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Cause of hospitalization and its outcome in patient with chronic myeloid leukemia in Patan Hospital

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Abstract

Introduction: Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by dysregulated proliferation of granulocytes because of reciprocal translocation of chromosome 9 and 22. Despite the advances in treatment of CML, it still has a significant burden in patients' life because of cost of medication, frequent hospitalization and effect on quality of life. The aim of this study is to find out the cause of hospitalization and its outcome in patient with CML.

Method: It is a retrospective cross-sectional study conducted at Patan Hospital. The study included data of hospitalization of CML patients over a period of 3 years from April 2020 to April 2023 which was obtained from the record files and discharge notes of the patients. The data included information regarding age and sex of the patients, phase of disease, name of Tyrosine kinase inhibitor (TKI) used, cause of hospitalization and outcome of the hospitalization.

Result: There were total of 102 admissions of which 82 admissions were analyzed. The mean age was 49 y, 56% were male, 70.7% were in chronic phase of disease and imatinib was the commonest TKI used (51.2 %). Disease related events were the most common cause of hospital admission (61%); 70 patients (85.4%) improved and were discharged whereas 12 patients (14.6 %) died during hospitalization.

Conclusion: The commonest cause of hospitalization in CML patient was disease related events i.e., disease progression, drug related adverse effects and new diagnosis. Transformation to blast crisis had worst prognosis with increased mortality.

Keyword: CML, hospitalization, TKIs

Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by dysregulated proliferation of granulocytes. It is associated with fusion of two genes BCR in chromosome 22 and ABL in chromosome 9 resulting in abnormal chromosome 22 also known as Philadelphia chromosome.[1] If untreated, CML presents as biphasic or triphasic disease with an early chronic phase followed by accelerated phase and blast crisis.[2] The diagnosis is typically confirmed by demonstration of Philadelphia chromosome, the BCR::ABL1 fusion gene by cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR).[1-3] The treatment of CML has changed drastically with the introduction of Tyrosine kinase inhibitor (TKI) as standard CML therapy. Before the TKI era, the annual mortality was 10-15% which has been reduced to less than 2% with imatinib therapy. More than half of the deaths are due to non CML related conditions such as infections, old age, road accidents, and cardiovascular causes.[2]

Despite the advances in treatment of CML, it still has a significant burden on patient's life because of cost of medication, frequent hospitalization and effect on quality of life.[5] Hospitalization in CML may be due to infections, cardiovascular morbidities, disease progression or drug induced adverse effects.[1-3, 6-7]

The aim of this study is to find out the cause of hospitalization and its outcome in patient with CML admitted to Patan Hospital which is one of the GIPAP (Glivec International Patient Assistance Program - The Max Access) centers of the Max Foundation.[8]

Method

It is a retrospective cross-sectional study conducted in department of Internal medicine of Patan Hospital, Patan Academy of Health Sciences (PAHS) situated in Lagankhel, Lalitpur, Nepal. Ethical approval was taken from the Institutional Review Committee of Patan Academy of Health Sciences. CML patients hospitalized in department of Internal Medicine (medical ward, geriatric ward, hematology ward and high dependency unit (HDU) and intensive care unit (ICU)) of Patan Hospital were included in the study whereas admitted patients whose records were incomplete and not available were excluded from the study.

The study includes data of hospitalization of CML patients in the last 3 years (April 2020-April 2023). The data was obtained from the record files and discharge notes of the patients. The record files were obtained from the record section of Patan Hospital whereas the discharge notes were retrieved from DCODE HEALTH software available in the hospital computer using the hospital number and encounter number of the patients. The preliminary admission data were retrieved from the nursing admission register (name of patient, hospital number, identification number (encounter number) of admission, admission diagnosis and discharge diagnosis) by the investigators during free hours. The details of the patient such as information regarding age and sex of the patients, phase of disease, name of TKI used, cause of hospitalization and outcome of the hospitalization were taken from the discharge note. Phases of CML were categorized as chronic phase, accelerated phase and blast crisis. Chronic phase was characterized by leukocytosis (with neutrophils in various stages of maturation), hypercellular bone marrow with marked granulocytic proliferation and blast of less than 5%, with or without splenomegaly.[1] Accelerated phase was defined as the presence of 15% or more peripheral blasts, 30% or more peripheral blasts plus promyelocytes, 20% or more peripheral basophils, cytogenetic clonal evolution (presence of chromosomal abnormalities in addition to Ph), and thrombocytopenia $<100\times10^9$/L On the other hand blast crisis was the phase with the presence of 30% or more peripheral or marrow blasts or the presence of sheets of blasts in extramedullary disease (usually skin, soft tissues, or lytic bone lesions).[2]

