CHRONIC MYELOID LEUKEMIA

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CHRONIC MYELOID LEUKEMIA

INCIDENCE

- The incidence of CML is 1.5 per 100,000 people per year .
- The incidence increases slowly with age until the middle forties when it starts to rise rapidly.

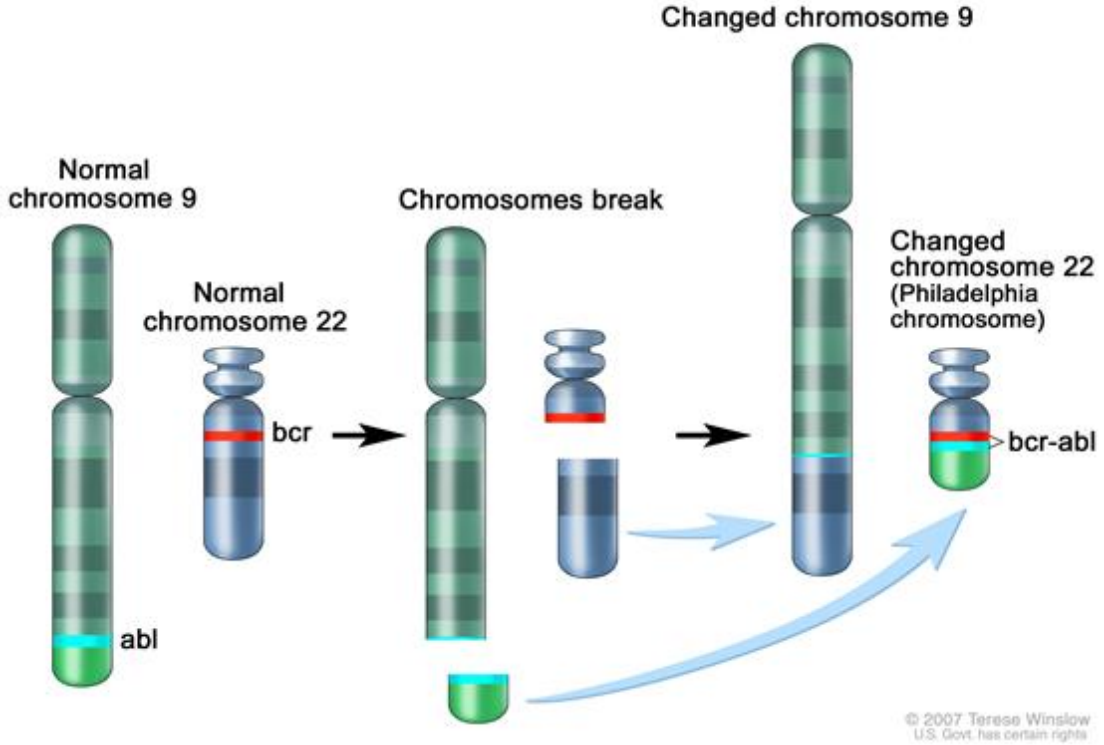
Definition

- The diagnosis of CML is established by identifying a clonal expansion of hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22.

- This translocation results in the head to tail fusion of the breakpoint cluster gene(BCR) on chromosome 22q11 with the ABL1 gene on chromosome 9q34.

- Untreated the disease is charecterised by the inevitable transition from a chronic phase to an accelerated phase and on to blast crisis in a median of 4 yrs.

PHILADELPHIA CHROMOSOME



Pathophysiology

- The chimeric gene is transcribed into a hybrid BCR-ABL1 mRNA in which exon 1 of ABL 1 is replaced by variable numbers of 5'BCR exons.

- Bcr-Abl fusion proteins,p210,are produced that contain NH2-terminal domains of Bcr and the -COOH terminals of Abl.

- Bcr-Abl fusion proteins can transform hematopoietic progenitor cells in vitro.

- Attachment of BCR sequences to ABL1 results in three critical functional changes.
- The Abl protein becomes constitutively active as a tyrosine kinase enzyme, activating downstream kinases that prevent apoptosis.
- The DNA protein binding activity of Abl is attenuated .
- The binding of Abl to cytoskeletal actin microfilaments is enhanced.

DISEASE PROGRESSION

- Chromosomal instability of the malignant clone resulting in the acquisition of an additional t(9;22),trisomy 8 17p-(TP53 loss) is a basic feature of CML.
- Acquisition of these additional genetic and/or molecular abnormalities is critical to the phenotypic transformation.
- Progressive de novo DNA methylation at the BCR-ABL1 locus and hypomethylation of LINE1 retrotransposon promoter herald blastic transformation.

- Interleukin 1beta may be involved in the progression of CML to blastic phase.
- Functional activation of the tumour suppressor protein phosphatase A2 may be required for blastic transformation.
- CML that develops resistance to imatinib is at an increased risk of progressing to accelerated blast crisis.

