CHRONIC MYELOGENOUS LEUKEMIA

Research Project / Library Assignment

submitted to the Department of Pathology

Government Medical College Ernakulam

By AKASH P SANTHOSH

2nd PROF. MBBS 2022 Batch

Government Medical College, Ernakulam

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DECLARATION

I hereby declare that this research project/ library assignment entitled "Chronic Myelogenous

Leukemia has been prepared by me under the guidance of Department of Pathology Government Medical College, Ernakulam and

is submitted to Department of Pathology, Government Medical College Ernakulam.

This has not been submitted by me to any other institutions or university.

The conclusions drawn are entirely my own.

Date:

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INTRODUCTION

Chronic myelogenous leukemia is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation. CML is one of the few cancers known to be caused by a single, specific genetic mutation. The disease is characterized by insidious onset of symptoms, progressive splenomegaly, anemia, leukocytosis and cytogenetically by the presence of Philadelphia chromosome in 90-95% of patients.

Study of cancer patterns in populations, however, can contribute substantially to knowledge about the origin of cancer. Major insights into the cause of cancer can be obtained by epidemiologic studies that relate particular environmental, hereditary and cultural influences to the occurrence of malignant neoplasms. Apart from the

occasional contribution of exposure to radiation, no other major predisposing "cause" for this leukemia has been identified. We do not know how precisely the BCR-ABL fusion gene is formed; it may in fact be a relatively common event as it can be found at extremely low levels in many normal persons and it only rarely occurs in pluripotent stem cells, where it causes leukemia.Newer researches are going on to identify possible aetiologies and risk factors for the development of Philadelphia chromosome and thence CML. There are several western studies regarding the clinical profile and risk factors of CML; but there is a paucity of Indian studies especially from Kerala.

Since the two populations are entirely different, clinical profile and risk factors has to be studied separately for better understanding.Imatinib mesylate is a competitive inhibitor at the ATP binding site of the Abl kinase in the inactive conformation, which leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction

REVIEW OF LITERATURE

Chronic myelogenous leukemia (CML)

Chronic myeloid leukemia (CML) is a clonal stern cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation". First case reports of Chronic Myeloid Leukemia were available in literature since 1845. The young man described by John Hughes Bennet in Edinburgh, who after being unwell for 20 months died of "suppuration of the blood" with an enormously enlarged spleen might have suffered from CML. Concurrently Rudolf Virchow in Berlin, wrote about "Weifs Blut" meaning white blood in German. The research over the next 100 years focused on its clinical and morphologic features of CML. The landmark study came in 1960 when Peter C. Nowell and David A. Hungerford documented an abnormal G group chromosome in cells from patients with CML. The new marker was later named the Philadelphia (Ph) chromosome in honor of the city in which it was discovered. This was the first time a consistent chromosome abnormality had been documented in a human malignancy. In 1973, Rowley

observed that the Ph chromosome resulted from a reciprocal translocation that also involved chromosome 9; the abnormality is now designated t (9;22)(q34;qll).

The application of molecular biologic techniques in the 1980s recognized the Ph chromosome as the cytogenetic result of a rearrangement of the ABL gene on chromosome 9 and the BCR gene on chromosome 22, which leads to the creation of a BCR-ABL fusion gene. The continued growth in our understanding of the role of BCR-ABL Chimeric protein in oncogenesis has made CML, a potentially curable disease.

Incidence and relationship to other myeloproliferative disorders

CML 0s principally a disease of adults with a yearly incidence of 1 in 100,000 in Western countries. There is an increasing frequency with age and a peak age of incidence of 53 years. Men are affected more often than women (3:2). It is uncommon in children and accounts for less than 5% of all childhood leukemias'.

CML 0s one of several chronic myeloproliferative diseases. Chronic myeloproliferative diseases are distinct, but closely related, clonal disorders of pluripotent stem cells in the marrow. In all chronic myeloproliferative diseases, the proliferative capacity of the neoplastic stem cell is not properly controlled and excessive hematopoiesis occurs initially. The neoplastic stem cell retains its ability to undergo complete differentiation, and as a result, a marked increase in the number of mature and immature cells in the blood and bone marrow occurs. These differentiated neoplastic cells generally have few, if any, morphologic or functional abnormalities.

WHO classification of chronic myeloproliferative diseases

- Chronic myelogenous leukemia [Ph chromosome (9;22) (q34;911), BCR/ABL positive].
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia (and the hyper eosinophilic syndrome)

- Polycythemia Vera
- Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
- Essential thrombocythemia
- Masto cytosis
- Chronic myeloproliferative disease, unclassifiable

Chronic myelogenous leukemia (CML)

In the WHO proposal, CML is defined specifically as a myeloproliferative disease that is characterized by the invariable presence of the Ph chromosome or the BCR/ABL fusion gene. Although in most cases the diagnosis is easily made from morphologic evaluation of the blood smear, confirmation by genetic studies is essential, particularly in view of the advent of therapy that targets the BCRJABL fusion protein.

WHO Criteria for accelerated and blast phases of CML , accelerated phase

Diagnose if one or more of the following is present:

1. Blasts 10% to 19% of peripheral blood white cells or bone marrow cells
2. Peripheral blood basophils at least 20%
3. Persistent thrombocytopenia (100 x 109/L) unrelated to therapy or persistent thrombocytosis (1000 09/L) unresponsive to therapy.
4. Increasing spleen size and increasing WBC count unresponsive to therapy.
5. Cytogenetic evidence of clonal evolution (the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML).

6. Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia.

CML, blast crisis:

Diagnose if one or more of following is present:

1. Blasts 20% or more of peripheral blood white cells or bone marrow cells
2. Extramedullary blast proliferation
3. Large foci or clusters of blasts in bone marrow biopsy

Chronic neutrophilic leukemia (CNL)

Fewer than 150 cases have been reported in the literature, and in a number of these cases CNL was found in association with another neoplasm, particularly myeloma. The normal cytogenetic studies and the "toxic" neutrophil morphology in most reported cases, raise the possibility that the neutrophilia is due to abnormal cytokine production by an associated tumor or abnormal inflammatory response. However, there are well characterized cases that do meet the criteria for CNL for which cytogenetic or molecular genetic studies have confirmed clonality of the neutrophil lineage. In view of these reports, the WHO included CNL in the CMPDS, with the recommendation that the possibility of an underlying disease be carefully excluded. If another neoplasm, such as myeloma, is present, the diagnosis of CNL should be made only if there is genetic evidence of a myeloid neoplasm.

Chronic eosinophilic leukemia or hyper eosinophilic syndrome

The diagnosis of CEL or HES can be made only after a number of infectious, inflammatory, and neoplastic diseases known to be associated with eosinophilia (including CML, AML with inv(16), other CMPDs, T-cell lymphoma, Hodgkin

lymphoma, and others) have been excluded. Then, if there is no evidence for clonality, the diagnosis of HES is preferred, whereas the finding of a clonal myeloid abnormality would support the diagnosis of CEL.

Chronic idiopathic myelofibrosis, prefibrotic stage

The criteria classically utilized for the diagnosis of CIMF include a leucoerythroblastic blood smear, organomegaly due to extramedullary hematopoiesis, and myelofibrosis of the bone marrow. The early prefibrotic phase of CIMF shares a number of clinical, laboratory, and even morphologic features with the early stages of polycythemia vera (PV) and with essential thrombocythemia (ET). However, the prominent neutrophil proliferation, decreased numbers of erythroid precursors, and marked atypia of the megakaryocyte lineage often aid in distinguishing the prefibrotic stage of CIMF from the other CMPDS. Although these findings must always be correlated with other clinical, laboratory, and genetic studies, the worse survival of CIMF in comparison with ET or PV indicates that recognition of this phase of CIMF is important.

