Atypical chronic myeloid leukaemia – a rare subtype of myelodysplastic/ myeloproliferative neoplasm

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Atypical chronic myeloid leukaemia (aCML) belongs to the group of myelodysplastic/myeloproliferative neoplasms. Changing diagnostic criteria and the rarity of the disease, with incidence approximately 100-times lower than the incidence of *BCR-ABL1*-positive chronic myeloid leukaemia, result in limited knowledge on aCML. At present the diagnosis is made based on the presence of granulocytic lineage dysplasia and precisely defined quantitative peripheral blood criteria, after exclusion of other molecularly defined myeloid neoplasms. Distinctive cytogenetic and molecular changes for aCML are missing, although recently *SETBP1* mutations were described in a significant proportion of patients. The majority of patients are male and elderly. The prognosis of aCML patients is very bad, with median overall survival ranging between 10.8 and 25 months, and acute myeloid leukaemia-free survival amounting to approximately 11 months. No treatment recommendations can be made based upon current evidence, although allogeneic haematopoietic stem cell transplantation seems to be able to induce long-term remission in eligible patients.

Key words: atypical chronic myeloid leukaemia, myelodysplastic/myeloproliferative neoplasms, *SETBP1* mutations, *CSF3R* mutations.

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Present and previous diagnostic criteria. Differential diagnosis

Atypical chronic myeloid leukaemia (aCML) was initially described as a subtype of myeloid neoplasm closely resembling chronic myelogenous leukaemia but lacking the pathognomonic Philadelphia chromosome [1]. The diagnostic criteria evolved with more evidence from cytogenetic and molecular studies, which in fact did not allow a more detailed identification of aCML, but helped to distinguish other defined neoplasms, clinically resembling aCML, from aCML. The classification systems that have been used for decades are presented in Table 1. It is necessary to be aware of them to understand that not all data on aCML available in the literature really cover the group of patients with what we now define as aCML. At present the diagnosis of atypical chronic myeloid leukaemia is made according to the World Health Organisation Criteria from 2008, revised in 2016 [2, 3]. Although the criteria have become more and more precise, the criterion of dysgranulopoiesis remains only descriptive, i.e. dysgranulopoiesis should be "marked". No detailed quantification has been supported so far.

Differential diagnosis of atypical chronic myeloid leukaemia encompasses chronic myeloid leukaemia *BCR-ABL1* positive and other myeloproliferative neoplasms, e.g. primary myelofibrosis, as well as myeloid/lymphoid neoplasms associated with rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2*. aCML needs also to be differentiated from other myelodysplastic/myeloproliferative neoplasms, with the biggest challenge being unclassifiable myelodysplastic/myeloproliferative neoplasm [2, 4].

Epidemiology. Patients' clinical and laboratory characteristics

Atypical chronic myeloid leukaemia is an infrequent entity with unknown epidemiological indices, although its relative incidence is estimated at one to two cases for every 100 patients with *BCR-ABL1*-positive chronic myeloid leukaemia [5].

All patients reported so far are adults, with male predominance. The patients presented with organomegaly and usually extensive proliferation of the granulocytic lineage. Both platelet count and haemoglobin concentration were either low, normal, or high, although approximately two thirds of patients were transfusion dependant. Similarly to other myeloproliferative neoplasms and myelodysplastic syndromes, aCML can transform into acute myeloid leukaemia. In the study of Wang *et al*. 10 (8%) patients had a prior history of cytotoxic exposure, including both chemotherapy and radiation (3.2%), chemotherapy only (0.8%), and radiation only (4%). All patients received treatment because of solid tumours [4]. Detailed patients' characteristics reported throughout the studies are presented in Table 2.

Cytogenetic and molecular changes in aCML

The frequency of cytogenetic changes differed among studies and ranged between 20 and 87.5% [4, 6–10]. The most frequently encountered abnormality was trisomy 8 (4.5–27%) [4, 6, 7, 9–11] and chromosome 20q deletion [6, 11]. The other reported changes included i17(q), -7/-7q, deletions of 5q, 13q, 17p, 12 q, and 11q, translocation t(6;8)(p23;q22), +21, +14, +19, and finally complex karyotype [4, 7, 8, 11].

