http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v10i6.11

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Paper

Cost effective drug response & Analysis of patients of "Chronic Myeloid Leukaemia" (CML) (Research period- 2015-2022)

Author
Dr Poonam Gupta -M.B.B.S- MD (Oncology)
Sr. Consultant –HPPCH Gorakhpur –India

Abstract
CML is "clonal hematopoietic disorder" caused by an acquired genetic defect in pluripotent stem cell, which is BCR –ABL protein which results from a reciprocal translocation involving chromosome 9 and 22 .The definite diagnosis of CML is obtained by demonstrating the presence of a BCR-ABL1 fusion. The cornerstone of CML treatment is represented by the use of TKIs utilized as monotherapy. The prognosis for CML changed so much with the introduction of cost effective drug "imatinib", that today CML-related deaths are rare and a normal life expectancy is possible for CML patients.

Introduction

Chronic myeloid leukaemia (CML) or chronic myelogenous leukaemia, is a neoplastic disease. It develop due to the malignant transformation of a pluripotent hematopoietic stem cell. The causative event of this transformation is represented by a chromosomal translocation between chromosomes 9 and 22 (Philadelphia or Ph chromosome). Diagnosed in most patients in a relatively asymptomatic condition named chronic phase (CP), but may evolve into a more aggressive condition called blast crisis (BC). In that condition leukemic cells lose their ability to differentiate, similarly to what happens in acute myeloid leukaemia. CML classically occurs in three stages: CP, accelerated phase (AP), and the terminal BC. Most patients (90% to 95%) are diagnosed in CP. When present, clinical manifestations include fatigue, malaise (60%), weight loss (21%), and symptoms secondary to splenomegaly (72%). Less frequent symptoms consist of haemorrhage, thrombotic events, priapism, fever, and gouty arthritis. Patients with advanced CML may additionally suffer from bone pain, night sweats, splenic infarction, infections, and symptoms due to leukostasis (dyspnoea, confusion, and lack of coordination) or bone marrow failure (infections and haemorrhages).

The differential diagnosis is Secondary leukocytosis usually differs from typical white blood cell elevation in CML patients as they rarely exceed levels of 50 × 10 9 /L, are frequently seen with toxic granulocytic vacuolation, and occur in the absence of basophilia and peripheral myeloblasts. History and clinical presentation of patients with reactive leukocytosis differ from CML patients, as CML occurs in many cases without symptoms. Likewise, cases of leukocytosis associated to the intake of corticosteroids can be distinguished