CLINICAL PRESENTATION

- The clinical onset of the chronic phase is generally insidious.
- Accordingly, some patients are diagnosed, while still asymptomatic, during health-screening tests;
- other patients present with fatigue, malaise, and weight loss or have symptoms resulting from splenic enlargement, such as early satiety and left upper quadrant pain or mass.
- Less common are features related to granulocyte or platelet dysfunction, such as infections, thrombosis, or bleeding.

- Occasionally, patients present with leukostatic manifestations due to severe leukocytosis or thrombosis such as vasoocclusive disease, cerebrovascular accidents, myocardial infarction, venous thrombosis, priapism, visual disturbances, and pulmonary insufficiency

- Progression of CML is associated with worsening symptoms.
- Unexplained fever,significant weight loss,increassing dose requirement of drugs,bone and joint pain,bleeding,thrombosis and infections suggest transformation into accelerated or blastic phases.
- Less than 10-15% of newly diagnosed cases present with accelerated disease or with denovo blastic phase CML.

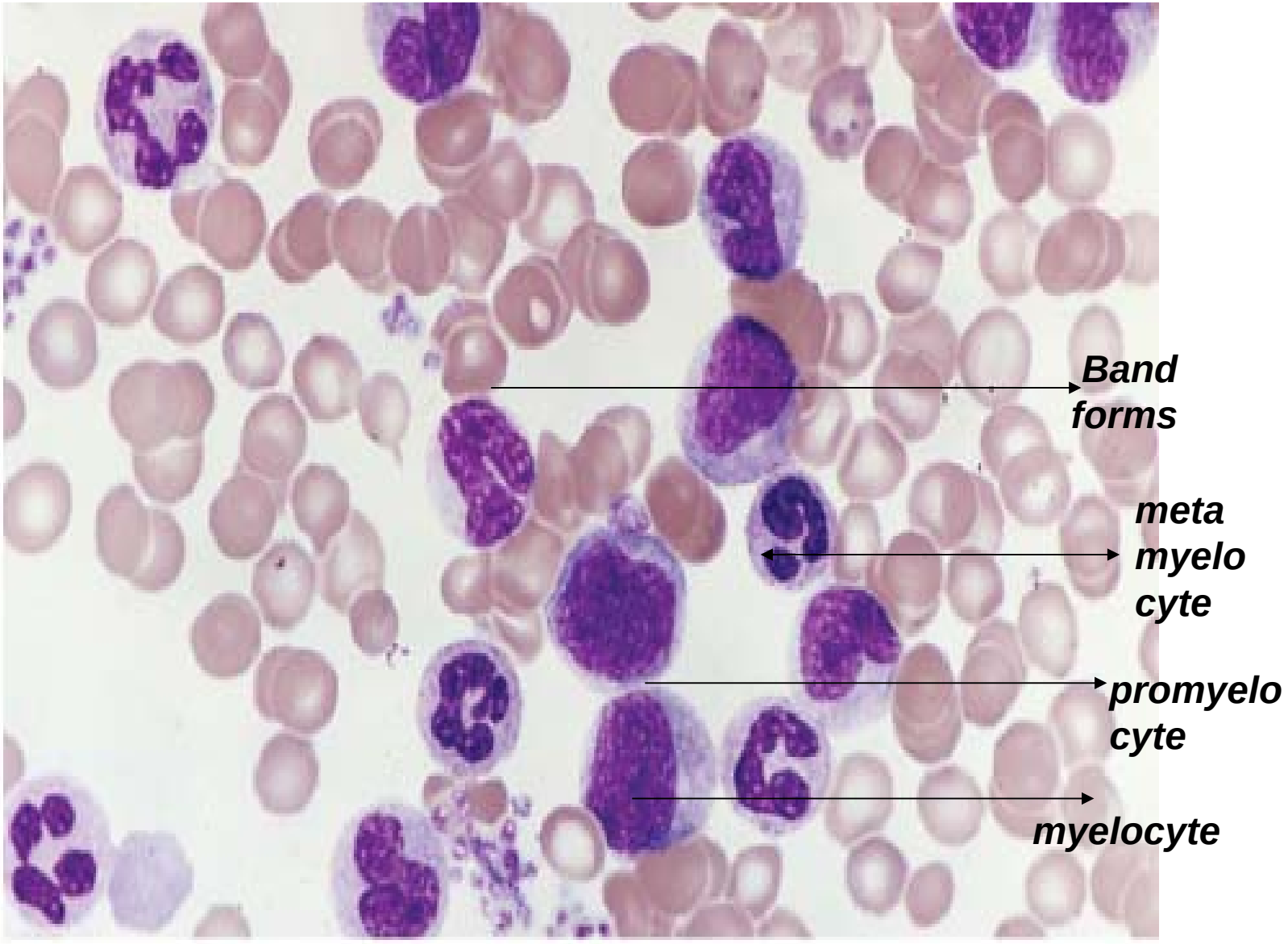
PHYSICAL FINDINGS

- Minimal to moderate splenomegaly is the most common physical finding.
- Mild hepatomegaly is found occasionally.
- Persistant splenomegaly despite continued therapy is a sign of disease acceleration.
- Lymphadenopathy and myeloid sarcomas are unusual except late in the course of the disease.When present,the prognosis is poor.