Information about cause of hospitalization was taken from the "final discharge diagnosis" section of the discharge notes whereas information about phase of the disease and name of the TKI used was retrieved from the history and treatment section of the discharge note and the record file of the patient. Causes of hospitalization were divided into four categories namely Disease-related, Infections, Cardiovascular and Others. Disease related causes included disease progression, drug induced adverse effects and new diagnosis. Disease progression meant a patient already on TKI presenting in an accelerated phase or blast crisis.[2] Common TKIs used were Imatinib, Nilotinib, Dasatinib, Bosutinib and Ponatinib.[2] Imatinib is considered as first generation TKI, Dasatinib, Nilotinib, and Bosutinib are referred to as second generation TKIs; Ponatinib is referred to as a third-generation TKI.[2] Common adverse effects of these TKIs were myelosuppression, thrombocytopenia, pleural effusion, fluid retention, skin rash, diarrhea, systemic hypertension and arterial-occlusive events.[2] Myelosuppresion was defined as total leukocyte count less than 4000/µL or platelets count less than 100000/µL. Arterial-occlusive events included cardiovascular, cerebrovascular and peripheral arterial events. Thrombocytopenia meant platelet below 100000/µL.[2] Common infections could be pneumonia or Urinary Tract Infection (UTI) or Undifferentiated febrile illness or any other infections which were taken from the discharge note.[5] Cardiovascular cause of admission could be a new or pre-existing condition such as Heart Failure, acute coronary syndrome or pericardial effusion.[6,7]

Outcomes of hospitalization were categorized as improvement followed by discharge and death during hospital admission. Improvement was defined as the patient being fit for discharge after treatment of the complaints for which the patient was admitted, which was decided by the attending physician during the time of hospitalization.

Data were entered in MS Excel. Mean, median and percentage of variables were calculated using tools of descriptive statistics.

Result

There were total of 102 admissions of CML patients from April 2020 to April 2023, of which 82 admissions were analysed because data of 20 admissions could not be retrieved. There were 11(13.4%) patients with multiple admissions where 9 patients were admitted twice and 2(2.4%) patients were admitted thrice during the study period. The mean age was 49 years, 56% were male, 58(70.7%) were in chronic phase of disease and imatinib was the commonest TKI used 46(51.2%) as depicted in, Table 1. Disease related event was the most common cause of hospital admission followed by infections and cardiovascular causes as shown in, Table 2. Seventy patients (85.4%) improved and were discharged whereas 12(14.6%) patients died during hospital admission as depicted in, Table 3.

Table 1. Demographic and clinical profile of CML patients admitted to Patan Hospital (N=82)

SN	Characteristics		Mean(%)
1	Age		49 y
2	Sex	Male	46(56%)
		Female	36(44%)
3	Phase of disease	Chronic phase	58(70.7%)
		Accelerated phase	4(4.9%)
		Blast crisis	20(24.4%)
4	Use of TKIs	Imatinib	42(51.2%)
		Dasatinib	17(20.7%)
		Nilotinib	4(4.9%)
		Bosutinib	5(6.1%)
		Ponatinib	14(17.1%)

Table 2. Causes of hospitalization in CML patients admitted to Patan Hospital (N=82)

S. No.	Causes			*f* (N)
1	Disease related			50(61%)
		1a	New diagnosis	10(12.2%)
		1b	Disease progression	24(29.3%)
		1c	Drug related adverse events	16(19.5%)
2	Infection			12(14.6%)
3	Cardiovascular causes			7(8.5%)
4	Others			13(15.9%)

Table 3. Outcome of hospitalization in CML patients admitted to Patan Hospital (N=82)

S. No.	Outcome	*f* (N)
1	Improved and discharged	70(85.4%)
2	Mortality	12(14.6%)

Discussion

The most common cause of hospital admission in Chronic Myeloid Leukemia (CML) patients was disease related events in our study. Disease progression to accelerated phase and blast crisis were the major disease related event. There were 24(29.3%) admissions for disease progression of which 20(24.4%) admissions were because of blast crisis and four patients being in accelerated phase. After the introduction of tyrosine kinase inhibitor (TKI), the transformation of chronic phase of CML on treatment to advanced phase has reduced drastically.[12] However, transformation to blast crisis remains a major cause of morbidity and mortality in patients with CML.[2,9-12] Most patients in blast crisis die due to infections and hemorrhage.[10-12] Our study included 20(24.4%) patients with diagnosis of blast crisis of which 12(14.6%) patients died during hospital admission. Four patients with accelerated phase in whom the first generation TKI was changed to second or third generation TKI improved following hospital admission.

