LEUKEMIA2020-2021

April 26-27, 2021

Coordinator: A.M. Carella
AIL President: S. Amadori

ASSOCIAZIONE ITALIANA
CONTRO LE LEUCEMIE-LINFOMI E MIELOMA
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fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica
sulle malattie ematologiche. FRANCO MANDELLI

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

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Atypical chronic myeloid leukemia

Massimo Breccia

Sapienza University

Rome

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Disclosures of MASSIMO BRECCIA

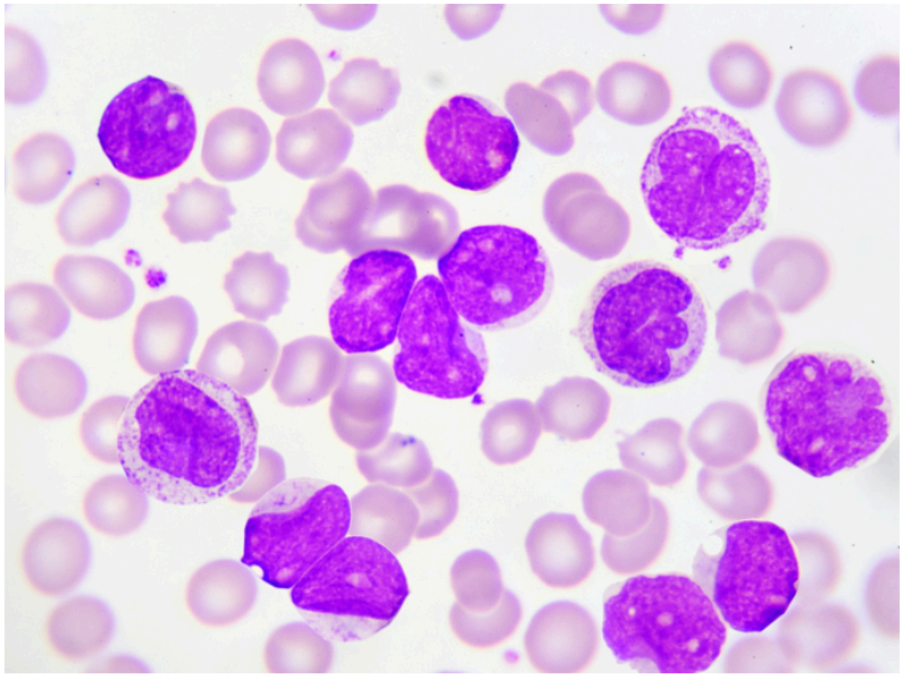
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			x			x	
Pfizer			x				
Incyte			x				
BMS/Celgene			x			x	
Abbvie						x	

Incidence and pathogenesis

- Is a rare malignancy with aggressive behaviour and poor prognosis
- The overall incidence is 1 per 100,000 or less, with approximately 1-2 cases per 100 cases of CML
- Initially described as a subtype of myeloid neoplasm closely resembling CML but lacking the pathognomonic BCR/ABL1 rearrangement, aCML is now an independent entity, classified under the group of myeloproliferative/myelodysplastic (MPN/MDS) disorders in the WHO classification
- The last few years have seen some advances in the understanding of the molecular biology of this disease and a hope for the development of targeted therapies

Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020

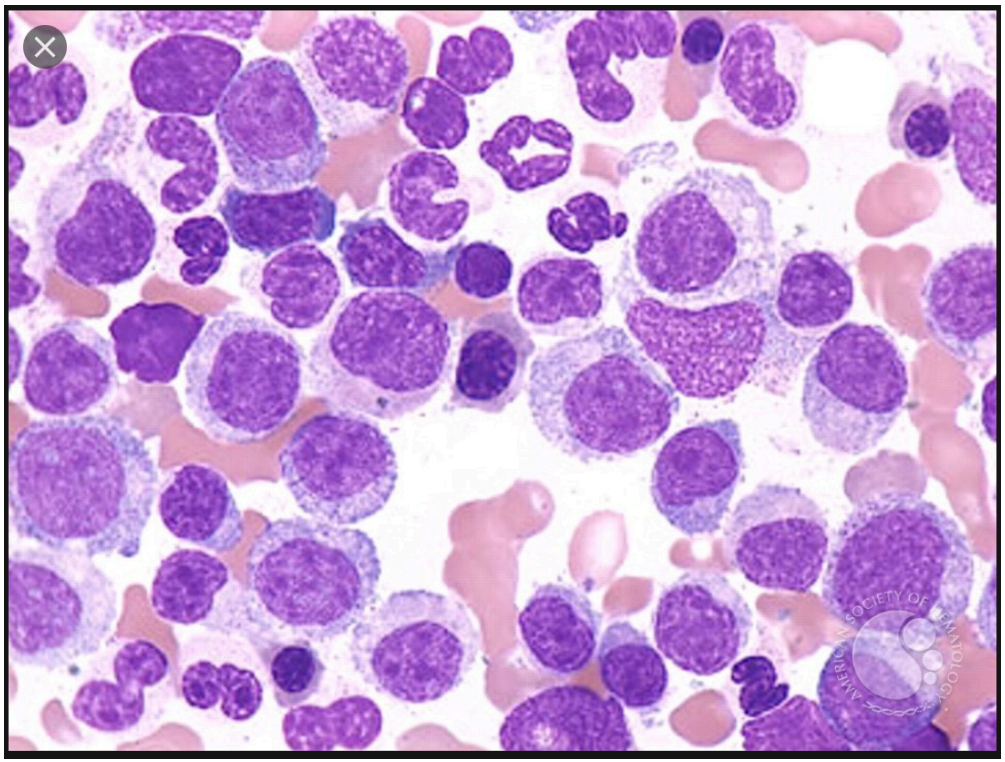
Morphological features in Pb



- Severe dysgranulopoiesis: neutrophils with chromatin clumping, abnormal nuclear segmentation (Pseudo-Pelger or hypersegmentation), cytoplasm with hypogranulation or abnormal enlarged granules.
- WBC count by definition at least 13 x 10^9/L
- At least 10% immature granulocytes including promyelocytes, myelocytes, metamyelocytes
- Absence of monocytosis (usually < 1 x 10^9/L)
- Basophils less than 2%
- Blasts are less than 20% in bone marrow and Pb

Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020

Morphological features in bone marrow



- Hypercellular
- Predominance of granulocytes, showing marked dysplasia
- More than half of cases with erythroid dysplasia
- Some degree of megakaryocytic dysplasia
- Variable degrees of increased reticulin fibrosis

Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020

Criteria for differential diagnosis

Sadigh et al Curr Opin Hematol 2020

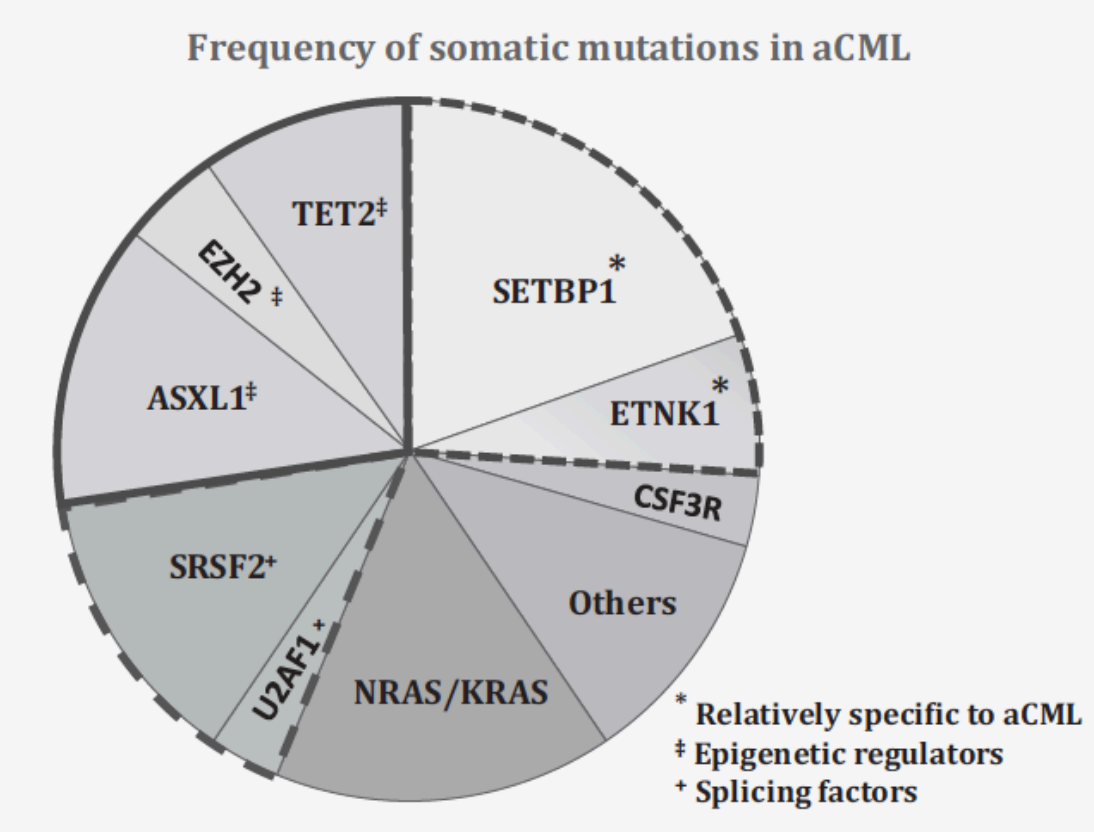
aCML	CMML	MDS/MPN-RS-T	MDS/MPN-U	CNL
PB leukocytosis at least 13×10^9/l, because of increased numbers of neutrophils and their precursors (with precursors ≥10% of leukocytes) No or minimal absolute basophilia; basophils less than 2% of PB leukocytes No or minimal absolute monocytosis; monocytes less than 10% of PB leukocytes <20% blasts in the blood and bone marrow	Persistent PB monocytosis at least 1×10^9/l, with monocytes accounting for at least 10% of the WBC count <20% blasts in PB and BM	Persistent thrombocytosis, with platelets at least 450×10^9/l <1% blasts in PB and less than 5% blasts in BM	Mixed MPN and MDS features at onset, not meeting the WHO criteria for any other MDS/MPN, MDS, or MPN neoplasm platelets at least 450×10^9/l associated with BM megakaryocytic proliferation and/or WBC at least 13×10^9/ l <20% blasts in PB and BM	PB WBC at least 25×10^9/l Segmented neutrophils and banded neutrophils at least 80% of leukocytes Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) constitute less than 10% of leukocytes Monocyte count less than 1×10^9/l PB blasts rarely observed; less than 5% blasts in BM
Dysgranulopoiesis, which may include abnormal chromatin clumping Hypercellular BM with granulocytic proliferation and granulocytic dysplasia +/- dysplasia in the erythroid and megakaryocytic lineages	Dysplasia in one or more myeloid lineages	Erythroid-lineage dysplasia, with or without multilineage dysplasia; at least 15% ring sideroblasts	Clinical and morphological features of one of the categories of MDS	Hypercellular BM with increased neutrophil with normal maturation No dysgranulopoiesis
	If myelodysplasia is absent/minimal, CMML can be diagnosed if above criteria are met and a clonal cytogenetic or molecular genetic abnormality is present or monocytosis (as previously defined) persists => 3 months and all other causes of monocytosis are excluded	*SF3B1* mutation or, in the absence of *SF3B1* mutation, no history of recent cytotoxic or growth factor No history of MPN, MDS (except MDS-RS), or other MDS/MPN neoplasm		*CSF3R* T618I or another activating *CSF3R* mutation If *CSF3R* mutation is absent, persistent neutrophilia (≥3 months), splenomegaly, and no identifiable cause of reactive neutrophilia
Not meeting WHO criteria for *BCR-ABL1*+ CML, PMF, PV or ET	Not meeting WHO criteria for *BCR-ABL*+ CML, PMF, PV, or ET	No t (3;3)(q21.3;q26.2), inv (3)(q21.3q26.2), or del (5q)c	No history of recent cytotoxic or growth factor therapy that could explain the MDS/MPN features	Not meeting WHO criteria for *BCR-ABL1*+ CML, PMF, PV or ET
No *BCR-ABL1* fusion. No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement, or *PCM1-JAK2* fusion				

Cytogenetics

- The frequency of chromosomal abnormalities is widely variable ranging from 20 to 88% in several series
- Recurrent abnormalities include the presence of aneuploidy in 1/3 of patients (most common trisomy 8)
- Loss of chromosomes 5, 7, del(20q) and isochromosome i(17)(q10) have also been documented to a lesser degree
- However, none of these abnormalities appear to be recurrent or specific to aCML

Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020

Mutational landscape in aCML

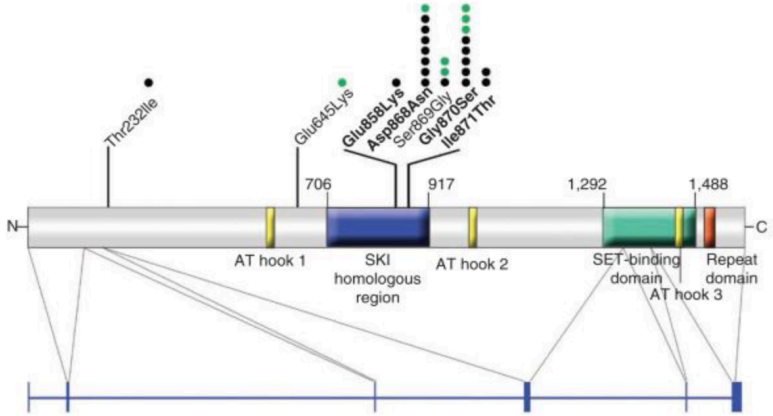


- Diagnosis of aCML first requires testing for the Ph chromosome and/or the BCR-ABL1 fusion gene to exclude CML
- The mutations identified in aCML are commonly found in other myeloid diseases
- Higher frequency mutations (eg, .20%) include SETBP1, ASXL1, N/K-RAS, SRSF2, and TET2, and lower frequency mutations (<10%) include CBL, CSF3R, JAK2, and ETNK1.3