HEMATOLOGIC FINDINGS

- Elevated white blood (cell) counts (WBCs), with increases in both immature and mature granulocytes, are present at diagnosis.
- Usually <5% circulating blasts and <10% blasts and promyelocytes are noted, with the majority of cells being myelocytes, metamyelocytes, and band forms.
- Platelet counts are almost always elevated at diagnosis, and a mild degree of normocytic normochromic anemia is present.

- Leukocyte alkaline phosphatase is low in CML cells.
- Phagocytic functions are usually normal at diagnosis and remain normal during the chronic phase.
- Histamine production secondary to basophilia is increased in later stages, causing pruritus, diarrhea, and flushing.



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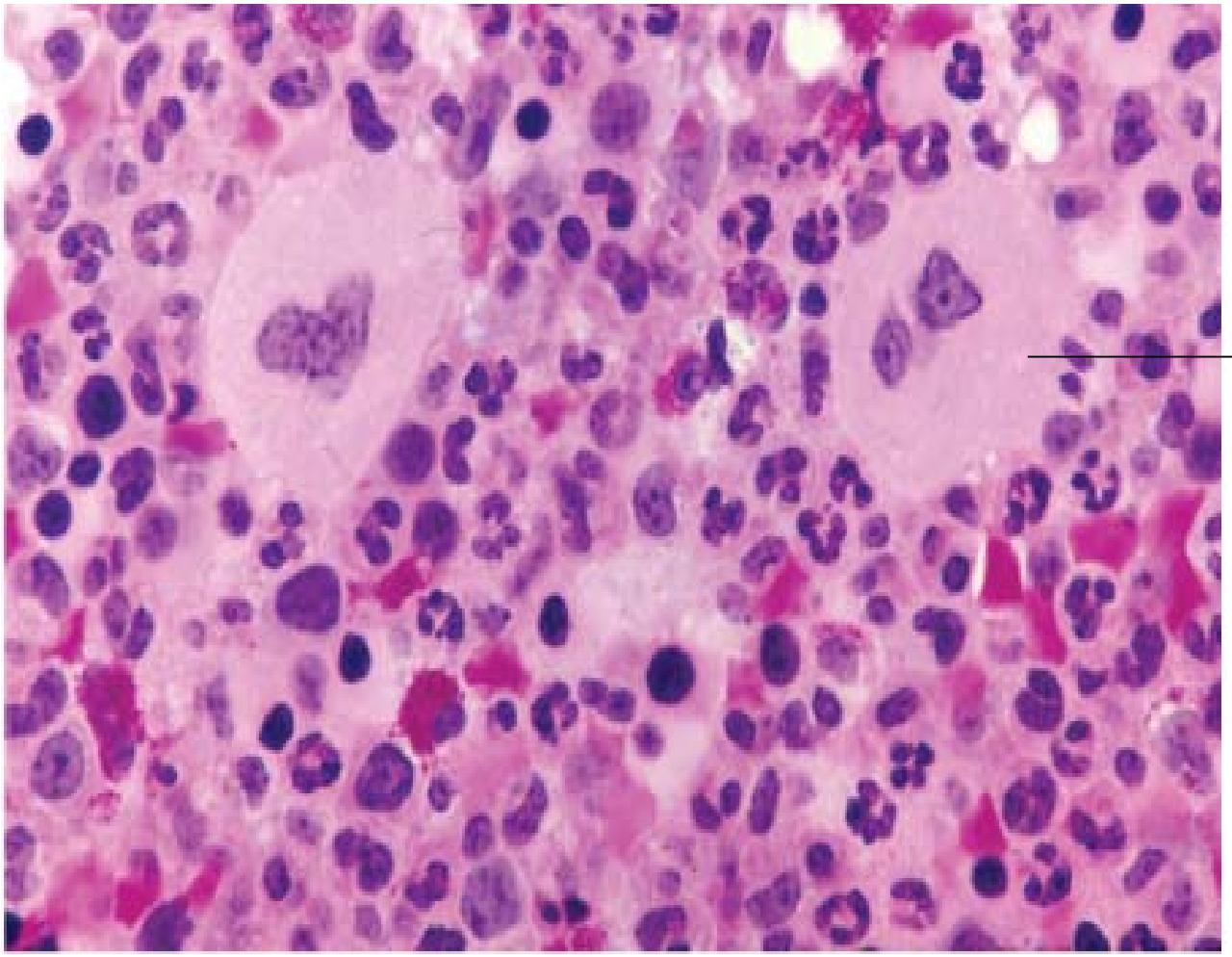
BONE MARROW

- At diagnosis, bone marrow cellularity is increased, with an increased myeloid-to-erythroid ratio.
- The marrow blast percentage is generally normal or slightly elevated.
- Marrow or blood basophilia, eosinophilia, and monocytosis may be present.
- While collagenfibrosis in the marrow is unusual at presentation, significant degrees of reticulin stain–measured fibrosis are noted in about half of the patients.

