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RESEARCH ARTICLE

CHRONIC MYELOID LEUKEMIA STUDY FOR RESPONSE PATTERN WITH TYROSINE KINASE INHIBITORS

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Abstract

Tyrosine kinase inhibitor like Imatinib, a small-molecule drug, targets and inhibits the BCR-ABL tyrosine kinase by competitive binding at the ATP-binding site.If Imatinib treatment fails, mutational analysis could identify highly resistant mutants of the kinase domain.

Materials and Methods: A retrospective observational study was conducted in a tertiary care institute to evaluate response of Tyrokinse inhibitors after 18 months of treatment. Results Most of the patients amongst the cohort of 30 had a favourable response to Imatinib at the end of 18 months.Four patients had response failure due to either mutation or high EUTOS score. However long term survival had increased in almost all patients.

Conclusions: Primary end point of regression of splenomegaly and hematological response was achieved within first three months in all except 3patients. cytogenic and molecular response was achieved in all except 4 patients at the end of 18months. Mutations were observed in only 2 cases.Survival benefit was present in all.

Introduction:-

Chronic myeloid leukaemia was the first neoplastic disease for which knowledge of the genotype led to a rationally designed therapy.

Because of its high sensitivity,quantitative PCR is a suitable way to monitor residual disease after cytogenetic remission.Molecular monitoring has shown that reduction of BCR-ABLtranscripts improves prognosis.

Tyrosine kinase inhibitor like Imatinib, a small-molecule drug, targets and inhibits the BCR-ABL tyrosinekinase by competitive binding at the ATP-binding site. The high rates of complete cytogenetic response with Imatinib necessitate molecular monitoring by quantitative PCR to measure residual disease. However treatment with Imatinib is complicated due to the development of resistance. The mechanisms of resistance can be divided into two groups. The first group is characterized by reactivation of Bcr-Abl kinase in spite of continual Imatinib presence. This can be caused by BCR-ABL amplification, over expression or mutation in Abl kinase domain. Imatinib might not even reach the target Bcr-Abl protein (possible causes: drug efflux or Imatinib binding to alpha1-acid glycoprotein). In

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the second group , the Bcr-Abl kinase is inhibited but the resistance is maintained due to other signal transducers (e.g. Src kinases). (1)

If Imatinib treatment fails, mutational analysis couldidentify highly resistant mutants of the kinase domain (e.g., Y253F/H, E255K/V, T315I,or H396P/R43,44), which need an alternative treatment strategy. Mildly resistant mutations (e.g., M244V, M351T, of F359V) might be overcome by an increase inImatinib dose to 600 or 800 mg daily.(2,3)

Materials and Methods:-

An observational, retrospective, study was conducted to determine response pattern to tyrosine kinase inhibitors in chronic myeloid leukaemia cases presenting to the outpatient department or admitted in a tertiary care public hospital.

Cases of chronic myeloid leukaemia proved by fluorescent in-situ hybridization method , visiting outpatient department or indoor admissions were screened. Patients on treatment with Tyrosine kinase inhibitors for more than 18 months were included in the study. Detailed history, clinical findings and laboratory parameters of the patients were analysed. Primary endpoints were regression in splenomegaly, reduction in leucocytosis, Cytogeneticresponse and molecular response. (Table1)

Observations and Results:-

The study group included 14 females and 16 males . Age group varying from 13 to 58 years.

Most common presenting symptomswerefever and easy fatigability with generalized weakness (both 46.67%) followed by abdominal lump/fullness.

Splenomegaly was the most common sign at the onset. The spleen varied from a just palpable spleen to massive splenomegaly of 16 cm. The mean spleen size of the study group was 7.138 cm. Spleen had regressed completely in almost all patients after 3 months of treatment.

Haemoglobin levels varied from 5.9 gm/dl to 14.8 gm/dl. The mean haemoglobin was 10.146 gm/dl.There was statistically significant increase in the haemoglobin within 3 months of treatment with a p value of 0.008.

The WBC counts of the patients in the study group varied from 35,340 permm^3 to 3,39,500 per mm^3 with a median countof 1,47,870 per mm^3.Therewas statistically significant reduction in the total WBC count after tyrosine kinase inhibitors with a p value of<0.001.(FIG 1)

The platelet counts varied from 2,00,000 permm^3 to 12,70,000 per mm^3. Maximum number of patients had normalplatelet counts (50%) with a median count of 4,46,000 per mm^3. None of thepatients had thrombocytopenia. Two patient had extreme thrombocytosis(platelet counts >10,00,000 per mm^3).(FIG 2)

The percentage of cells with Philadelphia chromosome detected by FISH atthe time of diagnosis varied from 41% to 100% with a median value of 91%. (Table 2)