Cytogenetics of CML

The Ph chromosome, the cytogenetic hallmark of CML, results from a reciprocal translocation of cytogenetic material after a break on chromosome 9 at band q34.1 that transposes the 30 segment of the ABL gene to the 50 segment of the bcr gene on chromosome 22 at band qll.21, resulting in the chimeric bcr-abl gene. It is found in approximately 95% of patients with CML. It is also observed in 5% of children and in 15% to 30% of adults with acute lymphocytic leukemia and in 2% of patients? with newly diagnosed acute myelocytic leukemia. Despite the presumed" specificity of the Ph chromosome and the bcr-abl gene, patients now have been found with typical clinical and hematologic characteristics of CML that lack the Ph chromosome but show the bcr-abl rearrangement13. It has been estimated that approximately 5% of patients with the phenotype of typical CML are Ph negative but BCILABL positive. The demonstration of the chimeric gene now becomes the sine qua non for the diagnosis of CML. The response to treatment and the course of disease of CML

patients who are Ph negative, BCR-ABL positive is the same as that of Ph-positive, BCR-ABL-positive patients.

Complex translocations involving three or more chromosomes sometimes may result in a "masked" Ph, which may account for the so-called Ph-negative, BCR-ABL-positive cases. There is no difference in survival in patients with standard compared with variant or complex translocations. Progression of CML from the chronic to the accelerated or acute phase is accompanied by additional cytogenetic abnormalities that occur more commonly in the myeloid than in the lymphoid transformation. The most common abnormalities include a second Ph chromosome, isochromosome 17, +19, or trisomy 8 (+8). Mutations or deletions of tumor-suppressor genes, such as pl6 and p53, may contribute to the malignant phenotype12. Sometimes aneuploid cells are found in routine cytogenetic studies; they do not increase in number and even with conventional therapy may regress. Lymphoid blast crises do not have specific aneuploid markers. Hypodiploidy is Common.

Philadelphia Chromosome-Negative CML

Approximately 10% of patients with a clinical and morphologic presentation consistent with CML are found not to have the Philadelphia chromosome on cytogenetic analysis. About half of these patients will have evidence of the BCR-ABL rearrangement, as noted above. Ph-negative, BCR ABL-negative patients in general are older and more often have thrombocytopenia, lower white blood cell counts, greater monocytosis, lower bone marrow myeloid: erythroid ratio, and less basophilia than BCR-ABL positive patients15. Patients in this BCR-ABL-negative group probably have a variety of hematologic disorders, including chronic myelomonocytic leukemia (CMML), as well as true BCR-ABL-negative, Ph-negative CML. The BCR-ABL negative, Ph-negative CML patient population is reported to have a low risk for blastic transformation, approximately 25%-50%16. However, the median survival of these patients is significantly shorter than that of patients with BCR-ABL-positive CML. The natural history of BCR-ABL-negative CML is characterized by progressive leukemic burden, extramedullary leukemic infiltrates, poor response to chemotherapy, and bone marrow failure.

Clinical presentation

The onset of CML is usually insidious, with most patients presenting in chronic phase. In the past, symptoms of vigorous hematopoiesis (fever, Sweats, bone pain, weight loss, and fatigue) or signs of extramedullary hematopoiesis (splenomegaly and left upper quadrant discomfort) caused patients to seek medical attention. Occasionally more unusual symptoms such as bleeding, thrombosis, arthralgia, leukemic infiltration in sites such as the skin, peptic ulceration, spinal cord compression, and priapism may be the primary presentation. However, with current medical practice it is becoming more common for patients to be diagnosed before the development of any symptoms because of periodic routine medical evaluation with physical examination and laboratory testing. Estimates now indicate that 10 to 30% of patients are diagnosed before the development of symptoms. About 10% of patients present in accelerated phase and another 10% of patients present in blast phase.

By following multiple clinical parameters in untreated patients, previous investigators have constructed regression curves describing the chronology of clinical events in CML. These observations indicate that approximately 6 years elapse from the time of the initial chromosomal translocation until patients become symptomatic. Once a leukocytosis is present, it takes approximately 19 months (range 7 to 24 months) for the white blood cell count to reach 100,000/uL. The median survival of patients with CML after diagnosis is about 4 to 5 years. Thus, the total duration of CML from its initiation appears to be about 10 years in the typical case. Increased absolute numbers of basophils are present in most patients early in the disease, even before the WBC is elevated. Anemia is not an early finding, but often thrombocytosis is noted. The leukocyte alkaline phosphatase level generally is low, even when the WBC Count is less than 20,000/uL, and falls further as the disease develops. The spleen rarely is palpable until the number of WBC exceeds 40,000/uL and symptoms usually appear when the WBC reaches levels between 30,0^0 and 90,000/uL.

At the time of presentation, the spleen varies in size, ranging from just a palpable tip to a mass filling the abdomen. Approximately 50% of patients have splenomegaly extending more than 10 cm below the costal margin at the time of diagnosis. Spleen size correlates reasonably well with the magnitude of the leukocyte count. The spleen is quite firm and usually nontender (unless splenic infarction is present), and

the hilum (notch) may be palpable. Hepatomegaly is less common. Splenic infarct is common, Sternal tenderness is a reliable sign of disease and usually is limited to a small area, most commonly the midbody (Ath intercostal space) of the sternum. If true sternal tenderness is present, the patient withdraws or complains spontaneously when firm pressure is applied to the tender area. Lymph nodes are palpable in most patients, but rarely are greater than 1 cm in largest diameter.

In chronic phase, the distinction must be made with reactive leukocytosis. The distinction between CML presenting in lymphoid blast crises and Ph (+) acute lymphocytic leukemia (ALT,) may be clinically difficult and additional diagnostic procedures are necessary. CML may also present in myeloid blast crisis, which may be distinguished from de novo AML using ancillary testing.

The progression to blast phase occurs at an approximate rate of 5% for the first year and 20 to 25% for each year thereafter. Most patients expire within 3 to 6 months once blast crisis develops. 50% of patients end up in myeloid blast crisis, about 30% in lymphoid blast crisis, 10 % in erythroid blast crisis and the rest is undifferentiated blast crisis. About 80% of patients die due to blast crisis and the rest due to unrelated illness.

Diagnosis Chronic Phase

The diagnosis of CML rests on the examination of a peripheral blood smear and marrow biopsy. The documentation of either a Ph chromosome by karyotypic analysis or the presence of the BCR-ABL translocation by Southern blot or polymerase chain reaction (PCR) assays confirms the diagnosis.

Peripheral Blood Findings

The most important histologic finding in the peripheral blood is a neutrophilic leukocytosis and basophilia. The leukocytosis ranges from 20,000/uL to more than

500,000/uL., with mean ranges of 134,000 to 225,000/uL in most studies. A decreased leukocyte alkaline phosphatase (LAP) is present as an early manifestation in almost all cases.

The leukocytosis is predominantly neutrophilic, with all' stages of neutrophilic maturation represented from myeloblast to segmented neutrophil. The myelocyte and segmented neutrophil usually predominate and all the neutrophilic precursors appear morphologically normal by light and electron microscopy. Pelger-Huet abnormalities may exist late in the disease. Myeloblasts do not usually exceed 3% of the total white blood count.

An absolute basophilia is invariably present and of critical importance; the diagnosis should be questioned without a documented Ph chromosome or BCR-ABL fusion product. Basophilia may also precede clinical manifestations by many years. There may be an eosinophilia as well, but its presence does not carry the diagnostic significance of the basophilia and neutrophilic leukocytosis. Occasional hybrid cells with mixed basophil-eosinophil granulation or mixed basophilic-mast cell granulation are found.

The marked leukocytosis in cases of CML typically is associated with an absolute monocytosis but relative monocytopenia. The mean percentage of monocytes is about 2% or less of the WBC count although the relative number of monocytes may increase with evolution to blast crisis. The absence of a marked monocytosis in the early phases of CML is helpful in distinguishing some cases from CMML, Absolute lymphocyte counts are variable, although a lymphocytosis is common.