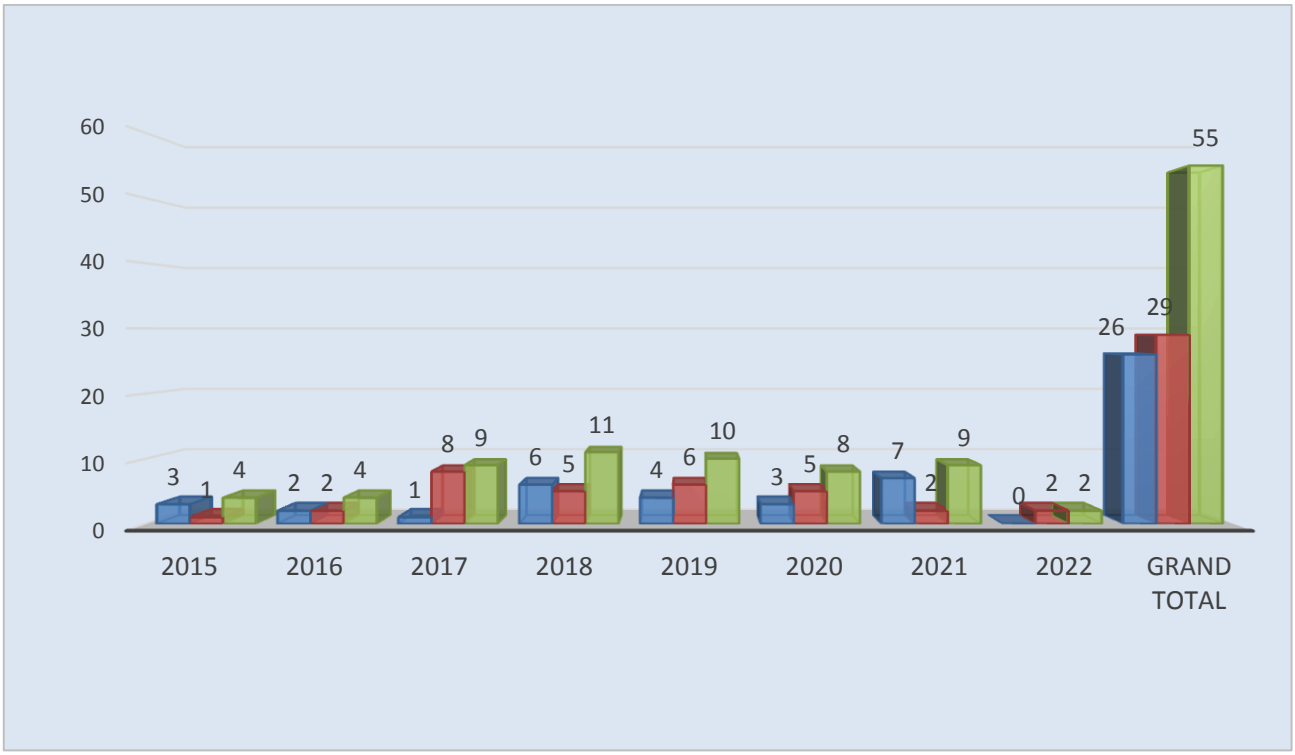
anamnestically but also through the absence of a left shift in the peripheral blood and they are transient in character. The classical differential diagnosis of CML is from other chronic myeloproliferative neoplasms. Here, all forms of myelofibrosis (primary myelofibrosis, essential thrombocythemia myelofibrosis, and postpolycythemia Vera myelofibrosis) can present with splenomegaly, neutrophilia, anaemia, and thrombocytosis. Likewise, both polycythaemia Vera rubra and essential thrombocythemia can be associated with leukocytosis and thrombocytosis. The absence of the BCR-ABL1 transcript and the detection of mutant JAK2, CALR, or MPL genes usually allow to distinguish between these forms of chronic myeloproliferative neoplasms and CML. It has to be remembered that rare cases of biclonal leukaemia's exist, with the simultaneous coexistence of two leukemic clones, one JAK2 mutation positive and the other BCR-ABL1 positive.

TKIs (imatinib, bosutinib, dasatinib, nilotinib) are presently approved worldwide for first-line treatment of CML patients. Imatinib represents the first and most commonly used drug. The usual dosage is 400 mg per day for imatinib. If the patient is symptomatic, symptoms will fade within 1 to 2 weeks. CHR is reached in >80% of cases within 4 weeks, and CCyR is obtained in 65% to 80% of patients within 12 months survival. CyR indicates that the hemopoietic system is no longer formed predominantly by leukemic cells but by normal cells.