According to the EUTOS score[2] patients were classified into high and low risk as
Low risk (<87) 25
High risk (87 or >87) 5 (TABLE3)
Bcr-Abl levels at each observation are as shown(TABLE 4,5)
Response status of patient at various stages of observation are given.(TABLE 6)
7 patients had suboptimal response or treatment failure during the period of the study. Mutational analysis was carried out in 5of these patients and only two out of these were found to have kinase domain mutation where as rest 3 did not have any kinase domain mutation.(TABLE 7)

In the study, 4 patients had adverse events in the form of severe leucopenia, severe enough to warrant change in therapy. Three of these required only dose reduction while one patient required to be switched to another TKI drug.

Discussion:-

In the present study 30 cases of proved chronic myeloid leukaemia in chronic phase following up in a tertiary care referral centre were retrospectively analysed for their response to tyrosine kinase inhibitors after minimum 18 months. The median age of the study population was 34 years, with maximum (30%) patients in the 20-29 years age group In India, median age at presentation is a decade younger compared with the age presented in European.(5) The study group included 14 females and 16 males with M:F ratio of 1.071 : 1.

The most common presenting symptoms were fever(46.67%) and easy fatigability (46.67%). The most likely cause of easy fatigability was anaemia.

Splenomegaly was present in 86.67% patients.The spleen size varied in our study from just palpable spleen to 16 cm spleen, below the left costal margin with a mean size of 7.138cm and median of 8 cm.

One male had presented with features of hyperviscocity in the form of priapism due to severe leucocytosis (>2,50,000 per mm^3)which subsequently reduced after Imatinib treatment. Hepatomegaly was observed in 4 cases . The cause of the hepatomegaly may be due to infiltration of liver by the leukemic cells or extramedullary haematopoiesis due to bone marrow infiltration.

The haemoglobin in this study varied from 5.9 gm/dl to 14.8 gm/dl with a median haemoglobin of 9.9 gm/dl.None of the patients had polycythemia.

The total WBC count varied from 35,340 to 3,39,500 per mm^3 with a median count of 147870 per mm^3. One patient had counts less than 50,000 per mm^3. Rest of the patients were almost equally distributed over each 50,000 interval with 8 patients (26.67%) having counts more than2,00,000 per mm^3. (FIG 1)

Although frequent high counts were observed but features of leucostasis such as retinopathy and mental obtundation were not observed in any of the patients except one case of Priaprism.

The platelet counts varied from 2,00,000 to 12,70,000 per mm^3 with a median count of 4,45,000 per mm^3. (Fig 2)However ischemic vascular events were not observed.(6)

Philadelphia chromosome was detected by FISH. The percentage of the Philadelphia chromosome positive cells varied from 41%to 100% with a median value of 91%.Maximum number of patients (50%patients) having >90% cells positive for Philadelphia chromosome. (TABLE 2)

Only one patient was found to be in accelerated phase at the first visit , rest all were in chronic phase at the time of presentation.(6,5,7)

All the BCR-ABL1 fusion protein exhibit dysregulated tyrosine kinase activity. Hence all these cases were subjected to first line TKI, Imatinib 400mg once a day.

Complete hematological response was achieved in all patients except three (10%) at the end of 3 months of treatment. (Table 6).Amongst the three patients who failed to achieve complete hematological response within initial three months, two achieved response at the end of 6 months of treatment and the third patient had to be shifted to second line tyrosine kinase inhibitors and achieved complete hematological response after 3 months of Dasatinib treatment. (9) (10)

As shown in table4,5,6,The cytogenetic response could be analysed in only 13 out of the 30 patients in the study group due to financial constrain and the study being retrospective. Among these 13, ten patients were in complete cytogenetic response on or before 12 months of treatment as nondetectable philaldephelia cells. One patient who did not achieve complete cytogenetic response at the end of 12 months could achieve the same at the end of18 months of treatment. Of the two patients who failed to achieve complete cytogenetic response, due to kinase domain mutation ,only one could be started on second line tyrosine kinase inhibitor(Dasatinib). who achieved complete molecular response after 18 months of treatment. (8,9). The higher rate of complete cytogenetic response in our study may be because of the lesser number of cases. (10)

The Bcr-Abl quantitative PCR report was not available in 3 patients and hence their response could not be commented on. Out of the remaining patients, 55.21% patients were in complete or major molecular response at the end of 18 months of treatment and 11.11% had molecular relapse or failure . (Table 4,5and 6)

The remaining patients either had a suboptimal response or they were responding and the Bcr-ABl report at the end of 18 months was not available and hence their exact response could not be documented..