Thrombocytosis is present in approximately half of cases; occasionally above 1,000,000/uL. Platelet counts of under 100,000/uL are very uncommon. The platelets may vary in appearance, occasionally being of large s0ze or diminished or absent granulation. Megakaryocytes are seen in the peripheral blood in approximately one-quarter of cases.

Most patients have a normochromic/normocytic anemia at the time of diagnosis, although normal or elevated hemoglobin levels are reported. As may be expected in proliferative, marrow-based processes, the severity of the anemia is directly proportional to the degree of leukocytosis. Minimal anisocytosis and poikilocytosis with occasional nucleated red blood cells are seen in most cases. A Coincidental

hemolytic anemia is rarely present. Significant abnormalities in RBC morphology should suggest an underlying RBC disorder or be part of the evolution to blast crisis.

Bone Marrow Findings

Marrow examination can be useful in distinguishing CML from other CMPDs and reactive processes. The bone marrow is markedly hypercellular predominantly because of a proliferation of neutrophilic precursors from myeloblasts to segmented neutrophils. The maturation sequence and morphology at each stage are normal, although the relative increase in myelocytes seen in the peripheral blood is also seen in the bone marrow. Myeloblasts do not usually exceed 5% of the marrow elements. The myeloid precursors usually are located in a periosteal location as seen in normal marrow. Increased numbers of basophils, eosinophils, hybrid cells, and their precursors as seen in the peripheral blood are also present.

Megakaryocytes are typically increased in number and occasionally clustered in groups of three or more in central intertrabecular regions. The megakaryocyte clustering is not as pronounced as it is in ET. The megakaryocytes of CML are slightly smaller than normal megakaryocytes and Occasional micromega karyocytes are present. Common or granulocytic CML has a decreased, normal, or slightly increased number of megakaryocytes whereas a marked increase in megakaryocytes may be called megakaryocyte CML. A clinical significance to this division has not been demonstrated.

Macrophages with coarse, granular, PAS-positive, cytoplasmic material (pseudo-Gaucher cells) are present in approximately one-third of patients. These inclusions are the result of increased lipid turnover from granulocytic membranes and are of three types: blue birefringent inclusions, the most common (Gaucher-like); blue nonbirefringent, sea-blue histiocytes; and gray green with birefringent. Iron stores in macrophages as detected by Prussian blue staining are decreased in virtually all cases, to amounts lower than in normal subjects.

Erythroid precursors may be present in increased, normal, or decreased numbers, although the myeloid to erythroid ratio is invariably increased. Erythroid precursors may be distributed unevenly as well, with virtually no erythroid cells in some microscopic fields and numerous in others.

Deposition of connective tissue as detected by reticulin or PAS stains is not noted in most cases. As a result, it is not surprising that most studies have indicated that reticulin fiber deposition is associated with a worse prognosis, although a small set of patients with marked fibrosis and early stage CML have been reported to have a prolonged course.

Cytogenetic Findings

Karyotypic analysis is usually best performed from the bone marrow material, although peripheral blood may be used. The finding of a simple or complex translocation between chromosomes 9 and 22, generally the t(9;22)(434;q|l), confirms the diagnosis, and 5 to 10% of the cases have a variant translocation leading to rearrangement of the BCR gene. Patients with variant and classic Ph-producing translocations are clinically and hematologically identical, and distinct from Ph () cases. Typically, the Ph chromosome remains the sole chromosomal abnormality throughout most of the chronic phase. In a small number of cases with clinical and morphologic features of CML, at (9:22) or some variant thereof is not identified by karyotypic analysis but may be demonstrated by molecular techniques such as Southern blot or PCR.

The variant Ph chromosomes fall into two subgroups: simple and Complex. In simple variant translocations, the segment from 22q is translocated onto a chromosome other than 9. Three or more chromosomes are involved in complex variant translocations. Although the disease appears identical among patients with classic and variant Ph chromosomes, there is Controversy whether the chromosomal break points and other molecular features are identical.

Although t(9;22) is the hallmark of CML, it is not exclusive to CML. Acute lymphoblastic leukemia (ALL) may be accompanied by a t(9;22) in 10 to 20% of adult and 2 to 5% of childhood cases. In addition, a t(9;22) appears to be found in some bona fide cases of de novo AML as well as very rare cases of lymphoma and myeloma. Recently, Ph(++) CNL has also been added to this group.

Ultrastructural Analysis and Immunophenotypic Findings

Flow cytometric analysis does not have a. significant role in the diagnosis of the chronic phase of CML because the phenotype of the cells in CML 0s the same as normal cells. The ultrastructural appearance of the majority of mature granulocytes of CML is the same as that of normal granulocytes. The neutrophil precursors show some differences from their normal counterparts, although none of the findings are diagnostic. Bundles of microfilaments, deep nuclear folds, and mitochondria in the perinuclear Hof are seen in myeloblasts and promyelocytes. Mixed-granule populations appreciated histologically are present by electron microscopy as well.

Extramedullary Disease

During the chronic phase, the cells of CML infiltrate the spleen and Liver. In the spleen the pulp cords are predominantly infiltrated and the Malpighian corpuscles diminish in prominence as the disease progresses. Foci of myelopoiesis may be seen in the sinusoids. This latter finding probably represents secondary extramedullary hematopoiesis and is not part of the primary disease process. Collections of infiltrating leukemic cells may also be seen in* hepatic sinuses. Lymphadenopathy should be worrisome for transformation to the terminal phase.

Blast Crisis or Accelerated Phase

CML usually transforms to a more aggressive disease after 2 to 4 years and occurs in at least two clinical manifestations: accelerated phase and blast crisis. Histologic, cytogenetic, and molecular findings accompany this transformation.

Histopathology

The transformation process may be abrupt, with a rapidly increasing percentage of blasts with a clinical course similar to de novo acute leukemia (blast crisis), or slower and more progressive, with marrow failure resulting in anemia and thrombocytopenia (accelerated phase). Blast crisis, an obvious cause of death, represents the transformation of CML to the equivalent of acute leukemia and is generally defined as more than 30% blasts in the peripheral blood or bone marrow

aspirate smear, or by microscopic identification of a large cluster of blasts in a marrow biopsy or extramedullary site biopsy. In approximately two thirds of cases of CML in blast transformation, the blasts are myeloid by traditional cytologic and immunophenotypic analysis. These myeloid cases can represent the spectrum of nonlymphocytic leukemias resembling myeloid (M-2), myelomonocytic (M4-5), erythroblastic (M6), or megakaryoblast (MI) leukemias. Auer rods are very rarely, if ever, observed. Cytochemical reactions with Sudan black and myeloperoxidase are markedly decreased and often absent, so negativity does not exclude the diagnosis of acute myeloblastic leukemia. Flow cytometric analysis demonstrates the presence of nonlymphocytic markers whereas electron microscopy demonstrates ultrastructural features (that is, granules) consistent with nonlymphocytic differentiation. These cases are usually negative for terminal deoxynucleotidyl transferase (TdT), although a significant number of TdT-positive myeloblastic cases have been reported.

In one-third of the cases of transformation the blasts have morphologic, immunophenotypic, and ultrastructural features of lymphoblasts. These blasts may exhibit the cytologic features of all types of AT J,, most Commonly LI or L2. Similar to the blasts in de novo ALL, Sudan black, myeloperoxidase, and chloroacetate esterase are negative. However, the blasts may have block periodic acid Schiff (PAS) positivity. Lymphoid antigens, usually B-cell antigens', as expressed on the cell surface. T-lymphoblasts arising in CML have been described, although they are very rare. The lymphoblasts" are TdT-positive in the majority of cases and have characteristics of B-cell precursor lymphoblasts. The majority are CD10 (CALLA) and CD19 without surface immunoglobulins. Cytoplasmic m heavy chains may be seen in Some cases.

