CML

Natural History

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Introduction

- divided into
  - Chronic phase
  - Accelerated phase
  - blast phases
- represent
  - the progressive shift in the nature of the disorder from
    - one of hyperproliferation, with production of mainly mature hemic elements,
    - to one characterized by differentiation arrest, with hyperproduction of predominantly immature (blast) cells characterized by
      - reversion to a stem cell phenotype,
      - block of apoptosis, and
      - therapeutic resistance.

Chronic phase

- marked expansion of the hematopoietic pools;
- morphologically, mature blood cells are produced with only subtle functional abnormalities.
- The neoplastic cells are generally restricted to
  - the bone marrow, liver, spleen, and peripheral blood.
- Therefore, symptoms are related to
  - organ infiltration,
  - hyperviscosity, and
  - the metabolic consequences of hyperproliferation,
- all of which are relatively easy to control.
- Similar to adults, approximately 95% of children with CML will present in CP.

Chronic phase: symptoms

- Patients usually present with nonspecific complaints, such as
  - fever
  - night sweats
  - weakness
  - left upper quadrant pain or fullness
  - bone pain
- marked hyperleukocytosis ➔
  - Neurologic dysfunction
  - respiratory distress
  - visual difficulties, or
  - priapism

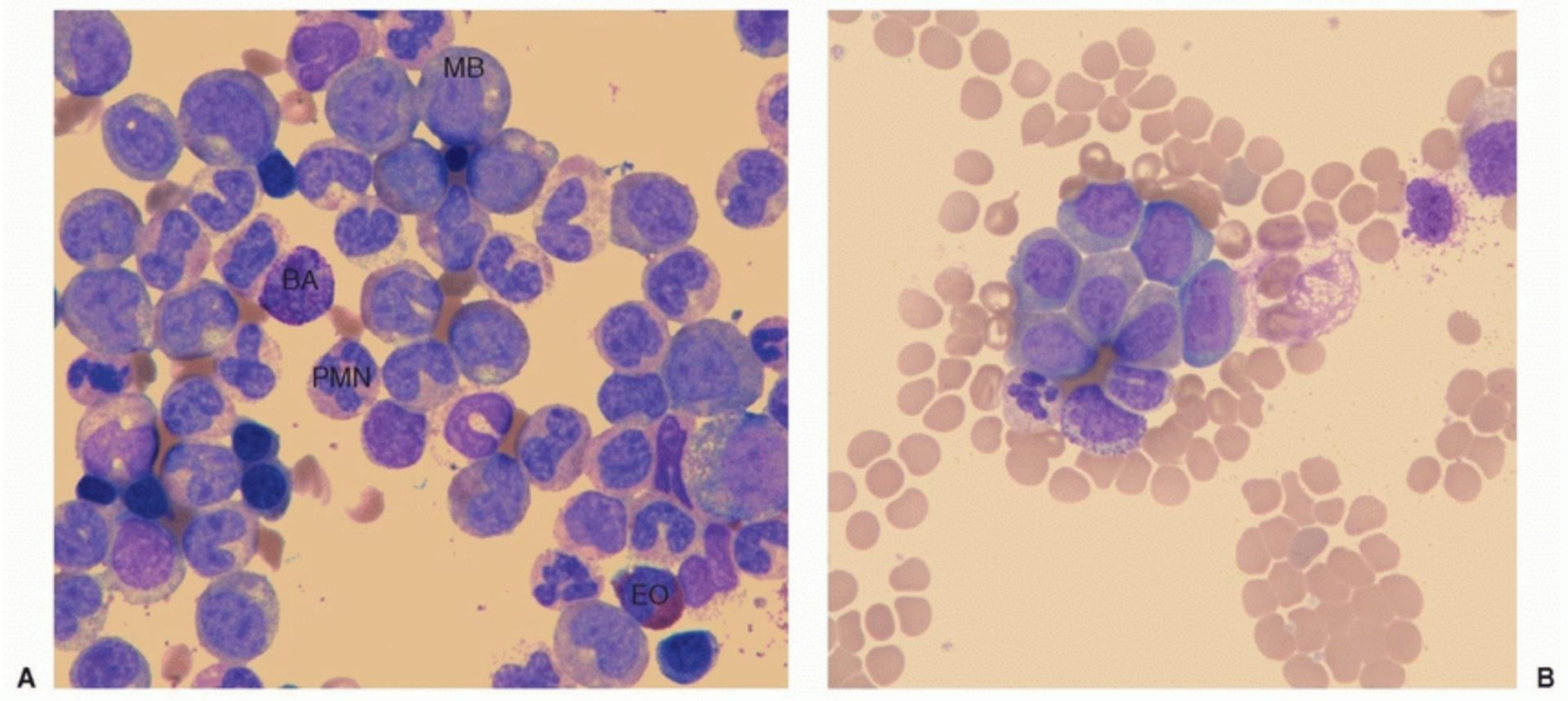
Chronic phase: Physical Findings

- The usual findings in CML-CP are
  - pallor,
  - low-grade fever,
  - ecchymosis,
  - hepatosplenomegaly, and
  - sternal tenderness.
  - Signs related to leukostasis
  - neurologic abnormalities, papilledema, retinal hemorrhages, priapism, tachypnea
  - are seen in patients with extreme hyperleukocytosis

Chronic phase: Laboratory Findings

- common laboratory findings
  - mild normochromic, normocytic anemia,
  - leukocytosis with left shift, and
  - thrombocytosis
- peripheral blood smear shows
  - myeloid cells at all stages of differentiation;
  - myeloblasts and promyelocytes generally comprise less than 15% of the differential count
  - Basophilia and eosinophilia are typical.
  - Hybrid eosinophilic-basophilic granulocytes may also be seen.
- mean platelet count in children is approximately 500,000/µL, similar to adults.
- .

Peripheral blood smears of chronic myeloid leukemia.
A: **Chronic phase**—marked leukocytosis showing the entire range of myeloid cells from myeloblast (MB) to mature polymorphonuclear luekocytes (PMN); a hypergranular eosinophil (EO) and basophil (BA) are present as well.
B**: Blast phase**—blast cells are now more prominent, and there is a hiatus in myeloid maturation



Chronic phase: Laboratory Findings