In our study, Imatinib was the first line therapy started in 28 out of the 30 patients (93.33%). It had to be discontinued or dose had to be decreased in 4 patients on account of adverse effects. All the four patients had cytopenias. Three out of the four patients responded to reduced dose of Imatinib. The fourth patient had severe recurrent pancytopenia whenever Imatinib was reintroduced in reduced doses and hence he was shifted to Nilotinib. Among hematological toxicity, most common were anemia,thrombocytopenia and neutropenia (8,9)

One female patient accidently conceived while on Imatinib, decided to continue with pregnancy even after counselling and explaining the risk and benefits of the therapy. However had a spontaneous abortion after 1.5 months of gestation.

Thus the safety of tyrosine kinase inhibitors in pregnancy still remains a concern..(11,13)

Patients with suboptimal response, failure of treatment or relapse at any point of time treatment constituted 7 out of 30. However by 18 months of treatment three of them responded either to increase in dose of Imatinib(600mg) or switching over to second line tyrosine kinase inhibitors and the number at end of 18 months decreased to4. Kinase domain mutations were performed in 5 of the 7 patients with suboptimal response or failure and it was found that only 2 of the patients who had suboptimal response had a kinase domain mutation (table 7). The mutations that were detected in the patients in this study included F359V and Y253H respectively.

Thus in majority of the patients the exact cause of the suboptimal response was not kinase domain mutation. This leads us to believe that there are other factors that may be responsible for suboptimal response or failure than kinase domain mutations alone. In these patients with suboptimal response without having any mutations, 4 patients had a high EUTOS score while 1 had a low risk EUTOS score. The patient with low EUTOSscore only had suboptimal response at the first visit and she further obtained complete hematological, molecular and cytogenetic response at the end of 18 months. Thus a high EUTOS score can be used as a predictor for suboptimal response or non response even in absence of gene mutations. (8)

In our study, out of the 4 patients who had hepatomegaly, one had suboptimal response. (13)

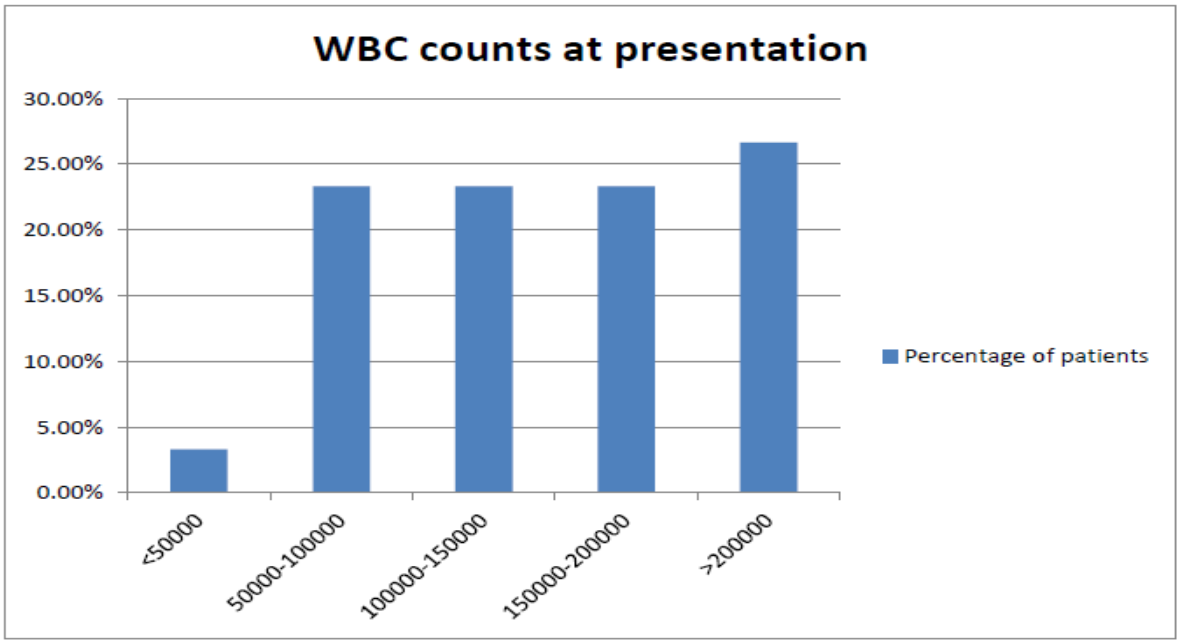
In this study mortality was not primary outcome. The median survival at the time of follow up was 2 years. However there were patients on treatment from 1.5 years to 9 years amongst the study group. The number of cases on treatment for more than 3 years were 11 out of 30 (36.67%). Thus there was an overall limprovement in the survival of the patients. This is consistent with a larger study in which the 8 year survival had increased from <15% before discovery of Imatinib to 87%after Imatinib therapy.(14)

Conclusions:-

Tyrosine kinase inhibitors cause significant clinical improvement , cytogenic and major molecular response in chronic myeloid leukemia patients in chronic phase.