Although the majority of cases of blast transformation are characterized by an increase of blasts in marrow and blood, a number of patients present with extramedullary manifestations. The cytologic, immunologic, and cytogenetic features of these cases are similar to those of other cases of blast transformation of CML occurring in the marrow.

Leukocyte Alkaline Phosphate

LAP values are often increased when CML transforms to blast crisis or accelerated phase. However, LAP values are quite variable, and are influenced by frequent coincident processes such as infection.

Cytogenetic Findings

The evolution of chronic phase CML to accelerated or blast phase is accompanied by cytogenetic changes in 70 to 80% of cases. The most common abnormalities in addition to the Ph chromosome are (in order of frequency): an additional Ph chromosome, trisomy, isochromosome 17, and +19. The second Ph seems to result from duplication of the first because additional abnormal chromosome 9 is not observed. The prognostic significance of additional chromosomal abnormalities without histologic changes may indicate a poor prognosis because these chromosome changes usually precede the hematologic manifestations by several months. Nevertheless, the development of additional chromosomal abnormalities alone 0s not specific for evolution to the terminal phase, as some patient's nave remained in chronic phase for prolonged periods.

Molecular Findings

Two molecular tests that detect the size or amount of the BCR-ABL mRNA transcript may be useful in evaluating transformation of CML, quantitative PCR, and the size of the BCR-ABL gene product.

Nutritional support for CM

Several nutrients, botanicals, and their derivatives show promising effects in the treatment of chronic myelogenous leukemia. All-trans retinoic acid, vitamin A, and vitamin D3 have shown potential benefit in patients with CML. In China, the flavonoid Indirubin is used to treat CML. In vitro studies show vitamin K2 and curcumin to inhibit CML cancer cell development. Patients with CML have been shown to be deficient in vitamin E and may have abnormalities in vitamin B12

metabolism. A decreased antioxidant status has also been found. Most nutrient research in CML is preliminary, warranting further study.

Prevention of Chronic Myeloid Leukemia

Cancer is largely a preventable illness. Two-thirds of cancer deaths in the U.S. can be linked to tobacco use, p00r diet, obesity, and lack of exercise. All of these factors can be modified, Nevertheless, an awareness of the opportunity to prevent cancer through changes in lifestyle is still under appreciated. The overwhelming majority of cases of CML cannot be prevented since we do not know the cause of this disease

Risk factors predisposing to malignancies

A risk factor is something that affects a person's chance of getting a disease such as cancer. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for a number of cancers. But risk factors are rarely absolute. Having a risk factor, or even several risk factors, does not mean that you will get the disease. And many people who get the disease may not have had any known risk factors. The chance of an individual developing cancer depends on both genetic and non-genetic factors. A genetic factor is an inherited, unchangeable trait, while a non-genetic factor is a variable in a person's environment, which can often be changed. Non-genetic factors may include diet, exercise, or exposure to other substances present in our surroundings. These non-genetic factors are often referred to as environmental factors. Some non-genetic factors play a role in facilitating the process of healthy cells turning cancerous (i.e. the correlation between smoking and lung cancer) while other cancers have no known environmental correlation but are known to have a genetic predisposition, meaning a person may be at higher risk for a certain cancer if a fairly member has that type of cancer.

Geographic and Environmental Factors

Remarkable differences can be found in the incidence and death rates of specific forms of cancer around the world8) For example, the death rate for stomach carcinoma in both men and women is seven to eight times higher in Japan than in the United States. In contrast, the death rate from carcinoma of the lung is slightly more than twice as great in the United States as in Japan, and in Belgium it is even higher than in the United States. There is high incidence of all malignancies especially hematological malignancies in Japan following atomic bomb explosion. Scientists have shown that chronic myeloid leukemia Occurs in Caucasians more often than in African-Americans. Skin cancer deaths, largely caused by melanomas, are six times more frequent in New Zealand than in Iceland, which is probably attributable to differences in sun exposure. Although racial predispositions cannot be ruled out, it is generally believed that most of these geographic differences are the Consequence of environmental influences. There is no paucity of environmental factors: They are found in the ambient environment, in the workplace, in food, and in personal practices.

The carcinogenicity of ultraviolet (UV) rays and many drugs are well known. Asbestos, vinyl chloride, and 2 naphthylamine can serve as examples of occupational hazards. The risks may be incurred in lifestyle and personal exposures (e.g. dietary influences). Alcohol abuse alone increase the risk of carcinomas of the Oro pharynx, larynx, and esophagus and through the intermediation of alcoholic cirrhosis, carcinoma of the liver. Smoking, particularly of cigarettes, has been implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, and bladder but most significantly is responsible for about 77% of lung cancer among men and 43% among Women. Cigarette smoking has been called the single most important environmental factor contributing to premature death in the United States Alcohol and tobacco together multiply the danger of incurring cancers in the upper aerodigestive tract. The risk of cervical cancer is linked to age at first intercourse and the number of sex partners. These associations point to a possible causal role for venereal transmission of cervical viral infections.

Age

Age is an important influence on the likelihood of being afflicted with cancer. Most malignancies occur in the later years of life. Some malignancies like Hodgkins's

lymphoma have bimodal age distribution. Each age group has its own predilection to certain forms of cancer. Here the striking increase in mortality from malignancies in the age group 55 to 74 years should be noted. The decline in deaths in the 75-year-and-over group merely reflects the dwindling population reaching this age. Also to be noted is that children under the age of 15 are not spared. Acute leukemia and neoplasms of the central nervous system are responsible for approximately 60% of these deaths.

Chemical carcinogens

Benzene is a principal component of light oil. Although use as solvent is discouraged, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents. Formerly it was widely used as solvent and fumigant (1) There are many studies about its role in leukemia and Hodgkin disease.

Ethylene Oxide widely used as ripening agent for fruits and nuts, in fumigants for foodstuffs and textiles, and in sterilant for hospital equipment is leukemogenic.

Radon and its decay products from decay of minerals containing uranium can be serious hazard in quarries and underground mines.

Arsenic and arsenic compounds a byproduct of metal smelting, Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips are known to cause Ca lung, skin and hemangiosarcoma.

Asbestos was formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire resistant textiles, friction materials (i.e. brake linings), underlayment and roofing papers, and floor tiles. But it is a risk factor for development of Ca Lung, mesothelioma and gastrointestinal tract malignancies.

Beryllium and beryllium compounds are used in missile fuel and space vehicles, Hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors. It is implicated in development of Ca Lung.

Cadmium and cadmium compounds (used in yellow pigments solders, batteries, metal plating), Chromium compounds (a component of metal alloys, paints, pigments, and preservatives), Nickel compounds (byproduct of stainless steel arc welding 12), and Vinyl chloride (refrigerant, adhesive for plastics) are proved to be carcinogenic.

Heredity

One frequently asked question is: "My mother and father both died of cancer. Does that mean I am doomed to get it?" Based on current knowledge, the answer must be carefully qualified. The evidence now indicates that for a large number of types of cancer, including the most common forms, there exist not only environmental influences, but als0 hereditary predispositions. For example, lung cancer is in most instances clearly related to cigarette Smoking, yet mortality from lung cancer has been shown to be four times greater among nonsmoking relatives (parents and siblings) of lung cancer patients than among nonsmoking relatives of controls.

Hereditary forms of cancers can be divided into three categories

Inherited Cancer Syndromes

Inherited cancer syndromes include several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor. The predisposition to these tumors shows an autosomal dominant pattern of inheritance. Childhood retinoblastoma is the most striking example in this category. Approximately 40% of retinoblastomas are familial. Carriers of this gene have a 10,000-fold increased risk of developing retinoblastoma, usually bilateral. They also have a bready increased risk of developing a second cancer, particularly osteogenic sarcoma. A cancer suppressor gene has been implicated in the pathogenesis of this tumor.