Gotlib, Blood 2017

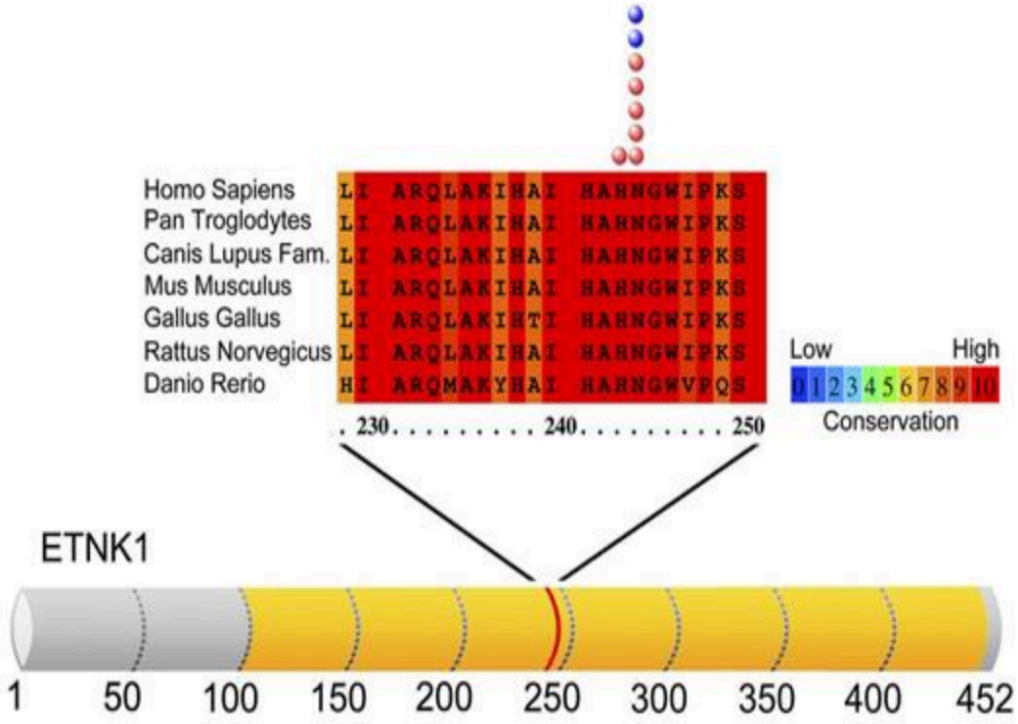
SETBP1 in aCML

- Recurrent SETBP1 mutations have been identified in 25% to 33% of aCML patients and represent one of the mostly frequently mutated genes in this disease
- Set binding protein (SETBP1) interacts with SET, a negative regulator of the tumor suppressor protein phosphatase2A (PP2A) with increased repression of activity and cellular proliferation
- Most SETBP1mutations are located within a 14-amino-acid stretch (codons 858-871), which is also mutated in Schinzel-Giedion syndrome, a rare genetic disease characterized by congenital malformations, mental retardation, and frequent epithelial tumors.
- SETBP1 mutations are associated with a higher leukocyte count, lower hemoglobin and platelet counts, and worse overall survival. Interestingly, SETBP1 mutations showed a strong association with ASXL1 and CBL mutations and were mutually exclusive of JAK2 and TET2 mutations.



Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020, Piazza et al, Nat Gen 2013