- Serologic findings include
  - Elevation of uric acid,
  - lactate dehydrogenase,
  - vitamin B12, and
  - vitamin B12-binding protein (transcobalamin 1)
- The bone marrow is
  - hypercellular, reflecting granulocytic (and often megakaryocytic) hyperplasia;
  - granulocyte maturation, eosinophilia, and basophilia
  - normal to increased numbers of megakaryocytes in clusters, and
    - these are often small and hypolobulated (***micromegakaryocytes***)
- The bone marrow and spleen occasionally contain ***lipid-laden histiocytes***

Clinical presentation and disease progression are different in adult and pediatric CML

- Children and adolescents, as well as young adults, in CML-CP tend to have clinical presentations with more aggressive features.
- The proportion of pediatric patients diagnosed with advanced-stage disease (accelerated phase [AP] or blast phase [BP]) is higher than for adult patient.
- The median hemoglobin (Hb) at presentation in children (11.1 g/dL) is significantly less than that in adults.

Clinical presentation and disease progression are different in adult and pediatric CML

- The leukocyte count at diagnosis ranges from approximately 8,000 to 800,000/µL; the median count in children (˜250,000/µL) is higher than adults
- extreme hyperleukocytosis (>500,000/µL) is more common in children
- young adults (18-29 years) had splenomegaly and a larger spleen more often than did older adults.
- In addition, young adults had lower complete cytogenetic response and MMR rates compared with older adult

Criteria Definition for Chronic Phase

- Documented t(9;22) or BCR-ABL1 fusion gene
- Does not meet any criteria for accelerated phase or blast phase

Accelerated Phase

- Clinically, the onset of the accelerated phase (AP) is characterized by
  - progressive systemic symptoms
    - fever,
    - night sweats,
    - weight loss,
  - increasing leukocyte counts with a high proportion of immature cells, and
  - basophilia.
- Occasionally, the first manifestation of metamorphosis is extramedullary

Accelerated Phase WHO Criteria

- Any one or more of:
  - Persistent of increasing WBC (>10,000/µL), unresponsive to therapy
  - Persistent or increasing splenomegaly, unresponsive to therapy
  - Persistent thrombocytosis (>1,000,000/µL), unresponsive to therapy
  - Persistent thrombocytopenia (<100,000/µL), unrelated to therapy
  - 20% or more basophils in PB
  - 10%-19% blasts in PB and/or BM
  - Specific additional clonal chromosomal abnormalities in Ph+ cells at diagnosis
  - Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy
  - Provisional TKI response criteria
  - Failure to achieve CHR to first TKI
  - Resistance to two sequential TKIs
  - Two of more BCR-ABL1 mutations detected during TKI therapy