On the other hand, drug related adverse events also lead to hospital admission in CML patients in our study. There were 16(19.5%) admissions for drug related adverse effects. We know that TKIs are the first line therapy in CML patients.[2] All the patients in our study were on some kind of TKI. Use of TKIs are often related to adverse effects which may require hospitalization, discontinuation of drug and treatment of the condition.[2,12,14] Imatinib, dasatinib, nilotinib, bosutinib and ponatinib are the TKIs that we commonly use.[12] Imatinib was the most common TKI used in our study 42(51.2%) followed by dasatinib 17(20.7%), ponatinib 14(17.1%), bosutinib 5(6.1%) and nilotinib 4(4.9%). Imatinib may lead to fluid retention, weight gain, nausea, rashes and fatigues whereas pleural effusion, pericardial effusion and myelosuppresion are common adverse effects of dasatinib.[2,12-14] Similarly, nilotinib is associated with higher rates of hyperglycemia, pruritus, pancreatitis, skin rashes, headaches and cardiovascular complications.[2,12] Gastrointestinal adverse effects particularly diarrhoea, renal and liver toxicities are associated with use of Bosutinib.[2,12-15] Ponatinib is associated with higher rates of skin rash, systemic hypertension, pancreatitis and arterio-occlusive disease.[2,12,16] These side effects are mostly dose dependent and are generally reversible with treatment interruptions and dose reduction.[2] In our study, nine patients with myelosupression were admitted; which was the most common drug related adverse effect requiring hospital admission. On the other hand, there were three admissions due to pleural effusion and four admissions because of acute gastroenteritis. All patients with pleural effusion were taking dasatinib and those with acute gastroenteritis were on bosutinib.

Pleural effusions are generally associated with the use of dasatinib and acute gastroenteritis; mostly diarrhoea is common side effect of bosutinib as explained above.

Infections are common in CML patients. The disease process and the use of TKIs both predispose the patient to different types of infections. Viral infections or its reactivation (Examples: Herpes Zoster, cytomegalovirus), pneumonia, fungal infections, etc. are examples of some common infections in CML patients.[4,17-21] Our study also revealed that Infection was a common cause of hospital admission in CML patients. Pneumonia, urinary tract infection, undifferentiated febrile illness, necrotizing fasciitis and neutropenic fever were the common infections that lead to hospital admission.

It has been postulated that use of TKIs is associated with cardiovascular adverse effects.[2,12,23] Its use may deteriorate pre-existing cardiovascular condition or lead to new event through its toxicity.[12,23] Common cardiovascular morbidities are heart failure, hypertension and arterio-occlusive disease.[2,12,22] Our study showed that 8.5% of total admissions were due to cardiovascular cause. The admissions were mostly due to heart failure and hypertensive urgency.

Apart from these, other causes of hospital admission in our study included one case each of intracranial haemorrhage, subdural hematoma, peptic ulcer disease, hemarthrosis, transverse myelitis and rotator cuff tendinitis. Haemorrhage like intracranial, subdural hematoma and hemarthrosis seen in these patients could be due to disease process or thrombocytopenia. Some TKIs may often lead to extreme thrombocytopenia which may predispose the patient to bleeding.[2,12] Similarly, disease progression from chronic phase to accelerated phase and blast crisis may also lead to bleeding from and into different sites of the body.[1,2,9,10] 85.4% of the patients in our study were discharged following improvement, whereas 14.6% died during hospital admission. All the mortalities were due to blast crisis as discussed above. Introduction of TKIs has revolutionized the prognosis of CML with annual mortality decreasing to less than 2% and most deaths occurring from conditions other than CML, such as old age, co-morbidities, accidents, suicides, other cancers, and other medical conditions.[1,2] Though the prognosis of CML has drastically improved following the introduction of TKIs compared to pre-TKI era, blast crisis still remains a significant therapeutic challenge and is associated with increased morbidity and mortality.[2,10-12]

Small sample size was one of the major limitations of this study. The small sample size was because of the COVID-19 pandemic which affected our region and hospital in the year 2020 and 2021. Patients who were admitted in COVID-19 ward, COVID-19 ICU and isolation ward were not included in this study. On the other hand, another reason for small sample size is due to exclusion of admitted patients whose complete data could not be retrieved from the review of record file and discharge note. The other limitation is the retrospective nature of the study, where we had to rely on the charts of the patients which was maintained by the treating physician.

Conclusion

The most common cause of hospitalization in CML patient was disease related events i.e., disease progression, drug related adverse effects and new diagnosis. Infections such as pneumonia and UTI and cardiovascular events such as heart failure also leads to hospital admissions. Most of the patients improved following hospital admission, but patients who had transformation to blast crisis had bad prognosis with increased mortality.

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Conflict of Interest

None

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Author Contribution

Concept, design, planning: AT, KM, ML; Literature review: AT, KM; Data collection: AT, ML; Data analysis: AT, KM, ML; Draft manuscript: AT; Revision of draft: AT, KM, ML; Final manuscript: AT, KM, ML; Accountability of the work: AT, KM, ML.

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