ETNK1 mutations and others in aCML

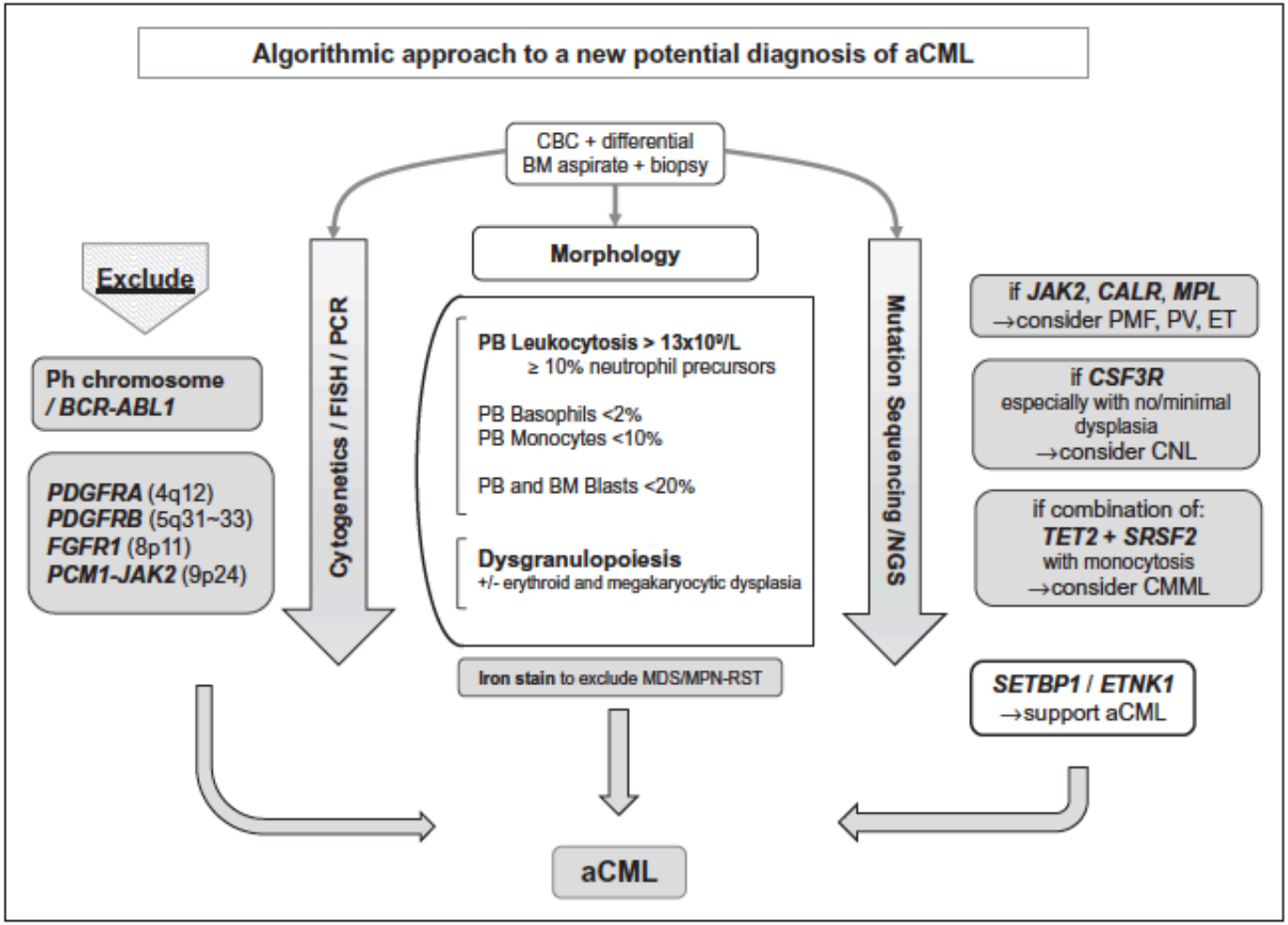


- Recurrent mutations in ETNK1 emerged as being relatively specific for aCML (up to 9% of cases) and CMML (3% of cases), and not found in other myeloid diseases.
- These mutations clustered in a small region of the kinase domain, encoding for H243Y and N244S (1/8 H243Y; 7/8 N244S). They were all heterozygous and present in the dominant clone.
- The most frequently mutated genes in aCML are ASXL1, NRAS, SETBP1, SRSF2, and TET2. It was recently shown that 69% of aCML cases harbour at least one mutation in the epigenetic modifier genes TET2, IDH1/2, DNMT3A, EZH2, and/or ASXL1.

- A significant number of aCML cases harbouring CSF3R mutations (a possible continuum between aCML, CNL and MDS/MPN-U)

Gambacorti-Passerini et al, Blood 2015; Sadigh et al, Blood reviews 2020

Diagnostic algorithm



Schwartz et al, Blood Rev 2018; Sadigh et al Curr Opin Hematol 2020

Prognostic factors

- Atypical CML has an aggressive disease course, with a poor prognosis and a median survival of ~25 months (range, 14–30 months)

