Chronic Myeloid Leukaemia: A Review Of Literature

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Introduction

CML is a clonal myeloproliferative disorder resulting from the neoplastic transformation of primitive haemopoetic stem cells. Monoclonal in origin, it affects myeloid, monocytic, erythroid, megakaryocte, B-cell, and sometimes, T-cell lineages. But stromal cells of the bone marrow are not involved [1].It is the most common type of chronic myeloproliferative disease.

Historical Perspectives

The earliest description of CML was in 1845. It is known as one of the first leukemias to be discovered .In 1845, two patients were described as having massive splenomegaly associated with leukocytosis (which seemed to be a novel entity not due to other causes of splenomegaly such as Tuberculosis, that were widely accepted in the 1840's). Its diagnosis was improved with the discovery of the Ph chromosome by Nowell & Hungerford in 1960[3].Then the understanding of the molecular cause of CML increased in 1975 when Janet Rowley discovered that the Ph chromosome is a reciprocal translocation between chromosome 9 and 22[2] .
Therefore, historically, CML is very relevant as it was the first disease in which a specific chromosomal abnormality was linked to its pathogenesis, implicating the activation of a specific oncogene in the chromosomal rearrangement[4-7].

Epidemiology:

It comprises approximately 15% of all adult leukemias [8] and is known to affect one to two persons per annum worldwide. It affects all age groups but is uncommon in children.

Aetiology:

High doses of radiation[9] are known to increase the risk of developing CML. The survivors of atomic disasters at Hiroshima and Nagasaki had a significantly higher incidence[9]. Therapeutic radiation has also been associated, as evidenced by spinal irradiation for the treatment of ankylosing spondylitis, and when used in women with uterine cervical cancer [10], in thyroid cancer or Hodgkin's Lyphoma.
Little evidence for genetic factors has been found, as offsprings of CML patients do not have a higher incidence of the disease. Nor do monozygotic twins.
The conclusion remains that CML seems to be acquired, although there may be some correlation with human leukocyte antigens (HLAs) CW3 and CW4[11].

Cytogenetics-

CML demonstrates the bcr-abl fusion genes resulting from a reciprocal translocation between chromosomes 9 and 22. This creates a karyotypic abnormality, the Philadelphia chromosome which is simply a shortened chromosome 22.Ninety to 95% of all patients with CML have the Ph Chromosome [12].
The Ph chromosome is translated into chimeric proteins with varied sizes that exhibit increased tyrosine kinase activity. Bcr-abl mutation occurs in 3 forms: p210, p190 and p230, all with substantial increase in tyrosine kinase activity.
Abnormal rise in the activity of tyrosine kinase causes activation of ras, myc, p13k pathways which[8] allows primitive haematopoetic cells to continuously enter the cell cycle. This results in increased number of mature cells in the blood.

Clinical Course

The disease classically runs a 3-phase clinical course as follows:
Chronic phase:
Diagnosis is usually made at this phase. However late presentation is not uncommon in developing countries, due to factors such as poverty, as some patients are detected in blastic phase before treatment is commenced. Untreated, the duration could last up to 10 years, but it

usually progresses after 3-5 years of initiation.

This phase is characterized by
- increase in the number of myeloid progenitor cells
- peripheral blood leukocytosis
- thrombocytosis
- neutrophilia, basophilia and eosinophilia
- blasts plus promylocytes usually < 12%

This phase is frequently asymptomatic and usually runs a benign course. Clinical presentations are fatigue, anorexia, upper abdominal pains, excessive sweating .Early satiety could be from splenic enlargement leading to weight loss. Rarely patients present with hyperviscosity symptoms such as tinnitus, priaprism, stupor, visual changes and cerebrovascular problems that are secondary to leukocytosis.
Signs include pallor, splenomegaly, hepatomegaly and sometimes, sternal tenderness.
Accelerated phase:
An intermediate phase, it is sometimes not very distinct. In about 20% of patients the chronic phase can progress to blastic phase, and so excludes this phase altogether.

The phase is associated with
- increasing leukocytosis
- increase in number of blasts , between 5-20%
- worsening anaemia
- thrombocytosis
- increasing basophilia and eosinophilia
- increasing marrow fibrosis
- and persistent splenomegaly

Additional chromosomal abnormalities are a marker of the acceleration of CML. Then, control becomes more difficult with myelo-supressive drugs.