Tumors within this group are often associated with a specific marker phenotype. For example, there may be multiple benign tumors in the affected tissue, as 0Ccurs in familial polyposis of the colon and in MEN. Sometimes, there are abnormalities in

tissue that are not the target of transformation (e.g., Lisch nodules and cafe-au-lait spots in neurofibromatosis type 1. As in other autosomal dominant conditions, both incomplete penetrance and variable expressivity are noted.

Familial Cancers

Virtually all the common types of cancers that occur sporadically have also been reported to occur in familial forms. Examples include carcinomas of colon, breast, ovary, and brain. Features that characterize familial cancers include early age at onset, tumors arising in two or more close relatives of the index case, and sometimes multiple or bilateral tumors. Familial cancers are not associated with specific marker phenotypes. The transmission pattern of familial cancers is not clear. In general, sibs have a relative risk between 2 and 3. A segregation analysis of large families usually reveals that predisposition to the tumors is dominant, but multifactorial inheritance cannot be easily ruled out. Certain familial cancers can be linked to the inheritance of mutant genes. Examples include linkage of BRCA1 and BRCA2 genes to familial breast and ovarian cancers.

Autosomal Recessive Syndromes of Defective DNA Repair

Besides the dominantly inherited precancerous conditions, a small group of autosomal recessive disorders is collectively characterized by chromosomal or DNA instability. One of the best studied examples is ataxia telangiectasia in which DNA repair is defective. They are highly prone for leukemias and lymphomas

Acquired Preneoplastic Disorders

The only certain way of avoiding cancer is not to be born; to live is to incur the risk. The risk is greater than average, however, under many circumstances, as is evident from the predisposing influences discussed earlier. Certain clinical conditions are also important. Because cell replication is involved in cancerous transformation, regenerative, hyperplastic, and dysplastic proliferations are fertile soil for the origin of a malignant neoplasm. There is a well-defined association between certain forms

of endometrial hyperplasia and endometrial carcinoma and between cervical dysplasia and cervical carcinoma. The bronchial mucosal metaplasia and dysplasia of habitual cigarette smokers are ominous antecedents of bronchogenic carcinoma. About 80% of hepatocellular carcinomas arise in cirrhotic livers, which are characterized by active parenchymal regeneration. Other examples Could be offered, but although these settings constitute important predispositions, in the great majority of instance es they are not complicated by neoplasia.

Certain non-neoplastic disorders like the chronic atrophic gastritis of pernicious anemia; solar keratosis of the skin; chronic ulcerative colitis; and leukoplakia of the oral cavity, vulva, and penis have such a well-defined association with cancer that they have been termed precancerous conditions. This designation is somewhat unfortunate because in the great majority of instances no malignant neoplasm emerges. Nonetheless, the term persists because it calls attention to the increased risk. Analogously, certain forms of benign neoplasia also constitute precancerous conditions. The villous adenoma of the colon, as it increases in size, develops cancerous change in up to 50% of cases.

Risk factors of leukemias

There are several known risk factors for leukemia and this include ionizing radiation, benzene, ethylene oxide, 1,3-butadiene, and genetic and medical risk factors. For other agents considered, such as dioxins, pesticides, and heavy metals, evidence is lacking of a causal relationship between these agents and leukemia, despite numerous studies conducted worldwide. Similarly, the influence of genetic polymorphisms, specifically within the cytochrome P450 family, has been associated with lung cancer rather than leukemia. There are specific factors predisposing to childhood leukemias. They include genetic conditions like Down syndrome, Fanconi syndrome, Bloom syndrome, Diamond-Black fan anemia, Schwachman syndrome, Klinefelter syndrome, telangiectasia, Turner syndrome, Neurofibromatosis, Ataxia Severe combined immune deficiency and li-Fraumeni syndrome

Viruses have been causally associated with the rare hairy cell leukemia and adult T-cell leukemia. They have also been suspected to cause leukemoid in childhood and adolescence, but there is still little convincing evidence that they play an important role. Several studies have associated parental smoking with childho0d

leukemia. While many other parental occupational and/o personal exposures (including pesticides, benzene, solvents, petroleum products, and spray paints) have also been implicated in childhood leukemia, most relevant studies have used poor exposure measures, and nave inconsistent results9. Our study is aimed at analysis of various suspected risk factors in the development of chronic myeloid leukemia. Risk factors of chronic myeloid leukemia

Risk factors of chronic myeloid leukemia

At this time, researchers do not know what causes CML and are trying to solve this problem. Scientists know that CML occurs in males more often than in females and in Caucasians more often than in African-Americans. However, they cannot explain why one person gets CML and another does not. Because the average age at diagnosis is over 67 years, it is suspected that unknown environmental exposure over a long period of time is required to cause CML. By learning what causes this disease, researchers hope to understand better how to prevent and treat it.

Heredity or Genetic Factors

There are no cedar hereditary factors ass0ciated with CML. Identical twins of patients with CML are at no greater risk of developing CML than other siblings. his strongly suggests that environmental factors are much more important than genetic factors in the development of CML. It is a scientific mystery as to why only one of a pair of identical twins will develop CML, since the genetics are identical and environmental exposures are similar, if not the same.

HLA 0s the histocompatibility system that is used to match people for bone marrow, liver and kidney transplants. One study has found that a specific HLA type, DR4, is associated with a lower incidence of CML; however, researchers have not yet identified the reason for this decrease.

Studies showed reduced risk for chronic myeloid leukemia in individuals with the cytochrome P-450 gene polymorphism CYPIA1*2A", Most cancers can be attributed to environmental factors that act in conjunction with both genetic and acquired

susceptibility. It has been suggested that individuals possessing a modified ability to metabolize carcinogens are at increased risk for cancer. In fact, germ-line polymorphisms of genes encoding carcinogen metabolizing enzymes, namely, phase I cytochromes P-450 (CYPs) and phase II glutathione S-transferases (GSTS), have been shown to influence the risk of variety of disorders thought to be caused by environmental exposure to toxic agents, including Parkinson disease and cancers of the gastrointestinal tract, skin, bladder, cervix, and lung. In contrast to these solid tumors, the etiologic role of chemical carcinogens is less obvious for many hematologic malignancies.

Kraljevic et al used polymerase chain reaction to examine the relationship between BCR-ABL+ CML and genetic polymorphisms in the CYP1A1, GSTMI, and GSTT1 gene loci. Genomic DNA of 141 BCR-ABU CML cases (78 males, 63 females) was randomly selected from a large institutional DNA bank where DNA of German CML Study Group patients were collected.

Study showed a reduced risk for CML in individuals carrying the mutant allele CYPIA1*2A. This finding is explained by the elevated metabolizing activity associated with CYP1A1*2A, which results in enrichment of reactive intermediates of some carcinogens for example, polycyclic aromatic hydrocarbons (PAHs), in phase I of metabolism. These intermediates must be detoxified by the phase II enzymes such as GSTs.

The result that CYP1A1*2A is a protective factor against CML means (1) that genetic susceptibility may be relevant for CML risk (2) that environmental carcinogens seem to play a role in the etiology of CML, and (3) that the carcinogens relevant for CML risk might differ from carcinogens relevant for other malignancies, for example, PAHs. Moreover, even different hematologic malignancies seem to be preferentially attributed to different chemical carcinogens. Taken together with other results, the available knowledge of inherited genetic and environmentally acquired susceptibility might be relevant for predicting individual risk patterns for hematologic and other malignancies.

Interleukin-10 and interferon-gamma cytokine gene polymorphisms

The association of cytokine gene polymorphic with the development of chronic myelogenous leukemia (CML) and whether there is an ass0ciation between gene polymorphisms Th1 and Th2 or regulatory- type cytokines and CML was studied by scientist. The results suggest that the IL-10 GCC/ATA and IFN-y T/A polymorphisms are potential risk factors, and that the IFN-y A/A polymorphism is a protective factor for CML.