Accelerated Phase ELN Criteria

- Any one or more of:
  - 15%-29% blasts in PB and/or BM, or <30% blasts but with 30% or more promyelocytes in PB and/or BM
  - 20% or more basophils in PB
  - Persistent thrombocytopenia (<100,000/µL), unrelated to therapy
  - Specific additional clonal chromosomal abnormalities in Ph+ cells at diagnosis

Accelerated Phase MDACC Criteria

- Any one or more of:
  - 15%-29% myeloblasts in PB
  - 30% or more myeloblasts and promyelocytes combined in PB
  - 20% or more basophils in PB
  - Persistent thrombocytopenia (<100,000/µL), unrelated to therapy
  - Additional clonal chromosomal abnormalities in Ph+ cells

Blast Phase/Blast Crisis

- loss of the leukemic clone's capacity to differentiate
- Clinical picture resembles that of an acute leukemia,
  - with anemia, thrombocytopenia, and increased numbers of blast cells in
- both the peripheral blood and the bone marrow
- marrow blast percentage of 30% or more is diagnostic of BP
- The signs and symptoms are those of a de novo acute leukemia;
- if basophilia is extreme ➔ may be hyperhistaminemia symptoms
  - pruritus,
  - cold urticaria,
  - gastric ulceration

Blast Phase/Blast Crisis

- Approximately 60% to 70% of adults and 30% of pediatric BP cases, the blast cell morphology is myeloblastic
- remaining patients have blast cells with lymphoid morphology, generally an early B-cell phenotype
- Rarely, blast cells may express T-lineage markers or a mixed myeloid/lymphoid phenotype
- BP is frequently associated with new molecular and cytogenetic abnormalities

Blast Phase Criteria

- WHO
  - Any one or more of:
    - 20% or more blasts in PB and/or BM
    - Extramedullary blast proliferation, except in the spleen
    - Large foci or clusters of blasts on BM biopsy
- ELN
  - Any one or more of:
    - 30% or more blasts in PB and/or BM
    - Extramedullary blast proliferation, except in the spleen
- MDACC
  - Any one or more of:
    - 30% or more blasts in PB and/or BM
    - Extramedullary infiltrates of leukemic cells, except in spleen

Differential Diagnosis

- Because most instances of CML-BP occur after a well-documented CML-CP, the diagnosis is usually clear-cut.
- The rare patient who presents in CML-BP without a recognized preceding CML-CP may pose diagnostic difficulty
- The combination of marked splenomegaly, basophilia, and the Ph1 chromosome distinguishes CML-BP from most types of de novo acute leukemia

Evaluations at diagnosis

Complete blood count (including differentials) and comprehensive metabolic profile

Spleen and liver size (should be measured as below costal margin)