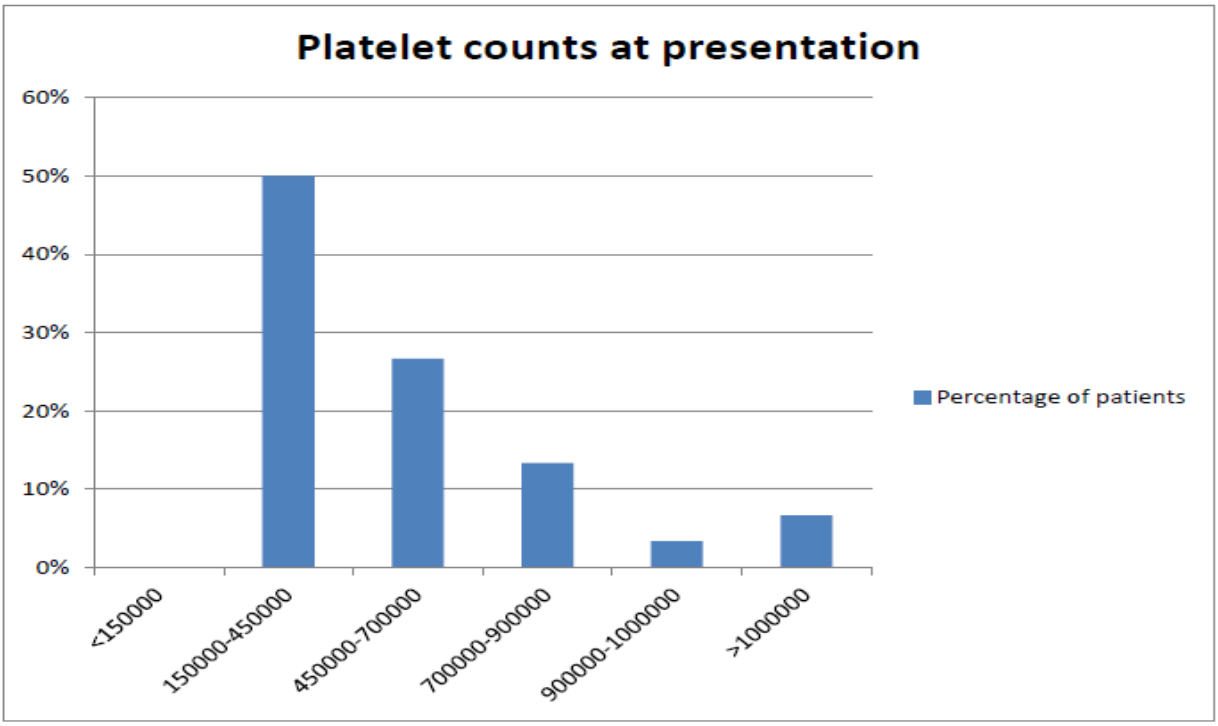
In patients with no kinase domain mutation, high EUTOS score can be a predictor of sub optimal response / failure of first line of therapy.

Fig 1:-



[redacted]5 – WBC counts at presentation

Fig 2:-



[redacted] – Platelet count at presentation

Table1:-

Response definitions

Type of response		Criteria
Hematological response	Complete hematological response (CHR)	Total WBC count <10000/mm^3 Platelets < 450000/mm^3 Basophils <5% No immature granulocytes No palpable spleen
Cytogenetic response	Complete cytogenetic response (CCyR)	0% cells with Philadelphia chromosome
	Partial cytogenetic response (PCyR)	1-35% cells with Philadelphia chromosome
	Minor cytogenetic response	36-65% cells with Philadelphia chromosome
	Minimum cytogenetic response	66-95% cells with Philadelphia chromosome
	No cytogenetic response	>95% cells with Philadelphia chromosome
Molecular response	Complete molecular response (CMR)	No detectable *BCR-ABL* transcripts
	Major molecular response (MMR)	*BCR-ABL* transcripts <0.1% in international scale by RQ-PCR

Table 2:-

Cells with Philadelphia chromosome	Number of patients	Percentage
91-100%	15	50%
81-90%	7	26.67%
71-80%	3	10%
61-70%	3	10%
51-60%	1	3.33%
41-50%	1	3.33%

Table 3:-

EUTOS score category	Number of patients	Percentage
Low risk (<87)	22	81.48%
High risk (87 or >87)	5	18.52%

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