Environmental or Non-Genetic Factors

The fact that only one of a pair of identical twins usually develops CML suggests that finding the specific cause for leukemia will be difficult if not impossible. However, by studying large numbers of people all over the world, researchers have found certain factors that increase a person's risk of developing CML.

Possible leukemogens identified for CML

Benzene

Despite the inevitable focus on the steelworks and coke byproducts plant as a benzene source, petrol exhaust and tobacco smoke (the primary source of benzene for smokers, and relevant to non-smokers through passive smoking) are the most significant sources of benzene in urbanized populations (19- 27). It is also a solvent used in the rubber industry. Food and water are not major sources of benzene exposure and the possibility of contamination of the water supply with benzene from local sources 1s possible.

While other hematological malignancies have been associated with occupational benzene exposure, the evidence has been considered strongest for AML. However, a recent review concluded that the few available studies of leukemia cel-types do not indicate larger or more consistent elevations in risk for AML than for other cell-types. Contact with benzene for some years may increase CML risk.

Ionizing Radiation

Ionizing radiation is one of the most studied and ubiquitous carcinogens in our environment. The main basis for radiation protection recommendations is the study of survivors of the Japanese atomic bomb, a population exposed primarily at high dose rates?8,29),30 The primary public health concern, however, is the protection of people from relatively low dose, protracted or fractionated exposures such as those received by the public in the general procedures environment, by patients through repeated diagnostic and by radiation workers. **Radiotherapy given for treatment of cancer could increase risk of developing CML.**

Diagnostic X-rays are the largest man-made source of radiation exposure to the general population, contributing about 14% of the total annual exposure worldwide from all sources. Although diagnostic X-rays provide great benefits, the fact that their use involves some small risk of developing cancer is generally accepted. There are studies to estimate the extent of this risk on the basis of the annual number of diagnostic X-rays undertaken in the UK and in 14 other developed countries

Magnetic fields of high voltage power lines and risk of cancer

Over the past 18 years, there has been considerable interest in the possible link between electromagnetic fields and cancer, especially leukemia. The story of this highly publicized research has been marked by mystery, contradiction, and confusion. The hypothesized cause was exp0sure to extremely low Frequency magnetic fields generated by the electrical current in power lines. The movement of any electrical charge creates a magnetic field that can be measured. Even the 60-Hz residential electric current creates a very weak oscillating field, which, like all magnetic fields, penetrates living tissue. These low-frequency electromagnetic fields are known as nonionizing radiation, since the amount of energy in them is far below that required to break molecular bonds such as those in DNA.

Melatonin, a hormone produced primarily by the pineal gland, has been Suggested to have antitumor activities as well as a role in the regulation of circadian and seasonal rhythms". Evidence has accumulated which indicates that melatonin, at least when administrated exogenously, may suppress estrogen synthesis, possibly through reducing luteinizing hormone/follicle stimulating hormone (LH/FSH) secretion interfere with the binding of estrogen to its receptors expressed in breast

cancer cells in vitro ameliorate immune functions and act as a scavenger of free radicals. These findings suggest that elevated endogenous immunomodulation and/or alterations of reproductive hormones or free oncostatic radicals.

Wertheimer and Leeper" reported a nearly 3-fold increase of breast cancer risk among women under 55 years of age who lived near power lines, suggesting that magnetic field exposure had accelerated development and growth of breast cancer. It is not known which organs are primarily involved in sensing magnetic fields and changes in magnetic fields. Electrophysiological studies have shown that some of the intrinsic cells of the pineal gland may be affected by an earth-strength magnetic fields and that these cells respond with a depression of their electrical activity. Concerning the mechanism of "magneto sensitivity', one can assume that magnetic field has a direct effect upon the pineal gland because of the electric current induced inside the body

Stevens hypothesized that magnetic fields can affect pineal gland melatonin secretion in vivo, which, in turn, can influence mammary (breast) carcinogenesis. Since then, a number of experimental studies have been conducted in order to test this hypothesis. Kato et al. reported that exposure of albino (Wistar-King) rats for 6 weeks to 50 Hz MF at 1 uT suppressed melatonin concentrations, both during the day and night, in both the plasma and pineal gland. Similar studies done indicates that different animal species respond differentially to different parameters of time-varying magnetic fields

In vitro studies by Hill and Blask and Hill et al. demonstrated that melatonin at physiological levels inhibits MCF-7 human breast cancer cell

growth. Using MCF-7 cells Liburd (34) reported that magnetic fields inhibited the antiproliferative effects of the hormone, allowing the cancer cells to grow in the presence of melatonin,

Furthermore, Liburd" revealed the first possible biological mechanism linking magnetic fields exposure to calcium signaling, a fundamental Cell process 9overning many important cellular functions. However, the VCa2+ theory is now subject to debates

Therapy Related Chronic Myeloid Leukemia

Some of the drugs and radiation used to treat other types of cancer may increase an individual's risk of CML, Low-dose radiation used in the past to treat variety of non-malignant conditions has been associated with an increased incidence of leukemia, of which 20-30% were CML. Various chemotherapy and immunosuppressive drugs have been associated with an increase in CML. Radioactive iodine treatment of thyroid cancer is also associated with an increased incidence of CML. CML has also been reported after heart transplants were radiation therapy was given.

Viruses and Chronic Myeloid Leukemia

Scientists have identified viral agents that seems to increase the risk for leukemias. Epstein Bar virus is a well-known risk factor for Burkitt's lymphoma. However, this has no known association with common forms of leukemia including CML

Diet

Diet is a fertile area for immediate individual and strict intervention to decrease the risk of certain cancers. Numerous studies have provided a wealth of often-contradictory information about the protective factors of different foods

There is Convincing evidence that excess body fat substantially increases the risk for many types of cancer. While much of the cancer-related nutrition information cautions against a high-fat diet, the real culprit may be an excess of calories. Studies indicate that there is little, any, relationship between body fat and rat composition of the diet. These studies show that excessive caloric intake from both fats and carbohydrates lead to the same result of excess b0dy rat. The ideal way to avoid excess body fat is to limit caloric intake and/or balance caloric intake with ample exercise.

It is still important, however, to limit fat intake, as evidence still Supports a relationship between cancer and polyunsaturated, saturated and animal fats. Specifically, studies show that high consumption of red meat and dairy products can

increase the risk of certain cancers. One strategy for positive dietary change is to replace red meat with chicken, fish, nuts and legumes.

High fruit and vegetable consumption has been associated with a reduced risk for developing different cancers. This may be a result of potentially protective factors such as carotenoids, folic acid, vitamin C, flavonoids, phytoestrogens and isothiocyanates, Theo are often referred to as antioxidants.

There is strong evidence that moderate to high alcohol consumption also increases the risk of certain cancers. One reason for this relationship may be that alcohol interferes with the availability of folic acid. Alcohol in Combination with tobacco creates an even greater risk of certain types of cancer.

Exercise

Higher levels of physical activity may reduce the incidence of some cancers, according to researchers at Harvard, if the entire population increased their level or physical activity by 30 minutes of brisk walking per day (or the equivalent energy expenditure in other activities), observe a 15% reduction in the incidence of colon cancer.

TREATMENT

The therapy of CML is changing rapidly because we have a proven Curative treatment (allogeneic transplantation) that has significant toxicity and a new targeted treatment (imatinib) with outstanding outcome based on 8-year follow-up data. It is recommended to start with TK inhibitors and reserving allogeneic transplantation for those who develop imatinib resistance The goal of therapy in CML is to achieve prolonged, durable, nonneoplastic, nonclonal hematopoiesis, which entails the eradication of any remission residual cells containing the BCR-Abl 1 transcript. Goal is complete molecular remission and cure.

Imatinib mesylate (Gleevec) functions through competitive inhibition the ATP-binding site of the Abl kinase in the inactive conformation, which leads to

inhibition of tyrosine phosphorylation of proteins involved in Bcr-Abl signal transduction. It shows specificity for Bcr-Abl, the receptor for platelet derived growth factor, and Kit TK. Imatinib induces apoptosis in cells expressing Bcr-Abil.