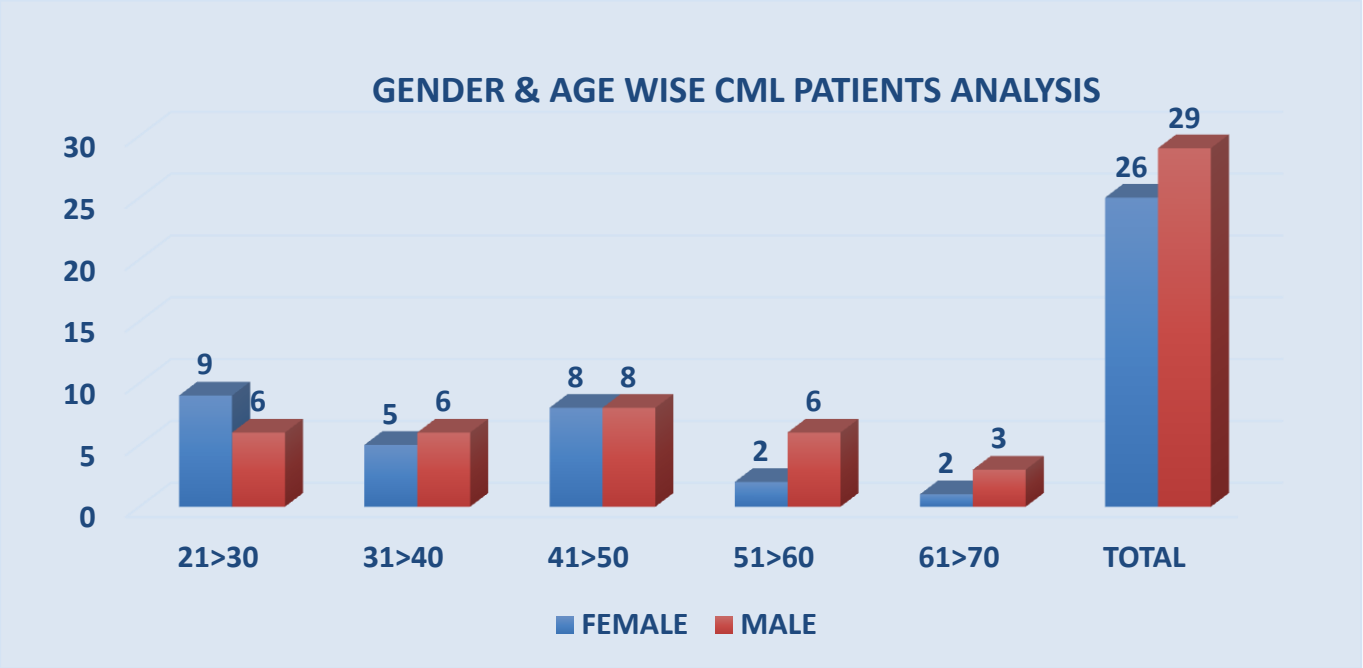
Material & Method

The retrospective study performed in 55 patients of CML in Hanuman Prasad Poddar Cancer Hospital & Research centre- Gorakhpur – India, from 2015 to 2022.The patients were the resident of different areas of northern India. there were both male and females. The ages were between 23 yr. to 65 yr .90% of them came with fatigue, wt. loss & raised TLC. Rest came with other vague complains and detected incidentally. All diagnosed with raised TLC (in lakhs), in USG abdomen there was splenomegaly, on bone marrow examination the chronic myeloid leukaemia found. All were BCR –ABL positive.

Patient's enrollment –year wise – male V/S females



Patient's characteristics – gender v/s age wise:



Results-low cost drug-Imatinib

- All patients treated with imatinib. They all received (100%) hematologic response in 1 to 2 months.
- 3(5.45%) patients developed accelerated phase.
- 2(3.63%) out developed blast crisis.
- 1(1.81%) patient developed severe pleural effusion so the treatment changed.
- 49 (89.09%) patients are surviving with normal routine life with imatinib and coming for fallow up.
- In total, 12 (21.81%) patients has reached to the major molecular response (MMR) with good quality of life.

Discussion

Many studies have been done to compare various TKIs used as first-line treatment for CML . In all cases, imatinib was used as the standard drug, and no study directly compared two different second-generation TKIs. The results of these studies can be summarized as follows: Second-generation TKIs uniformly produced a faster and deeper decrease in BCR-ABL1 messenger RNA values as detected by QRPCR, although in some studies, this difference tended to fade after the initial 12 months. Some but not all studies showed a significantly higher CCyR rates at or by 12 months in patients receiving second-generation TKIs. No study showed a significant difference in progression to AP or BC CML (progression-free survival) nor in OS; as most CML-related progressions and deaths happen in the initial 2 years after diagnosis, a longer follow-up of these studies is unlikely to change these results. Similarly, no subanalysis performed on subgroups of patients (e.g., those with high risk defined by Sokal or other scoring systems) identified statistically significant differences. Overall, these results showed that imatinib produced high and durable rates of responses; these values grew better with time, probably reflecting both the increased familiarity with this drug and the availability of second generation TKIs for relapsed/refractory patients. Second-generation TKIs such as dasatinib and nilotinib may be used for resistance to imatinib or patients with poor prognostic features. For those who do not respond adequately to the TKIs or who lose response, allogeneic transplantation remains an important option. About 70% of good-risk patients achieve long-term DFS.

Abbreviations

- QRPCR –quantitative real time polymerase chain reaction
- CHR -complete hematologic response
- CCyR - complete cytogenetic response

Conclusions

Imatinib is relatively well-tolerated and cost effective oral medication that has been shown to be effective in CML in both chronic and accelerated phases. This agent has been a paradigm for molecularly targeted therapies and is now used as upfront therapy for CML. The patients can carry the normal quality of life with treatment.

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