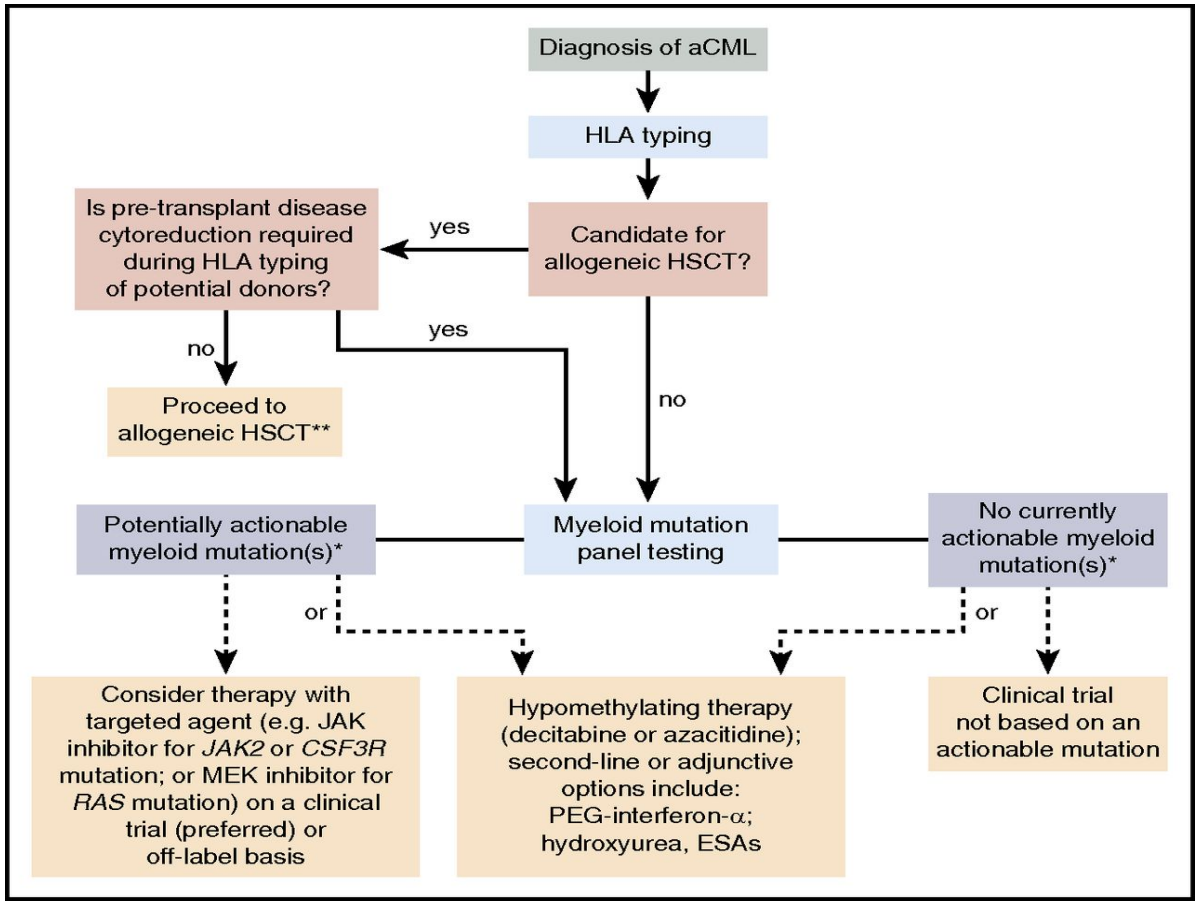
- A leukemic transformation has been noted in about a third of patients. Progressive leucocytosis or complications of cytopenias may be the cause of death even in the absence of leukemic transformation.

- Age more than 65 years, female, hemoglobin less than 10 g/dl, leukocyte count more than 50 x 10^9/l and immature circulating precursors have been described as the adverse prognostic factors in two studies.

- Patnaik et al. demonstrated that increasing age, progressive anemia and the presence of TET2 mutations, but not SETBP1 and ETNK1 mutations, were associated with worse outcomes. Based on the prognostic factors, a hazard ratio-weighted prognostic model was created, and patients were stratified into two risk categories: low (0–1 risk factor) and high (>2 risk factors), with median OS of 18 and 7 months, respectively.

Dakhal et al, Fute oncol 2018

Treatment algorithm



- No standard of care exists for the treatment of aCML. In addition, no consensus recommendations or risk-based treatment algorithms exist to help guide a watch-and-wait approach vs initiation of therapy.

Gotlib Blood 2017

Palliative treatments

- The most commonly administered adjunct therapy is HU typically utilized to control leucocytosis or symptomatic splenomegaly. There have been multiple reports of both HU and IFN-α inducing complete and partial hematologic responses in aCML, however the duration of response is usually limited to months.

- A phase II study of pegylated-IFN-α-2b (PEG-IFN-α), was shown to have improved tolerability over standard IFN-α in BCR-ABL1 negative MPNs. This long acting formulation is associated with a better toxicity profile and offers a treatment option for those ineligible for clinical trials or HSCT.

- Progressive anemia with development of transfusion dependence is common in aCML, contributing to increased morbidity. Splenectomy is generally not recommended in the management of this disease given its limited clinical response, anecdotal risk of accelerated neutrophilia, and relatively high perioperative morbidity already known in MPN patients.