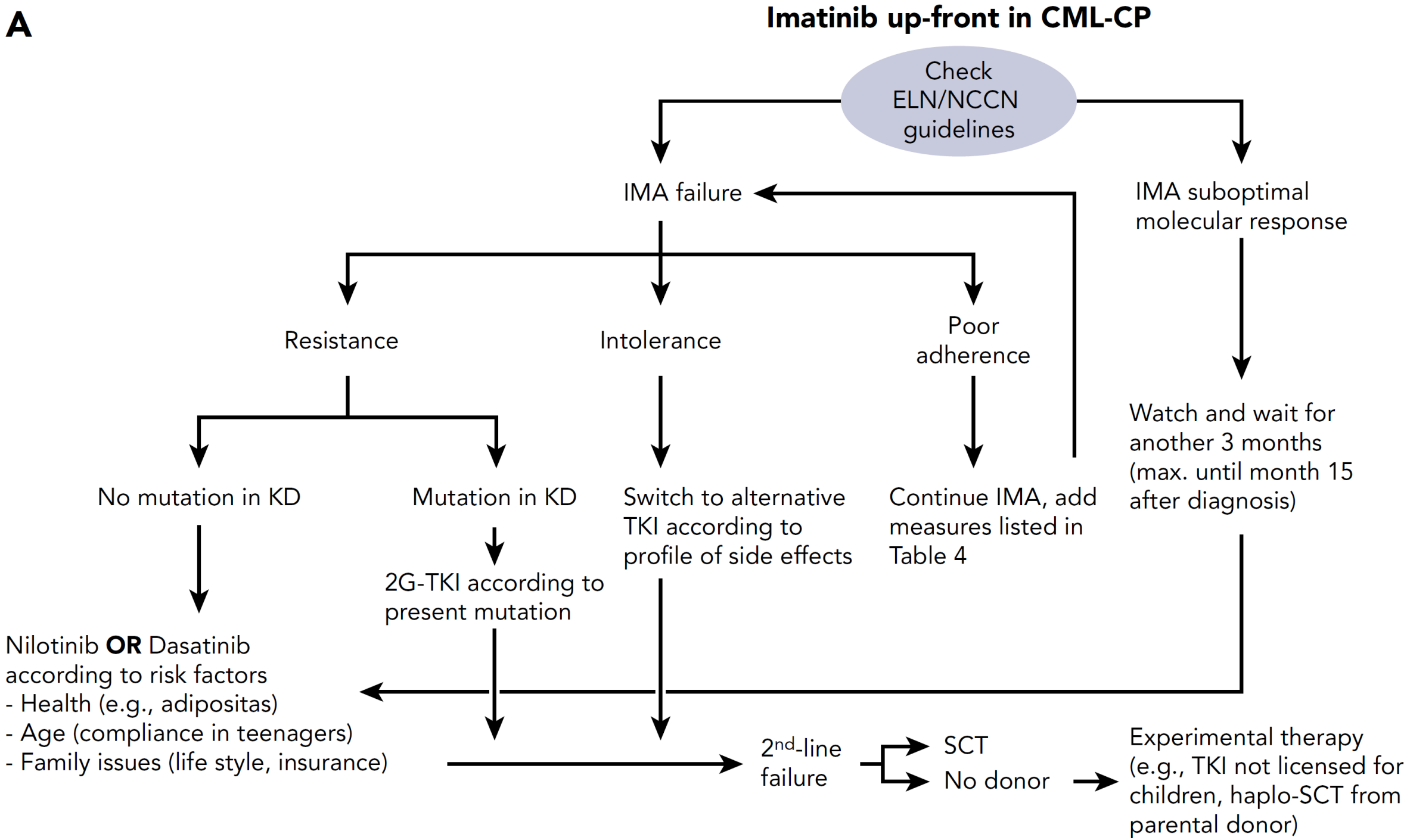
Bone marrow aspirate and biopsy (differentials and karyotype)

Baseline molecular genetics (qRT-PCR for BCR-ABL1) with transcript type (eg, e14a2)

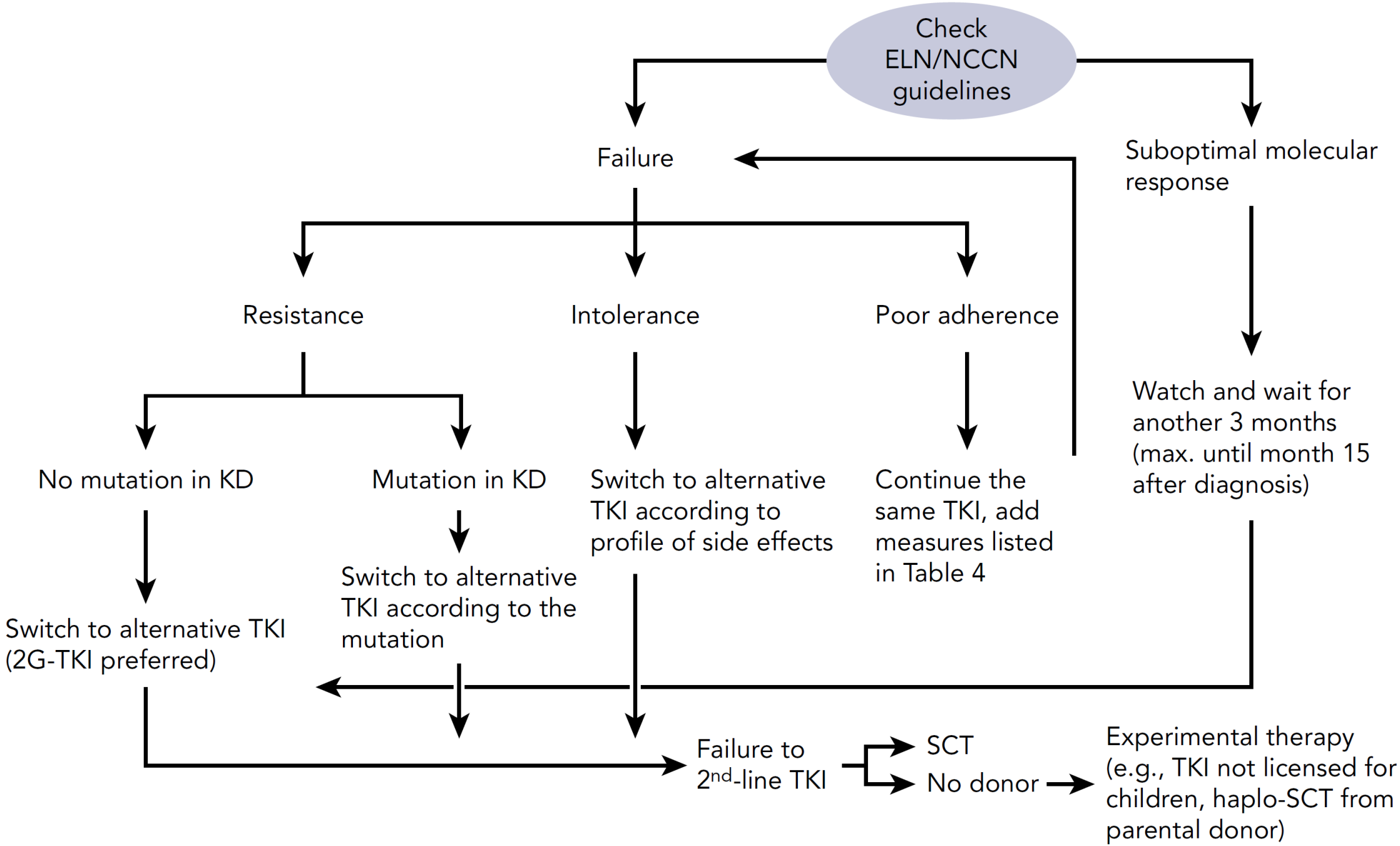
Categorize stage of disease (CML-CP, CML-AP, CML-BP), identify additional risk factors (eg, additional chromosomal aberrations)