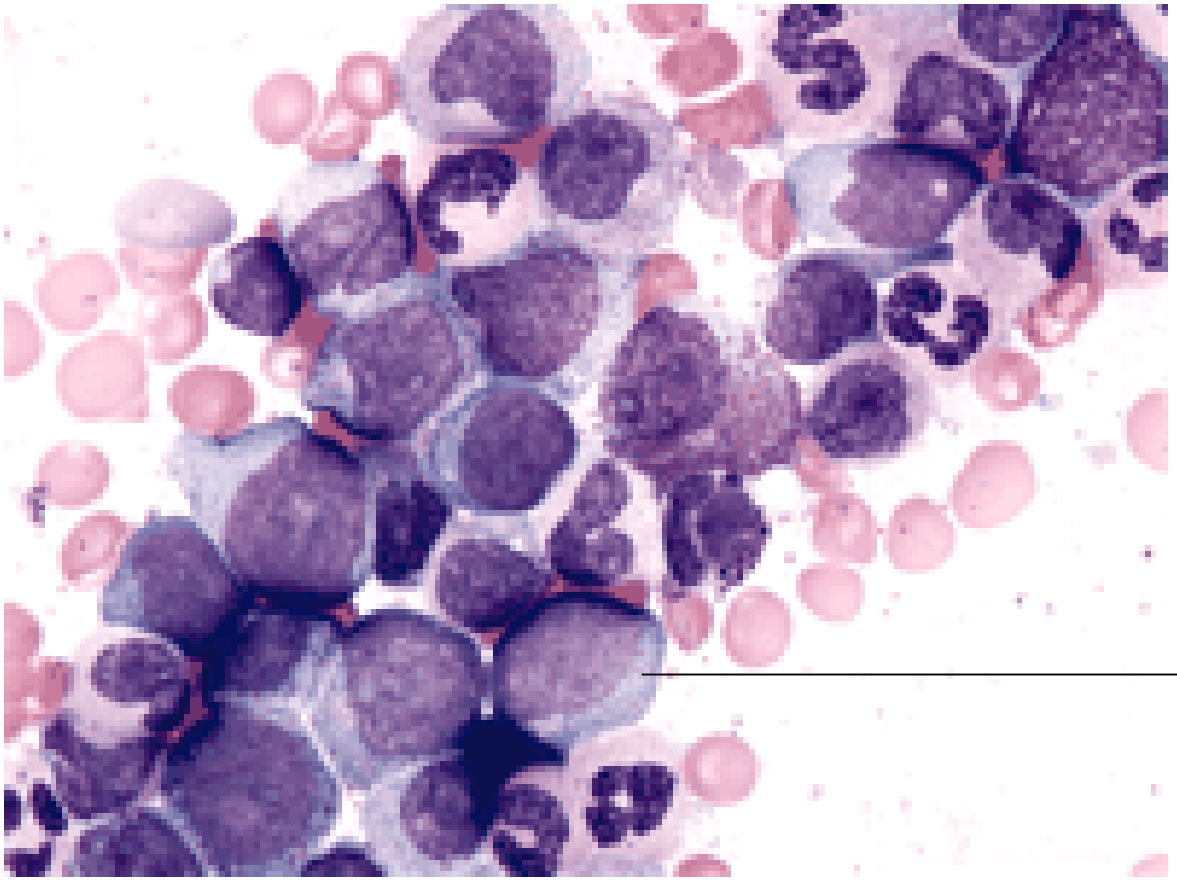
BONE MARROW PICTURE



Accelerated phase

- Disease acceleration is defined by the development of increasing degrees of anemia unaccounted for by bleeding or therapy;
- cytogenetic clonal evolution; or
- blood or marrow blasts between 10 and 20%, blood or marrow basophils 20%, or
- platelet count <100,000/L.