- ESAs also have limited data in aCML with only one study reporting a poor response

Schwartz et al Blood Rev 2018

Allogeneic transplant

- A limited number of HSCT procedures for aCML have been published. Most are included in series of patients with heterogeneous MDS/MPN where long-term disease free–survival of 40% to 50% has been recorded.

- Koldehoff et al. described favorable outcomes with over 80% OS at 5 years in 21 patients who have received allogeneic HSCT. Significantly worse outcomes were described by Mittal et al. because of high-transplant-related mortality from graft versus host disease, sepsis and other causes. Onida et al. demonstrated a transplant-related mortality of 24% at 5 years but a relapse rate of 40%.

- HSCT may be considered in younger patients who desire curative intent therapy, older fit patients or those with higher risk features such as anemia, leukocytosis or circulating myeloid precursor cells, or possibly those with SETBP1 and ASXL1 mutations.

- Survival after HSCT was not influenced by ASXL1, CBL, NRAS, or TET2 mutations.

Gotlib Blood 2017; Dackal et al Future Oncol 2018 ; Schwartz et al 2018

Hypomethylating agents

Study (year)	Number of patients	Treatment	Overall survival	Hematological response
Onida *et al.* (2017)†	42	HSCT	Relapse-free survival at 5 years – 36%; nonrelapse mortality – 24% at 5 years	87%
Koldehoff *et al.* (2012)	21	HSCT	81% at 60 months	
Patnaik *et al.* (2017)	25	Mainly hydroxyurea (n = 15) ESA (n = 4) Azacitidine (n = 4)	10.8 months	Stable disease in 40% with azacitidine
Kantarjian *et al.* (2003)	7	Decitabine	13 months	Hematologic response – 43% 2nd chronic phase – 14%
Tong *et al.* (2015)‡	4	Decitabine	75% at a median follow-up of 12 months	75%
Breccia *et al.* (2006)	55	Hydroxyurea (n = 48) Low dose ara-C (n = 4) IFN (n = 3)	24 months	
Onida *et al.* (2002)	76	IFN-α or IFN-γ (n = 17) Hydroxyurea (n = 9) Decitabine/azacitidine (n = 5) Chemotherapy (n = 11)	24 months	
Jabbour *et al.* (2007)§	5	PEG-IFN-α-2b		40%

- WBC count >13 x 10^9/L and bone marrow blasts >10% were adverse prognostic factors for response to azacitidine
- Hypomethylating agents should be considered as a bridge in younger patients to HSCT or as stand-alone Tx in patients without an option of care

Gotlib Blood 2017; Dackal et al Future Oncol 2018

Ruxolitinib

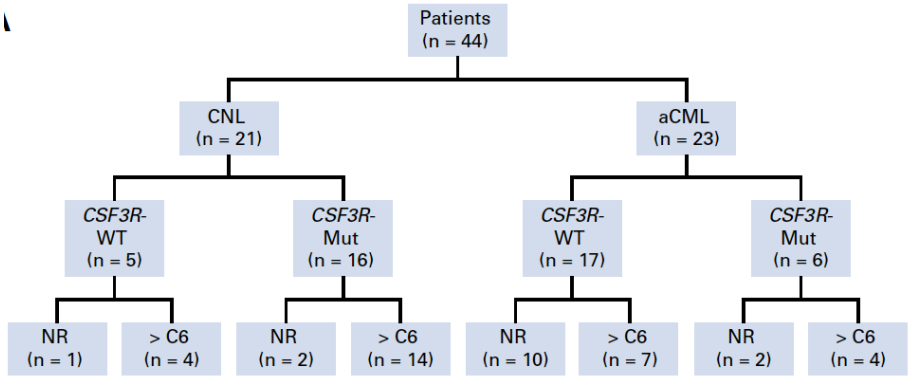
- Although uncommon, the identification of CSF3R T618I or JAK2 V617F in cases of aCML provides an opportunity to consider JAK inhibitor therapy because both of these mutations result in JAK-STAT pathway activation.