A summary of the reported molecular abnormalities frequencies is presented in Table 3. Although somatic *CSF3R* mutations were initially reported to be pathogenetically associated with aCML, with T618I being the most common [12], this relation was not confirmed by latter studies [4, 13–15]. At present it seems that the mutations of *SET-binding protein 1* (*SETBP1*), which are encountered in 12–33% of aCML patients [7, 15–17], are the most important. *SETBP1* localises on chromosome 18q21.1 and codes for protein with a predominantly nuclear localisation that is expressed in haematopoietic stem/progenitor cells and also in committed progenitors, with mainly unknown function. While germline mutations are associated with Schinzel-Giedion syndrome (skeletal malformations, mental retardation, developmental delay), somatic mutations are responsible for leukaemogenesis. They are probably responsible for the development of dysplasia in granulopoietic and megakaryopoietic lineage. According to Meggendorfer *et al*., mutations of *SETBP1* are a later event in disease progression rather than an initial mutation. In their study mutations of *SETBP1* were associated with mutations of *ASXL1* in 65% of cases [17], similarly as in the study of Piazza *et al*., where *ASXL1* mutations were present more frequently in cases with *SETBP1* mutations (36% vs. 19%, respectively) [16]. Additionally, *SETBP1* mutations were more often associated with *SRSF2* mutations ($p = 0.004$) while, additionally, *SRSF2* mutations also often co-occurred with mutated *ASXL1* ($p = 0.010$) [15]. *TET2* mutations were more prevalent in cases with wild-type *SETBP1* (28% vs. 14%, respectively) [16]. In the study by Maxson *SETBP1* mutations were accompanied by *CSF3R* mutations in 5% of aCML cases [12].

Interestingly, in aCML, *SETBP1*-mutated patients showed a higher haemoglobin concentration compared to *SETBP1wt* patients (12.0 vs. 9.9 g/dl; $p = 0.016$) [15].

Mutations of *ETNK1* lead to loss of catalytic activity of ethanolamine kinase responsible for biosynthesis of phosphatidylethanolamine necessary for maintenance of cell-membrane architecture and topology of transmembrane proteins, synthesis of diacylglycerols, fatty acids and phosphatidic acid, cytokinesis, and many other processes [18]. The mutations are encountered in approximately 8% of aCML and 2.6–14% of chronic myelomonocytic leukaemia patients [7, 14, 18]. They can also be found in cases of systemic mastocystosis with eosinophilia [18], but they are not present in other tumours [14].

Prognostic factors. Prognostic score

The first score, proposed by Onida *et al*. [11], enabled stratification of patients into two risk groups, i.e. a low-risk group (0-1 points) and a high-risk group (2-3 points). Three simple parameters were taken into consideration while counting the score: 1) age over 65 years, 2) anaemia with haemoglobin concentration below 10 g/dl, and 3) severe leukocytosis with white blood cell count over 50 × 10^9/l, which were each assigned one point. Additionally, abso-

Table 1. Subsequent classifications used in the diagnosis of aCML

	Diagnostic criteria
FAB [10]	absence of Ph chromosome, absence of BCR/ABL fusion gen basophils < 2% monocytes ≥ 3% and <10% dysgranulopoiesis (++) immature granulocytes 10–20% blasts > 2%
Onida *et al*. [11]	absence of Ph chromosome on analysis of at least 20 metaphases hypercellular bone marrow with granulocytic hyperplasia, leftward shift in myeloid maturation bone marrow blasts < 30% absence of significant dysplasia persistent, unexplained peripheral granulocytic leukocytosis (WBC count > 10 × 10^9/l) peripheral blast cells < 30% monocyte percentage < 10% in the peripheral blood cells and absolute monocyte count < 1 × 10^9/l in patients with WBC counts < 20 × 10^9/l absence of substantial bone marrow myelofibrosis
WHO 2001 [30]	persistent leukocytosis absence of Ph chromosome and BCR/ABL fusion gene evidence of marked multilineage dysplasia monocytosis < 1 × 10^9/l basophils < 2% immature circulating precursors > 10% bone marrow blast count < 20%
WHO 2008 [5]	persistent leukocytosis (≥ 13 × 10^9/l) presence of immature circulating myeloid precursors (≥ 10% leukocytes) marked dysgranulopoiesis* absent/minimal monocytosis (≤ 1 × 10^9/l and < 10% of leukocytes) absence of basophilia (< 2%) absence of BCR-ABL1 or rearrangements of PDGFRA, PDGFRB, or FGFR1
WHO 2016 [2, 3]	emphasis on molecular changes (ETNK1, SETBP1) persistent leukocytosis (≥ 13 × 10^9/l) presence of immature circulating myeloid precursors (≥ 10% leukocytes) dysgranulopoiesis absence of basophilia (< 2%) absent/minimal monocytosis (< 10% of leukocytes) hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages < 20% blasts in the blood and bone marrow no rearrangements of PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2 WHO criteria for BCR-ABL1 positive chronic myeloid leukaemia, primary myelofibrosis, polycythemia vera or essential thrombocytopenia not met