ACCELERATED PHASE

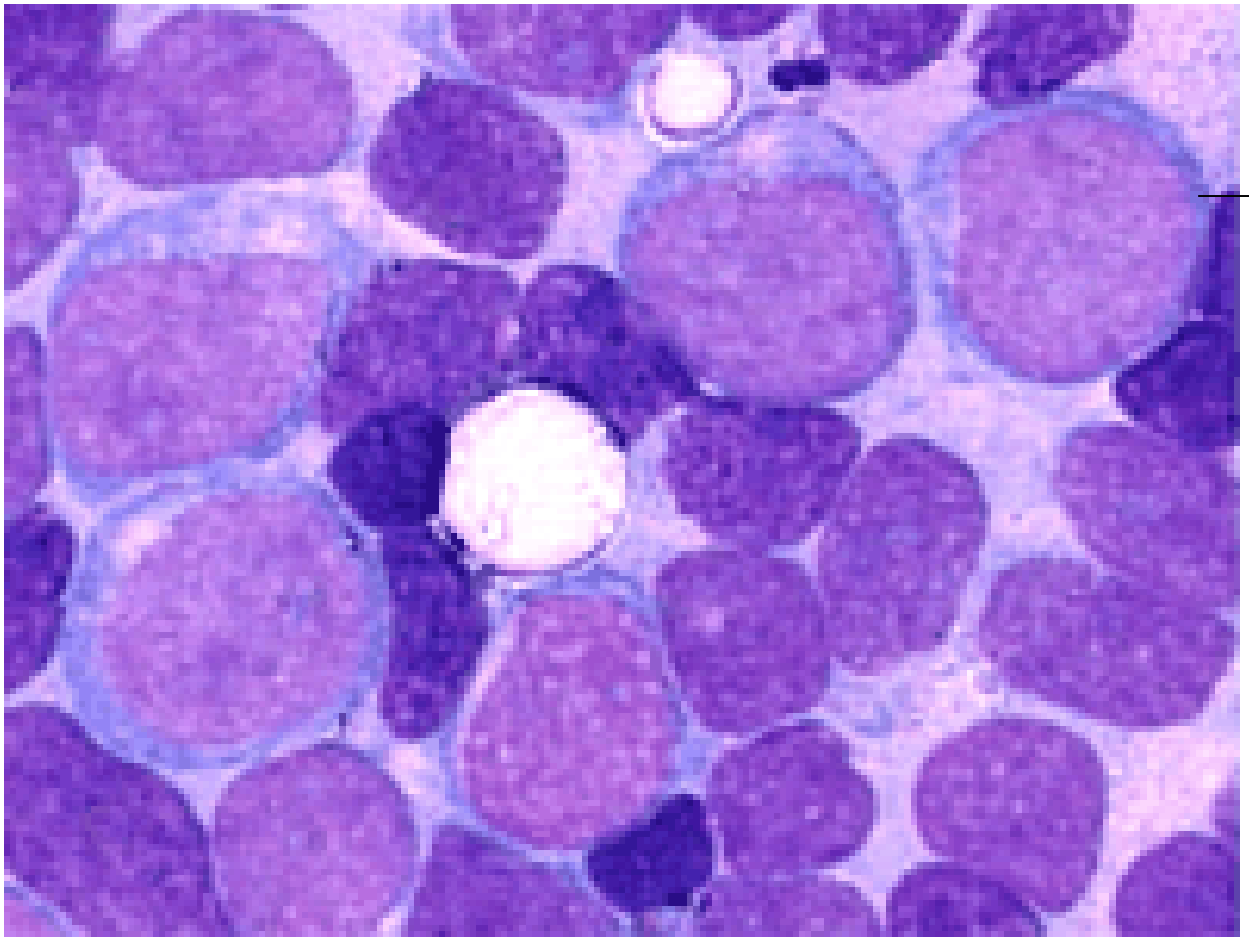


MYELOB
LAST

Blast crisis

- Blast crisis is defined as acute leukemia, with blood or marrow blasts 20%.
- Hyposegmented neutrophils may appear (Pelger-Huët anomaly).
- Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated, based on morphologic, cytochemical, and immunologic features.
- Occurrence of de novo blast crisis or following imatinib therapy is rare.

BLAST CRISIS PHASE



MYELOBLAST

Other abnormalities

There is increase in

- Uric acid level
- Vitamin B12 level.
- Lactate dehydrogenase.
- Increase in the level of angiogenic factors.
- Increase in histamine levels.

CHROMOSOMAL FINDINGS

- The cytogenetic hallmark of CML, found in 90–95% of patients, is the t(9;22)(q34;q11.2)

- Some patients may have complex translocations (designated as variant translocations) involving three, four, or five chromosomes (usually including chromosomes 9 and 22)

- However, the molecular consequences of these changes are similar to those resulting from the typical t(9;22).
- All patients should have evidence of the translocation by molecular / cytogenetics / FISH to make a diagnosis of CML.

- Identification of philadelphia chromosome can be done by conventional cytogenetic karyotyping,FISH,RT-PCR.

Conventional cytogenetics

- Entire chromosomal complement is evaluated to identify philadelphia chromosome and other abnormalities.
- Can be done on both peripheral blood and bone marrow.