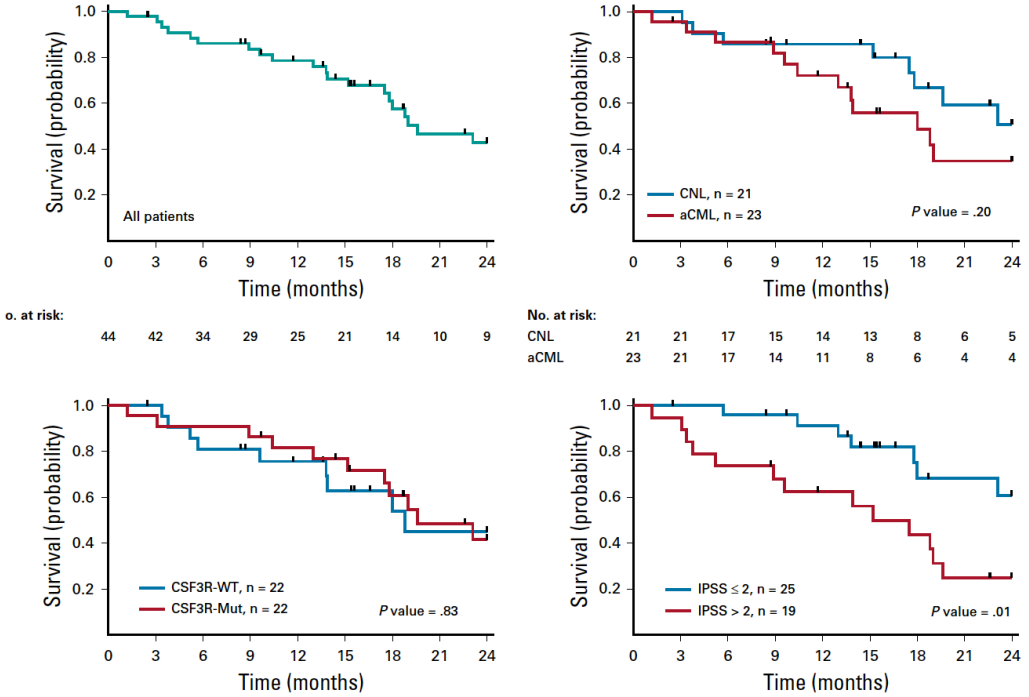
- The potential benefit of ruxolitinib in CSF3R T618I–mutated disease was first demonstrated in a patient with CNL with CSF3R T618I who achieved a marked reduction in neutrophilic leucocytosis and improvement of anemia and thrombocytopenia.

- Subsequently, a patient with hydroxyurea-refractory aCML dosed with ruxolitinib 10 to 20 mg twice daily resulted in similar hematologic improvements (reduced splenomegaly and peripheral blood myeloid immaturity, reverted weight loss and improved symptom scores, without change in CSF3R mutant allele frequency)

Gotlib Blood 2017; Dackal et al Future Oncol 2018; Schwartz et al 2018

Phase II trial with Ruxolitinib





- 44 patients enrolled (35% overall response): only 2 patients with aCML obtained a PR.
- Grade> 3 anemia and thrombocytopenia were observed in 34% and 14% of patients, respectively.

Dao et al JCO 2019

Other emerging treatments

- In addition to mutated CSF3R activation of the JAK-STAT pathway, CSF3R truncation mutations preferentially activate SRC family-TNK2 kinase signaling offering another option for targeted therapy.

- **Dasatinib**, also a SRC family kinase inhibitor, is postulated to have potential therapeutic value in aCML given in vitro studies of cell lines with CSF3R truncation mutations having demonstrated dysregulation in the SRC family-TNK2 kinases with sensitivity to dasatinib. No in vivo reports have been published so far.

- In vitro data in RAS-driven leukemias, known to activate the MAPK signaling pathway, have been found to be sensitive to **trametinib**, a MEK1/2 inhibitor, which inhibits the extracellular signal-regulated kinase (ERK) directly downstream from the MAPK pathway. A case report of an aCML patient harboring an NRAS mutation attained a near complete hematologic response within several months of treatment with trametinib.

- **Midostaurin, tazemetostat**, and **fingolimod** are other potential mutation-specific drug targets with therapeutic potential against specific molecular mutations found in aCML.

Schwartz et al Blood Rev 2018

Conclusions

- aCML is a rare BCR–ABL1 negative myelodysplastic/myeloproliferative neoplasm characterized by increasing leukemic cell burden, organomegaly, anemia, and bone marrow failure.

- Adverse prognostic factors include: age > 65 years, female gender, leucocytosis >50 x 10^9/L, and SETBP1 mutations.

- The molecular pathogenesis of aCML is heterogeneous, with mutations involving SETBP1, CSF3R, ASXL1, and ETNK1 the most studied to date. It is reasonable to screen all patients with aCML for targetable CSF3R, JAK2, and RAS mutations.

- Younger patients with high-risk disease features should be screened for HSCT eligibility at time of diagnosis.

- Use of palliative chemotherapy (HU, IFN-α, ESA, and HMA) is most commonly used as a bridge to transplant or for patients ineligible for HSCT and/or clinical trials. Participation in clinical trials is encouraged whenever possible.

- Targeted therapy with JAK inhibitor (ruxolitinib), SRC kinase inhibitor (dasatinib), and MEK inhibitor (trametinib) all show therapeutic promise in aCML.