Blastic phase:
It resembles acute leukemia. It is characterized by at least 30% blasts in bone marrow or in the periphery.
Survival in this phase is worse as the patients not on treatment usually die within 3-6 months. More symptoms including bone pains, infectious complications and bleeding are likely be seen here. This is because tissue infiltration can occur, most frequently to the lymph nodes, skin, subcutaneous nodules and the bone. These extramedullary deposits are called chloroma or myeloblastomas[13].

The signs of subcutaneous nodules or tender haemorrhagic lesions and lymphadenopathy are more common. Signs of central nervous system can also be observed[14].

Occasionally, it transforms into myelofibrosis in few patients. Thus, death occurs from bone marrow failure.

Chemotherapy in blastic crisis is usually tailored to the predominant blast type (myeloid or lymphoid).In this phase, it is usually ineffective.

Laboratory features:
Peripheral blood-
Elevated white blood cell count above 50,000 μL [normal value is 4,000-11,000μL] is the common finding, with differential count revealing granulocyte in all stages of maturation from blasts to matured cells, basophilia [20% or more signals acceleration], eosinophilia, lymphocytosis usually of T-lymphocyte type, thrombocytosis or thrombocytopaenia which also signals progression of the disease.
Anaemia is mild except in untreated patients.

Bone marrow-
B.M is usually hypercellular, with little fat present.
Myeloid to erythroid ratio is between 10:1 and 30:1[normal is 2-5:1], fibrosis increases with disease progression.
Samples of marrow are needed for cytogenetic studies such as Fluorescent in-situ hybridization [FISH] and Reverse transcriptase-polymerase chain reaction [RT-PCR].

Other features
There is reduction in the activity of alkaline phosphatase[15].
The serum level of uric acid [from Tumor lysis syndrome], lactate dehydrogenase & Vitamin B12 and transcobalamin I & II is increased.

Differential diagnosis:

These are other myeloproliferative disorders such as Polycythaemia Vera, Essential thrombocytopaenia, Myelofibrosis and leukemoid reactions which can present with features suggestive of CML.

Management:
There are 2 main types of therapy- supportive and definitive.
Supportive therapy includes
- counseling the patient on the nature of the disease
- duration and cost of the treatment[sometimes treatment might have to be delayed till the family's finances can bear the cost]
- complications of the definitive therapy
- Use of Allupurinol and intake of lots of water to facilitate speedy removal of toxic and chemotherapeutic agents

Definitive therapy & History
- In the 19th century, Fowler's solution containing

primarily Arsenic was used actively against CML cells[8].

- In the 1920, 1930 through 1950, total body or splenic radiation[8] was the only treatment used and life time expectation was 30 months.
- Busulphan [Myelaran®], because of its toxicity to stem cells , was introduced into the UK and offered the first definitive improvement to survival rates[median is $2^{1/2}$ - $3^{1/2}$ or 4 years].It is also cheap but its therapeutic effect especially in the killing of normal stem cells continues long after drug administration is stopped.
- Due to Busulphan's dangerous side effects, Hydroxurea [Hydrea®] became popular in 1960, made widely available in 1972, is a cell cycle-specific inhibitor of DNA as it is less toxic, is easily reversible, but requires additional doses to act longer.
- Cytosine arabinoside[Ara-c] is a good substitute for Busulphan.
- All the drugs above, combined or singly, have only haematologic action and cannot induce any cytogenetic remission. Hence Interferon-α came into use.
- New therapies including the use of Glivec [Imatinib mesylate] which is a tyrosine kinase inhibitor, Farnesyl transferase which blocks the localization of Ras proteins to the cell membrane and Arsenic trioxide [16], are all being tested with better median survival results.
- Glivec is effective in all stages of the disease. In the chronic phase, the standard dose is 400mg daily for as long as the patient can tolerate it. In accelerated and blastic phases, the dose is usually increased to 600mg daily until patient reverts back to chronic phase.
- Other agents occasionally used include melphalan, mercaptopurine, thioguanine, homoharringtonine[16].
- Bone marrow Transplantation, both allogeneic and autologous, is an alternative. However, the patients will still require high dose chemotherapy to suppress rejection. Moreover, it is very expensive.
- Splenectomy and leukopharesis techniques are employed to reduce excessive leukocytosis.

Conclusion:

CML is a relatively common disorder in Nigeria. OAUTHC is currently the only centre in West Africa for the implementation of the newest therapy (Glivec) that is effective in all stages of the disease. This undoubtedly indicates a need for extensive research and detailed studies targeted at improving access to treatment centres and experienced personnel.

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