** no detailed quantification supported*

Table 2. Patients' characteristics based on published reports. Continuous variables are summarised as median (range), nominal variables as percentage

Parameter	Wang *et al.* [4]	Breccia *et al.* [6]	Onida *et al.* [11]	Hernandez *et al.* [8]	Kurzrock *et al.* [9]	Patnaik *et al.* [7]	Drozd-Sokołowska *et al.* [31]
Classification used for diagnosis	WHO 2008	WHO 2001	Described in detail in Table 1	FAB	Described in detail in Table 1	WHO 2008, WHO 2016	WHO 2008
Number of cases	65	55	76	10*	8	25	18
Age (years)	72 (42–86)	62 (46–81)	66 (24–88)	63.5 (16–84)	60 (39–68)	70 (49–91)	65 (40–81)
Sex – male (%)	69%	43%	55%	50%	88%	84%	72%
WBC (× 10^9/l)	40.8 (13.8–227.1)	23.7 (14–150)	38 (11.1–296)	39.5 (18–68)	36 (22–300)	32 (8.3–192.7)	97 (23.8–342)
Blood immature myeloid precursors (%)	17 (10–65)	13 (10–20)	13 (0–52)	–	–	–	27.5 (12–72)
Haemoglobin (g/dl)	9.4 (5.7–13.6)	11 (4–18)	10.6 (7.3–16.1)	9.9 (5.1–14.2)	11.7 (8.9-15)	9.1 (6.3–14.9)	8.6 (3.9–14.9)
PLT count (× 10^9/l)	87 (7–974)	319 (44–2675)	160 (8–1105)	115 (9–732)	270 (50–1046)	95 (12–647)	66 (34–833)
Blast count – PB	2 (0–17)	1	–	–	–	1 (0–12)	2 (0–19)
Blast count – BM (%)	3 (0–17)	2 (0–20)	1 (0–29)	1.5 (0–10)		2 (0–15)	3.6 (1–19)
Monocytes (%)	–	2 (3–8)	2 (0–10)	2.5 (0–8)	–	–	1.4 (0–7)
Basophils (%)	–	1 (0–2)	0 (0–10)	0 (0–2)	–	–	0 (0–1)
Increased LDH activity (U/l)	–	–	Activity 1389 (210–6960)	–	–	–	–
Transfusion dependence	–	65%	–	–	–	64%	67%
Significant bone marrow fibrosis	30.8%	22% (traces of reticular fibrosis)	Exclusion criterion	–	–	–	–
Presence of dysplasia in: Erythroid line Megakaryocytic line Granulocytic line	–	 53% 49% 32% (severe)	Exclusion criterion	 90% 89% 100%	–	 16% 20% 100%	 50% 22%
Splenomegaly	–	54%	50%		75%	52%	61%
Hepatomegaly	–	49%	–	–	–	–	39%

BM – bone marrow; PB – peripheral blood; PLT – platelet; WBC – white blood cells
** the original report covers 11 cases; 1 case is however a transformation of MDS-RA*

lute monocytosis (monocytes >1.0 × 10^9/l), the presence of > 10% peripheral blood immature myeloid cells (including blasts), and LDH > 2000 U/ml adversely affected survival.