Recommended tyrosine kinase inhibitors in case of BCR-ABL1 resistance mutations

Mutation	Recommended tyrosine kinase inhibitor(s)
T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib,* or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib,* or ponatinib


A
Imatinib up-front in CML-CP
Check ELN/NCCN guidelines
IMA failure
IMA suboptimal molecular response
Resistance
Intolerance
Poor adherence
Watch and wait for another 3 months (max. until month 15 after diagnosis)
No mutation in KD
Mutation in KD
Switch to alternative TKI according to profile of side effects
Continue IMA, add measures listed in Table 4
2G-TKI according to present mutation
Nilotinib OR Dasatinib according to risk factors
- Health (e.g., adipositas)
- Age (compliance in teenagers)
- Family issues (life style, insurance)
2nd-line failure
SCT
No donor
Experimental therapy (e.g., TKI not licensed for children, haplo-SCT from parental donor)

2G-TKI up-front in CML-CP



Evaluations at follow-up visits

Complete blood count (including differentials) and comprehensive metabolic profile
Spleen and liver size (should be measured as below costal margin)
Bone marrow every 6 mo until complete cytogenetic response
Molecular monitoring from peripheral blood by qRT-PCR (monthly in the first 3 mo, every 3 mo thereafter)
Classify response according to treatment time as recommended by the ELN[44] or NCCN[42] (Table 3) In advanced phases of CML, also monitor bone marrow cytogenetics to detect clonal evolution

Table 3. Definition of molecular response based on the IS; adopted from ELN guidelines and NCCN guidelines, which reasonably can be used in children

Milestone, mo.	Optimal response	Warning	Failure
3	BCR-ABL1 <10% IS	BCR-ABL1 ≥10% IS	
6	BCR-ABL1 <1%* IS	BCR-ABL1 1-10% IS	BCR-ABL1 ≥10% IS
12	BCR-ABL1 <0.1% IS	BCR-ABL1 0.1-1% IS	BCR-ABL1 ≥1% IS

Table 3. Recommendations for monitoring and supportive care in children with CML receiving TKI therapy

- Accurate measurement of height and weight at each visit and close monitoring of growth velocity. Consider bone scan and DEXA scan and refer to endocrinology if there is evidence of an abnormal growth pattern.
- Tanner staging at each visit. Consider checking gonadotropins and sex steroids and refer to endocrinology if there is evidence of a pubertal delay.
- Thyroid function (TSH, free T4) 4 to 6 weeks after start of TKI and annually thereafter.
- Counseling on reproductive considerations for young women of childbearing age.
- Annual echocardiogram and electrocardiogram.
- Live vaccines are not recommended. Inactivated vaccines may be given safely, but their efficacy has not been proven.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