Disadvantage

- Presence of cryptic or submicroscopic BCR-ABL arrangement cannot be identified

Fluorescent insitu hybridisation

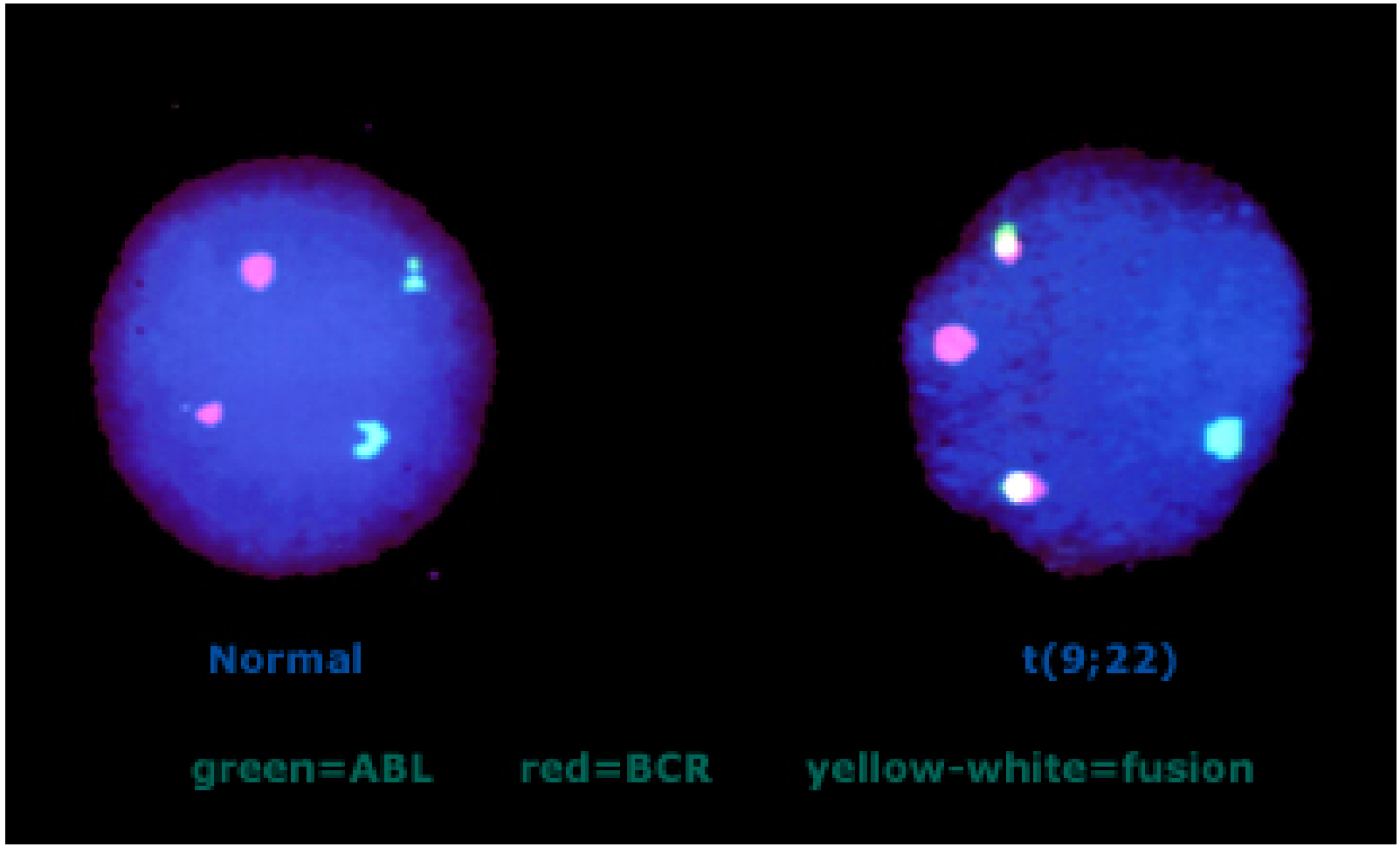
Advantage

- Fast results,greater sensitivity than conventional cytogenetics.
- Submicroscopic or cryptic molecular alteration can be detected.

Reverse transciptase-PCR

- Detects different length products corresponding to chimeric BCR-ABL proteins of 190,210 and 230 kda.
- So helps in distinguishing CML from ALL.

Fluorescent insitu hybridisation



Prognostic factors

Sokal index

- Percentage of circulating blast,spleen size,platelet count,age and cytogenetic clonal evolution.
- Was developed based on chemotherapy treated patients.

Hassford system

- Developed on interferon alpha treated patients.
- Includes% of circulating blast,spleen size,platelet count,age,% of eosinophils and basophils.

