cytogenetic response. In this study, we observed that maximum number of patients (30%) had undetectable BCR-ABL/ABL ratio, followed by patients with <0.1% ratio (28%). The results of study by Kantarjian HM et al.\[13\] revealed that in a single center (median follow-up of 45 months; n = 261 patients), the CCyR rate was 63%, the major molecular response (MMR) rate (BCR-ABL/ABL ratio < 0.05%) was 31% and the complete molecular response (CMR) rate was 15%. Study by Razmkhah F et al.\[16\] showed that 46.7% of patients showed CMR, 43.3% showed partial molecular response and 10% showed no molecular response to Imatinib. We also observed relation between types of blood groups and molecular response to therapy. It was found that patients with O+ and B+ blood groups showed maximum molecular response with treatment therapy. A significant relation (P-value < 0.05) was observed statistically between blood groups and BCR-ABL/ABL ratio (%) at 6 months of treatment. In our study, we observed that 75% patients showed CHR and 25% showed PHR. Similar findings in relation to haematological and molecular responses were observed in a study by Gupta A et al.\[17\]. We also observed that patients with B+ and O+ blood groups (41.33%) showed maximum haematological response, followed by patients with A+ (10.67%), AB+ (4%) and A− (2.67%) blood groups. Thus, best haematological response was observed in patients with B+ and O+ blood groups. In this study, it was observed that maximum number of patients suffered from symptom of abdominal lump (37%), followed by fatigue (26%), tiredness (17%) and pain in abdomen (11%). Only 9 patients showed no clinical symptoms. In B+ blood groups, 66.67% patients were asymptomatic, followed by O+ (22.22%) and AB+ (11.11%) blood groups. Patients with A+, A−, B−, AB− and O− blood groups were not found to be asymptomatic. Patients with B+ and O+ blood groups (34.62% each) showed fatigue, followed by patients with A+ (19.23%), AB+ (7.69%) and A− (3.85%) blood groups. Imatinib is associated with mild to moderate toxicity, mostly reversible by dose reduction or discontinuation of the drug. In a study by Francis J et al.\[18\] it was observed that thrombocytopenia was the most common adverse effect with a percentage occurrence of 57.9%, which is midway between the frequency reports in earlier Indian studies (17.5%–98.0%). Whereas, it was observed that maximum number of patients (46%) was having no side effects of Imatinib therapy; 23% patients suffered from edema, 12% from rashes, 9% with asthenia, 6% hyper pigmentation, 3% hypo pigmentation and 1% with pleural effusion. In B+ blood groups, no side effects were observed in patients. Around 100%, 66.67%, 33.33% and 83.33% of patients showing side effects of pleural effusion, hyper pigmentation, rashes and hyper pigmentation were of O+ blood group. In our study, it was found that patients with O+ and B+ blood groups showed maximum haematological, cytogenetic and molecular response with Imatinib therapy. Physicians should carefully monitor the patients with blood groups other than O+ and B+, as these patients are more prone to get resistance to Imatinib.

### Conclusion

This study revealed the associations of ABO blood groups in CML patients. The response to imatinib with respect to blood group of the patients is may be a mere association rather than causality. We observed that no study has been reported yet that correlate cytological, molecular and haematological responses of Imatinib therapy in CML patients with different types of blood groups. This study will give an insight to new perspective in CML patients with different blood group types in relation to Imatinib therapy. Thus, for future perspective, type of blood groups can also be a predictive factor for molecular response to therapy, although more studies are required to establish the association and to define the mechanisms by which ABO blood group type may influence myeloid leukemia risk and affect the treatment response.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.
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