In newly diagnosed CML, Imatinib (400 mg/d) is more effective than TEN- and cytarabine. The complete hematologic remission rate of patients treated with Imatinib was 95%. The complete cytogenetic remission rate at 18 months was 76%.

Molecular response can be used as a treatment goal in CML. NCCN milestones, chronic-phase CML patients who do not achieve any cytogenetic remission following 6 months of Imatinib should be offered other treatment approaches while in the ELN milestones, the same recommendation is offered following 3 months of Imatinib treatment. Progression to accelerated/blastic phases of the disease was noted in 3% of patients treated with Imatinib as Compared to 8.5% of patients treated with IFN- and cytarabine during the first year. The annual incidence of disease progression on Imatinib decreased gradually to <15 during the fourth year and beyond, and no patient who achieved major molecular response by 12 months progressed to the accelerated / blastics phases of the disease.

The treatment landscape for CML has undergone a significant transformation since the introduction of targeted therapies. The first-line therapy for newly diagnosed CML is imatinib mesylate (Gleevec), a tyrosine kinase inhibitor (TKI) that selectively inhibits the BCR-ABL tyrosine kinase. Imatinib's mechanism of action involves competitive inhibition of the ATP-binding site of the BCR-ABL protein, thereby blocking downstream signaling pathways responsible for cell growth and survival.

The recommended starting dose of imatinib is 400 mg taken orally once daily. This regimen is based on pivotal clinical trials that demonstrated its effectiveness and tolerability. For patients in the chronic phase of CML, imatinib has achieved a complete hematologic remission rate of approximately 95%. This high remission rate signifies normalization of blood counts and resolution of symptoms, reflecting the drug's potent anti-leukemic activity.

In addition to hematologic response, imatinib treatment has demonstrated substantial cytogenetic efficacy. After 18 months of therapy, around 76% of patients achieve complete cytogenetic remission, characterized by the absence of Philadelphia chromosome-positive cells in bone marrow samples. This outcome is a critical indicator of treatment success and is associated with improved long-term survival.

Molecular monitoring plays a vital role in the management of CML. The achievement of a major molecular response (MMR)—defined as a reduction of BCR-ABL transcript levels to ≤0.1% on the International Scale—is an important treatment milestone. Monitoring BCR-ABL levels through quantitative polymerase chain reaction (qPCR) is essential for assessing therapeutic effectiveness and determining whether treatment modifications are necessary.

Guidelines from the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) provide clear recommendations for monitoring treatment response. According to NCCN, patients who do not achieve cytogenetic remission by six months of imatinib therapy should be considered for alternative treatments. Similarly, the ELN recommends reevaluation of therapy if there is no cytogenetic response after three months.

Resistance to imatinib can develop in some patients, often due to point mutations in the BCR-ABL gene. These mutations can alter the structure of the kinase, leading to decreased sensitivity to imatinib. In cases of imatinib resistance or intolerance, second-generation TKIs, such as dasatinib and nilotinib, are valuable alternatives. These agents exhibit greater potency and have activity against a broader range of BCR-ABL mutations, making them crucial options for treatment-experienced patients.

For patients who progress to advanced phases of CML or develop resistance to TKIs, allogeneic hematopoietic stem cell transplantation (HSCT) remains a potentially curative option. HSCT involves the replacement of the patient's malignant

hematopoietic cells with healthy stem cells from a compatible donor. Although HSCT can offer a cure, it carries significant risks, including graft-versus-host disease and other complications. Therefore, careful patient selection and thorough pre-transplant evaluation are essential to optimize outcomes.

Clinical studies have shown that the incidence of disease progression has dramatically decreased with the introduction of imatinib. Approximately 3% of patients treated with imatinib progress to accelerated or blast phases during the first year, a significant improvement compared to historical data from earlier treatment modalities. Additionally, the annual incidence of disease progression decreases over time, with no patients who achieve MMR by 12 months advancing to more aggressive phases of the disease.

The overarching goal of CML treatment is to achieve prolonged, durable nonneoplastic hematopoiesis while eradicating residual BCR-ABL-positive cells. Achieving complete molecular remission (CMR)—defined as the absence of detectable BCR-ABL transcripts in blood and bone marrow—remains the ultimate objective. CMR is associated with improved long-term outcomes and overall survival, highlighting the importance of achieving deep molecular responses.

Supportive care is an essential component of the comprehensive management of CML. This includes the management of treatment-related adverse effects, such as gastrointestinal symptoms, fluid retention, and potential impacts on metabolic parameters. Addressing these issues is critical for maintaining patient quality of life and ensuring adherence to therapy.

Emerging research continues to explore innovative treatment strategies for CML. This includes the development of newer agents, combination therapies, and potential strategies for treatment-free remission. The goal is to enhance treatment efficacy while minimizing toxicity, which is particularly important given the chronic nature of CML and the need for long-term management.

As we move forward, the treatment of CML is expected to become even more personalized, incorporating genetic profiling and biomarker assessment to tailor therapies to individual patients. Ongoing clinical trials will likely yield new insights into optimal treatment regimens and strategies for overcoming resistance.

CONCLUSION

The landscape of Chronic Myeloid Leukemia (CML) treatment has undergone a transformative evolution, significantly impacting patient outcomes and survival rates. This research has provided an extensive overview of CML, highlighting its classification, molecular pathogenesis, and the advancements in therapeutic strategies that have redefined management paradigms.

CML is classified into three phases: chronic, accelerated, and blast crisis, with the chronic phase being the most prevalent at diagnosis. The pathogenesis is primarily driven by the BCR-ABL fusion protein, resulting from the Philadelphia chromosome, which initiates a cascade of signaling pathways that promote proliferation and inhibit apoptosis. Understanding this molecular basis has been instrumental in developing targeted therapies, particularly tyrosine kinase inhibitors (TKIs).

The introduction of imatinib mesylate marked a watershed moment in CML treatment, achieving high rates of complete hematologic and cytogenetic responses. Subsequent generations of TKIs, such as dasatinib and nilotinib, have expanded treatment options, particularly for patients with imatinib resistance or intolerance. These advancements have emphasized the importance of personalized medicine, where treatment is tailored to individual patient profiles based on molecular and genetic characteristics.

Regular monitoring of treatment response through molecular and cytogenetic assessments has become standard practice, allowing for timely interventions and adjustments in therapy. The goal of achieving major and complete molecular remissions is now a key focus, directly correlating with improved long-term outcomes and overall survival.

Despite these successes, challenges remain in managing resistance and advanced disease phases. Ongoing research is crucial to further understand the mechanisms underlying resistance and to develop novel therapeutic strategies that can overcome these hurdles. Allogeneic hematopoietic stem cell transplantation remains a viable option for selected patients, offering a potential cure but also posing significant risks.

As we look to the future, the integration of cutting-edge technologies, such as next-generation sequencing and personalized genomic profiling, holds promise for refining treatment strategies and enhancing patient care. The goal is to transition from effective management of CML to achieving durable cures, allowing patients to live longer, healthier lives free from the burdens of this disease.

In summary, the advancements in CML treatment reflect a remarkable journey from traditional chemotherapy to targeted therapies, underscoring the importance of molecular understanding in shaping treatment paradigms. The commitment to continuous research and innovation will be essential in overcoming existing challenges and paving the way for future breakthroughs in CML management. As we advance, the ultimate objective remains clear: to transform CML from a chronic condition into a curable disease.

BIBLIOGRAPHY

1. Champlin RE, Golde DW. Chronic myelogenous leukemia: Recent advances. Blood 1985; 65:1039-47,

2. Kantarjian HM, Talpaz M, Gutterman JU. Chronic myelogenous leukemia: Past, present, and future. Hematol Pathol 1988; 2:91-120.