Treatment

- Drugs
- Stem cell transplant.
- Leukaphresis and splenectomy.

Drugs

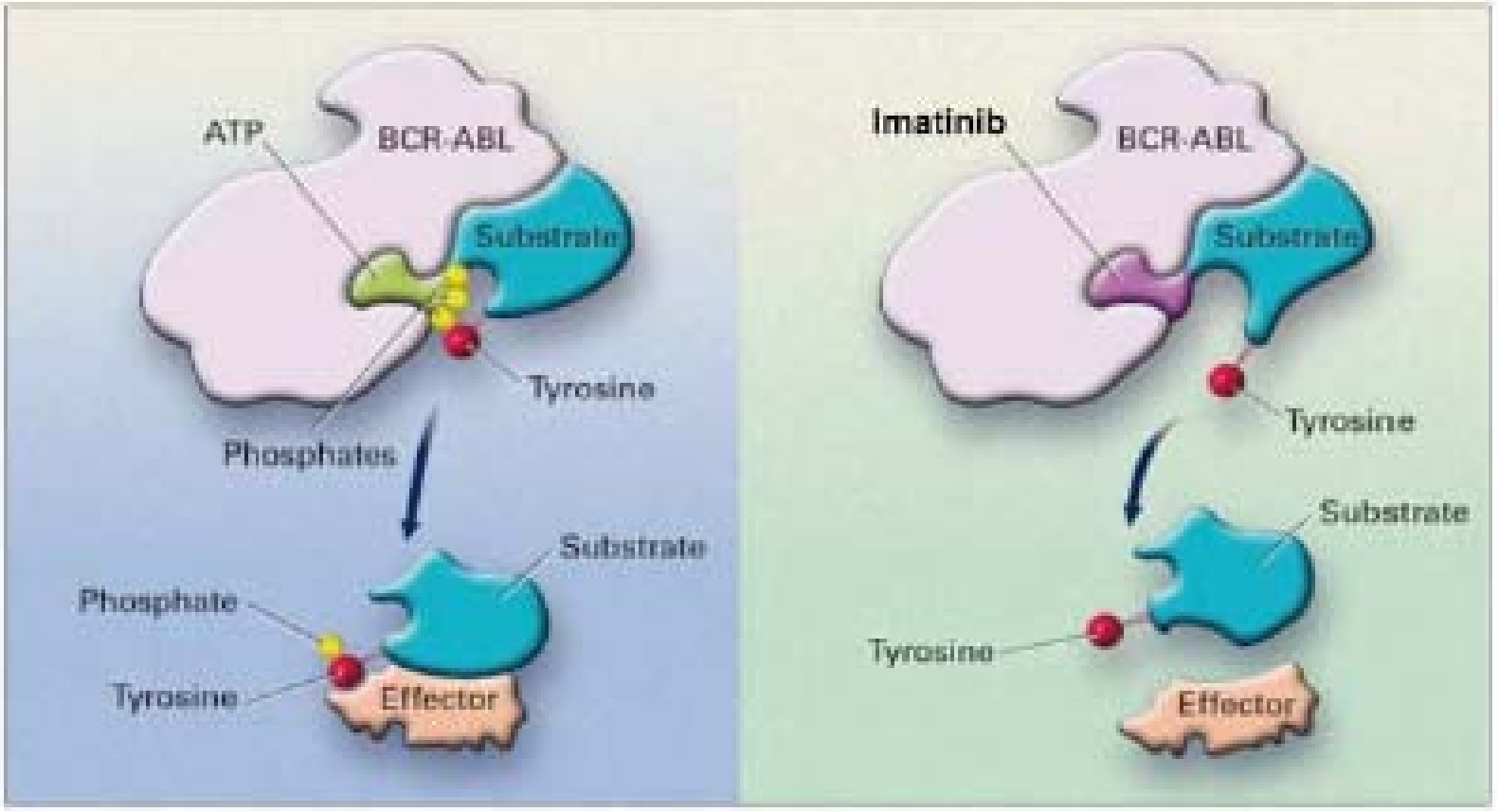
- Imatinib mesylate,dasatinib,nilotinib
- Hydroxyurea
- Busulphan
- Interferon-alpha

- Treatment should be started with TK inhibitors and allogenic transplantation is reserved for those who develop imatinib resistance.
- At present, the goal of therapy in CML is to achieve prolonged, durable, nonneoplastic, nonclonal hematopoiesis, which entails the eradication of any residual cells containing the BCR-ABL1 transcript.
- Hence, the goal is complete molecular remission and cure.

IMATINIB MESYLATE

- Imatinib mesylate (Gleevec) functions through competitive inhibition 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.
- It shows specificity for Bcr-Abl, the receptor for platelet-derived growth factor, and Kit TK.
- Imatinib induces apoptosis in cells expressing Bcr-Abl.