In the study by Wang *et al.* both a higher white blood cell count, either as a continuous variable or a cutoff of 50 × 10^9/l, and a higher percentage of peripheral blood myeloid precursors as a continuous variable were adverse prognostic factors for overall survival (OS) and acute myeloid leukaemia-free survival (AMLFS) in univariate analysis [4]. In this analysis, also a higher number of bone marrow blasts was a significant hazard for AMLFS but not for OS [4]. Increased activity of lactate dehydrogenase or platelet count, cytogenetic categories, and peripheral blood blasts were not significant for survival. The authors did not perform multivariate Cox regression analysis because too few factors were significant in the univariate analysis. Breccia *et al.* identified older age (> 65 years, HR = 0.869, 95% CI: 0.698–1.260, $p = 0.04$), female sex (HR = 0.715, 95% CI: 1.063–1.991, $p = 0.0001$), leukocyte count > 50 × 10^9/l (HR = 0.737, 95% CI: 1.073–2.014, $p = 0.001$), and the presence of immature circulating precursors (HR = 0.634, 95% CI: 1.069–1.986, $p = 0.05$) as prognostic factors of survival in multivariate analysis. In their study neither haemoglobin concentration nor dyserythropoiesis influenced survival. Factors predictive for acute myeloid leukaemia (AML) transformation were: palpable hepato- or splenomegaly (HR = 0.6, 95% CI: 1.158–1.992, $p = 0.03$), monocytosis (> 3 and <8% with monocytes < 1 G/L, HR = 0.87, 95% CI: 1.18–2.081, $p = 0.03$), increased bone marrow blasts > 5% (HR = 0.631, 95% CI: 1.145–1.97, $p = 0.007$), marked dyserythropoiesis (HR = 0.45, 95% CI: 1.419–1.796, $p = 0.004$), and transfusion dependency (HR = 0.65, 95% CI 0.085–0.638, $p = 0.01$) [6]. Patients with normal platelet count and haemoglobin concentration higher than 10 g/dl had superior survival in the analysis by Hernandez *et al.* [8]

In the most recent study by Patnaik *et al*. [7] advanced age (p = 0.02), low haemoglobin concentration (p = 0.01), red blood cell transfusion dependency (p = 0.03), high white blood cell count (p = 0.02), mutations of *TET2* (p = 0.03), *NRAS* (p = 0.04) and *PTPN11* (p = 0.02), as well as the presence of at least three gene mutations (p = 0.006) were adversely associated with overall survival in univariate analysis; *ASXL1*, *SETBP1*, and *ETNK1* mutations did not impact OS. In multivariate analysis, advanced age (> 67 years; HR = 10.1, 95% CI: 1.3–119, p = 0.003), low haemoglobin concentration (< 10 g/dl, HR = 8.2, 95% CI: 1.6–23.2, p = 0.008), and *TET2* mutations (HR = 8.8, 95% CI: 1.6–47.7, p = 0.01) retained prognostic significance. Based on the parameters significant in multivariate analysis, i.e. age > 67 years, haemoglobin < 10 gm/dl, and the presence of *TET2* mutations (each counted as one risk factor), the authors proposed a hazard ratio-weighted prognostic model allowing effective stratification of patients into two risk categories, low (0–1 risk factor) and high (≥ 2 risk factors), with a median OS of 18 and seven months, respectively.

To conclude, despite two prognostic scores having been proposed for the stratification of aCML patients, none seems to be useful in everyday practice. The Onida score was calculated for patients diagnosed with aCML using unique diagnostic criteria (Table 1), not fully compatible with current criteria, while the score proposed by Patnaik *et al*. requires molecular studies that are not always available in everyday practice.

Prognosis

The prognosis of patients diagnosed with aCML is very poor. Overall survival ranges between 10.8 months and 25 months [4, 6, 8] or even 29 months for smaller series [9], while AML-free survival amounts to 11.2 months [4].

Twenty-four out of 65 patients (37%) in the study of Wang *et al*. [4], 20 out of 55 (40%) in the study by Breccia *et al*. [6], one among eight in the study of Kurzrock *et al*. [9], and two (8%) in the study of Patnaik *et al*. [7] transformed into AML. In the study by Onida *et al*. blastic transformation preceded death in eight out of 26 patients (31%), with a median time from referral to blast crisis of 11.5 months (range, 1–34 months) [11]. It is, however, worth noting that in none of these studies was cumulative incidence of AML-transformation rate calculated with use of competing risk analysis. Additionally, in the study by Onida *et al*., transformation to AML was considered only for increase of blast cells count to more than 30%, and not to 20% [11].