3. Rowe JM, Lichtman MA. Hyperleukocytosis and leukocytosis: Common features of childhood chronic myelogenous leukemia. Blood 1984;63: 1230-4

4. Vardiman JW, Harris NL, Brunning RD The World Health Organization (WHO) classification of the myeloid neoplasms Blood, 2002;100: (7) 2292-23001.

5. Silver. RT. Chronic Myeloid Leukemia, Hematol Oncol Clin N Am 17 (2003) 1159-1173.

6. Kolibaba KS, Druker BJ, Current Status of Treatment for Chronic Myelogenous Leukemia Medscape General Medicine 2(2), 2000. Medscape

7. Steriti R Nutritional Support for Chronic Myelogenous antj other Leukemias: A Review of the Scientific Literature Altern Med Rev 2002;7(5):404-409.

8. Landis SH, et al: Cancer statistics, 1998. Cancer J Clin 48:6,1998

9. Howe GR, Burch JD, Miller AB, et al. Tobacco use, occupation coffee, various nutrients, and bladder cancer. J Natl Cancer Inst.1980; 64:701-713.

10. Lee DJ. LeBlanc W. Fleming LE Gomez-Marin O.Pitman T.Trends in US smoking rates in occupational groups: the national health interview survey 1987-1994.J Occup Environ Med 2004;46:538-48

11. World Health Organization, Benzene (Environmental Health Criteria No.150) Geneva: International Program Meon chemical safety, 1993.

12. Cecchi F, Bulatti E, Kriebel D, Nastasi L, Santucci Adenocarcinoma of the nose and paranasal sinuses in shoemakers and wood workers in the province of Florence, Italy (1963-77). Brit 3 Ind Med 1980;37-222-5.

13. Ponder BAJ: Genetic predisposition to cancer. In Holland JF,et al (eds): Cancer Medicine, 4th ed. Baltimore, Williams & Wilkins, 1997, p245.

14. Lavin MF, Shiloh Y: The genetic defect in ataxia-telangiectasia. Ann Rev Immunol 15:177,1997.

15. Evans SC, Lozono G: The Li-Fraumeni syndrome: an Inherited susceptibility to cancer. Mol Med Today 3:390,1997.

16. Miligi L, Seniori Costantini A, Crosignani P, et al. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. Am J Ind Med. 1999;36: 60-69.

17. Wormhoudt LW, Commandeur JNM, Vermeulen NPE. Genetic polymorphisms of human N-acetyltransferase, cytochrome P450, glutathione-S-transferase, and epoxide hydrolase enzymes: relevance to xenobiotic metabolism and toxicity. Crit Rev Toxicol 1999; 29: 59-124.

18. Perera FP: Environment and cancer: who are susceptible? Science 278:1068,1997.

19. World Health Organization. Benzene (Environmental Health Criteria No. 150). Geneva: International Programme on Chemical Safety, 1993.

20. In SN, Hayes RB, Linet MS, LI GL, et al. A cohort study of cancer among benzene-exposed workers in China: overall results. Am J Indust Med 1996, 29: 227-235.

21. Hayes RB, Yin S-N et al. Benzene and the dose-related incidence of hematologic neoplasms in China. / Natl Cancer Inst 1997; 89: 1065-1071.

22. Rinsky RA, Alexander B et al. Benzene and leukaemia: an epidemiological risk assessment. NEngl J Med 1987; 136: 1044-1050.

23. Christie D, Robinson K. A prospective study in the Australian petroleum industry. Br J Indust Med1991; 48: 507-510.

24. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene Dose response analyses. Br J Indust Med 1981; 44: 382-395.

25. Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Indust Med 1997; 31: 287-295.

26. Boffetta, Paolo MD et al. Risk of Acute Myeloid Leukemia After Exposure to Diesel Exhaust: A Review of the Epidemiologic Evidence. Journal of Occupational & Environmental Medicine. 2004; 46(10):1076-1083.

27. Insky RA, Alexander B, Smith MD, Hornung R, et al. Benzene and leukaemia: an epidemiological risk assessment. N Engl J Med 1987; 136:1044-1050

28. E Cardis et al. Risk of cancer after low doses of lontzing radiation retrospective cohort study in 15 countries BM) 2005231-77090

29. Berrington de Gonzalez A, Darby S. Risk of cafeer from diagnostic X-rays estimates for the UK and 14 other countries. Lancet2004063: 345-51

30. Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Parti. Cancer: 1950-1990. RadiatRes 1996; 146:1-27,

31. Donadieu, J., Roudier, C., Saguintah; M., Maccia, C, Chiron, R. (2007). Estimation of the Radiation Dose from Thoracic CT scans in a Cystic Fibrosis Population. Chest 132: 1233-1238.

32. Pia K Verkasalo, Eero Pukkala et al. Magnetic fields of high voltage power lines and risk of cancer in Finnish adults: nationwide cohort study. BMJ 1996; 313:1047-1051.

33. Wertheimer, N. and Leeper, E. Adult cancer related to electrical wires near the home. Int. J. Epidemiol., 11, 345-355.

34. Liburdy, R.P. (1992) Calcium signaling in lymphocytes and ELF fields. FEBS Lett., 301, 53-59.

35. Lindstrom, E., Lindstrom, P., BerglundA, Hansson, K. and Lundgen, E. (1993) Intracellular calcium oscillations in a T-cell line by a weak 50 Hz magnetic

field. /. Cell Physiol., 156, 395-398.

36. Alexander FE. Viruses, clusters and clustering in childhood leukaemia: a new perspective? Eur J Cancer 1993; 29A: 1424-1443.

37. Bjork J, Albin M, Welinder H, Tinnerberg H, Mauritzson N, Kauppinen T. Are occupational, hobby, or lifestyle exposures associated with

Philadelphia chromosome positive chronic myeloid leukaemia? Occup Environ Med. 2001; 58:722-727,

38. HARRISON'S Principles of Internal Medicine, 18th edition

39. DAVIDSON'S Principles and Practice of Medicine 20th edition

40. Current Medical Diagnosis and Treatment

41. Kumar L, Kumari M, Kumar P, Kochupillai V. Chronic Myeloid Leukemia: An Update: Indian Journal of Hemat and Blood transf. 2002, 21 (2) 44-49.

42. Study of clinical Profile of CML and assessment of response to Imatinib Rajendra Varaprasad, Krishna Prasad A, Senthil A Rajappa.Nizam's Institute of Medical Sciences, Hyderabad. APICON 2009, JAPI-2009

43. Chronic phase CML: Response to Imatinib and significance of Sokal score, age, disease duration in predicting the hematological and cytogenetic response. M Usman, N N Syed, Kakepoto, Adil SN. Aga Khan University Karachi, Orginal article from JAPI Vol 55, Feb 2007

44. Ichiro Wakabayashi, Kunihiro Sakamoto et al. Case-Control Study on Risk Factors for Leukemia in a District of Japan. Internal Medicine Vol. 33, No. 4 (April 1994).

45. E Cardis et al Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ. 2005 July 9; 331 (7508): 77.

46. Brenner, D. J., Hall, E. J. (2007). Computed Tomography - An Increasing Source of Radiation Exposure. NEJM 357: 2277-2284.

47. Maria Feychting, Michael Alhbom et al Magnetic Fields Cancer in Children Residing Near Swedish Fligh-voltage Power Lines American Journal of Epidemiology Vol. 138, No. 7; 457. 481.

48.J Bjork, M Albin et alAre occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukaemia? Occup Environ Med 2001; 58:722-727

49. Dominique Pobel Jean-Francois Vielet al. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited BMJ 1997;314:101 (11 January

50. Erera FP. Environment and cancer: who are susceptible? Science. 1997; 278:1068-1073

51. Imatinib Response in CML, University of Texas, Dep. Of Leukemia Am J of Haematology 2003 Aug 73(4)

52. Treatment Response of Imatinib mesylate in 32 proven cases of CML, KMC Mangalore, Gupta A, Prasad K, Thomas),japi 2009