Signal Transduction and Tyrosine Kinases



Goldman JM et al. *N Engl J Med.* 2001;344:1084-1086. Reproduced with permission.

- All imatinib-treated patients who achieved major molecular remission (26%), defined as 3 log reduction in BCR-ABL1 transcript level at 18 months compared to pretreatment level, were progression-free at 5 years.

- The progression-free survival (PFS) at 5 years for patients achieving complete cytogenetic remission but less pronounced molecular remission is 98%.

- The 5-year PFS for patients not achieving complete cytogenetic remission at 18 months was 87%.

- These results have led to a consensus that molecular responses can be used as a treatment goal in CML

IMATINIB TREATMENT ALGORITHM FOR NEWLY DIAGNOSED CML PATIENTS

TIME IN MONTHS	EXPECTED OUTCOME	FAILURE
3	COMPLETE HEMATOLOGIC REMISSION	NO COMPLETE HR
6	ANY CYTOGENETIC REMISSION	NO COMPLETE CR
12	COMPLETE OR PARTIAL CYTOGENETIC REMISSION	MINOR OR NO CR
18	COMPLETE CYTOGENETIC REMISSION	PARTIAL,MINOR OR NO CR

- 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-alfa and cytarabine during the first year.
- Over time, the annual incidence of disease progression on imatinib decreased gradually to <1% during the fourth year and beyond, and no patient who achieved major molecular response by 12 months progressed to the accelerated/blastic phases of the disease

ADVERSE EFFECTS

- The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes.
- The management of these side effects is usually supportive.
- Myelosuppression is the most common hematologic side effect.
- Myelosuppression, while rare, may require holding drug and/or growth factor support. Doses <300 mg/d seem ineffective and may lead to development of resistance.

DEVELOPMENT OF RESISTANCE

- Gene amplification,
- Mutations at the kinase site,
- Enhanced expression of multidrug exporter proteins, and
- Alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms. All four mechanisms are being targeted in clinical trials.

- BCR-ABL1 gene amplification and decreased intracellular imatinib concentrations are addressed by intensifying the therapy with higher (up to 800 mg/d) imatinib doses.

Newer tyrosine kinase inhibitors

Dasatinib

- Structurally unrelated to imatinib binds to the ABL kinase domain.
- Side effect-myelosuppression,pleural effusion,prolongation of QT interval.

Nilotinib

- Structural derivative of imatinib binds to ABL kinase domain.
- Side effects-rashes,transient elevation of indirect bilirubin levels and myelosuppression.

Hydroxy urea

- Inhibitor of ribonucleotide reductase.
- Lower the blood counts in 1-2 days.
- Dose is 1-4g/day.
- The dose should be halved with each 50%reduction in leukocyte count.
- Side effect-nausea and skin rash.
- Given for patients intolerant to imatinib.

Busulphan

- Gradually lowers the blood counts.
- Dose-6-10 mg/day.
- Should not be used in patients expected to undergo bonemarrow transplantation.

- Its use is not recommended because of its serious side effects, which include unexpected, and occasionally fatal, myelosuppression in 5–10% of patients;
- Pulmonary, endocardial, and marrow fibrosis;
- Addison-like wasting syndrome.

Allogenic stem cell transplant

- Outcome depends on patients age,phaseof disease,type of donor,preparative regimen,graft vs host disease,post transplantation treatment.
- Patients age should be less than 70 years.transplantation from donor should be HLA matched.
- Peripheral blood can be used a source of haemotopoietic progenitor cells.preoperative regimen like cyclophosphamide plus total body irradiationis used.
- Complications-graft vs host disease.

LEUKAPHERESIS

- Intensive leukapheresis may control the blood counts in chronic-phase CML;
- It is useful in emergencies where leukostasis-related complications such as pulmonary failure or cerebrovascular accidents are likely.
- It may also have a role in the treatment of pregnant women, in whom it is important to avoid potentially teratogenic drugs.

SPLENECTOMY

- Splenectomy is now reserved for symptomatic relief of painful splenomegaly unresponsive to imatinib or chemotherapy, or for significant anemia or thrombocytopenia associated with hypersplenism.
- Splenic radiation is used rarely to reduce the size of the spleen.

TREATMENT OF BLAST CRISIS

- Treatments for primary blast crisis, including imatinib, are generally ineffective.
- Only 52% of patients treated with imatinib achieved hematologicremission (21% complete hematologic remission), and the median overall survival was 6.6 months.
- Patients who achieve complete hematologic remission or whose disease returns to a second chronic phase should be considered for allogeneic HSCT.

- Other approaches include induction chemotherapy tailored to the phenotype of the blast cell followed by TK inhibitors, with or without additional chemotherapy and HSCT.
- Blast crisis following initial therapy with imatinib carries a dismal prognosis even if treated with dasatinib or nilotinib.


THANK YOU