Treatment

No guidelines exist on the treatment of aCML patients. Published results, due to small patient groups, are inconclusive in respect to best treatment choice. Onida *et al*. were unable to show any advantage from the treatment; however, there are major concerns about the diagnostic criteria used for this study, and these results should be interpreted with caution [11]. So far, different therapeutic modalities were used, including hydroxyurea [4, 6–9, 11], busulfan [11], hypomethylating agents [4, 7, 11, 19], histone deacetylase inhibitors [4], low-intensity chemotherapy, including low-dose cytarabine [4, 6], induction chemotherapy [4, 8], combination chemotherapy [11], tyrosine kinase inhibitors [4], JAK2 tyrosine kinase inhibitors (i.e. ruxolitinib) [4, 20, 21], or RAS [4], FLT3 [4], MAPK [4], MYC [4], or AKT inhibitors [4]; immunomodulatory agents i.e. thalidomide [4, 7], lenalidomide [4, 7], or interferon [4, 6, 7, 9, 11]; and supportive care only [4, 7, 11]. Reports on allogeneic haematopoietic stem cell transplantation (alloHSCT) are scarce, frequently coming from either case reports or small case series [8, 22–26]. Recently a study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation on the results of alloHSCT in aCML was published, covering 42 patients, being the largest group reported so far [27]. In alloHSCT the majority of patients were in first chronic phase (69%); EBMT risk-score by Gratwohl [28] was as follows: low-risk (score = 0–2) in 45%, intermediate-risk (score = 3) in 31%, and high-risk (score = 4–7) in 24% of patients. AlloHCT was performed from matched unrelated donor in 15 cases (36%), and from HLA-identical siblings in 27 cases (64%). Twenty-four per cent of patients received reduced intensity conditioning (RIC) (median age 58 years), while 76% of patients received myeloablative conditioning (MAC) (median age 46 years). Total body irradiation was incorporated in 56% of MAC. Following alloHSCT two patients (5%)

Table 3. Frequency of molecular changes

Molecular change	Frequency (%)	Reference
SRSF2	12–40	[7, 15]
RAS (KRAS/ NRAS)	8–35	[4, 7, 11, 14]
RUNX1	12	[7]
JAK2	3–8	[4, 7, 15]
CSF3R	0–40	[4, 7, 15, 29]
U2AF1	0–20	[7, 14]
CALR	0–4	[4, 7, 15, 32]
MPL	0–2	[4, 7, 15]
CEBPA	11.8	[4, 7]
KIT	0	[4]
FLT3	7.1	[4]
FLT3-TKD	4	[7]
IDH1/IDH2	0–4	[4, 7]
EZH2	8–20	[7, 14]
ASXL1	20–66	[7, 14, 15]
NPM1	0	[4, 7]
SETBP1	12–33	[7, 14–17]
CBL	0–10	[7, 15, 33]
ETNK1	8–8.8	[7, 14]
TET2	16–41	[7, 15]
SF3B1	8	[7]
PTPN11	4	[7]
ZRSR2	4	[7]
IKZF	0	[7]

suffered from primary graft failure and two patients (6.5%) were non-responders, while overall response rate amounted to 93.5% – 26 (87%) complete remissions and two (6.5%) partial remissions. Five-year overall survival was assessed at 51%, relapse-free survival at 36%, non-relapse mortality at 24%, and relapse incidence at 40%. Acute graft-versus-host disease (aGvHD) grade II–IV occurred in 12 patients, while chronic graft-versus-host disease was seen in 21 patients, with nine patients developing extensive form. The factors predictive for overall survival were age and Gratwohl score, while solely the donor type was significantly associated with relapse incidence and relapse-free survival, favouring patients transplanted from an unrelated donor. The type of conditioning did not impact either overall survival or relapse-free survival, as well as relapse incidence or non-relapse mortality.

There are no indications concerning the timing of alloHSCT in the available literature. Taking into consideration the bad prognosis of aCML patients, it seems reasonable to qualify patients for this procedure early.

Assuming that at least some patients with aCML may harbour mutated *CSF3R*, known to signal downstream through both Janus kinase (JAK) and SRC tyrosine kinase pathways [29], it is amenable that these patients may respond to JAK2 or SRC kinase inhibitors, e.g. ruxolitinib and dasatinib. *CSF3R* mutations are classified into two classes: nonsense or frame-shift mutations leading to premature truncation of the cytoplasmic tail of the receptor (truncation mutations) and point mutations in the extracellular domain of CSF3R (membrane proximal mutations). Depending on the type of mutation, different downstream signalling pathways are involved (*CSF3R* truncation mutations – SRC-TNK2; *CSF3R* membrane proximal mutations – JAK-STAT).

In conclusions, aCML is a very rare disease, with changing diagnostic criteria throughout the last decades, with some of the exclusion criteria used for older studies being inclusion criteria for the newer ones. Therefore, the information obtained from older epidemiological studies should be interpreted with caution. Although aCML is frequently associated with *SETBP1* mutations, driver mutations for this entity remain unknown. The prognosis of aCML patients is still very poor. No treatment guidelines exist, and there is urgent need for the development of new effective therapeutic strategies. At present only allogeneic haematopoietic stem cell transplantation can induce long-term remission.

The authors declare no conflict of interest.

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