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.

Contemp Oncol (Pozn) 2018; 22 (1): 14–19 DOI: https://doi.org/10.5114/wo.2018.74388

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

Joanna E. Drozd-Sokołowska, Anna Waszczuk-Gajda, Krzysztof Mądry, Jadwiga Dwilewicz-Trojaczek

Department of Hematology, Oncology and Internal Diseases, Medical University of Warsaw, Poland

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 PDGFRα, PDGFRβ, 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 i(7q), -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 complete 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 mastocytosis 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 | WHO 2001 | WHO 2008 | WHO 2016 |
|---------------------|----------|----------|---------|
|                   | absence of Ph chromosome and BCR/ABL fusion gene | evidence of marked multilineage dysplasia | emphasis on molecular changes (ETNK1, SETBP1) |
|                   | marked dysgranulopoiesis* | absence of basophilia (< 2%) | persistent leukocytosis (≥ 13 × 10^9/l) |
|                   | absence of significant dysplasia | absence of immature circulating myeloid precursors (≥ 10% leukocytes) | presence of immature circulating myeloid precursors (≥ 10% leukocytes) |
|                   | immature circulating precursors > 10% | bone marrow blast count < 20% | hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages |
|                   | absence of BCR-ABL or rearrangements of PDGFRα, PDGFRβ, or FGFR1 | absence of basophilia (≥ 2%) | < 20% blasts in the blood and bone marrow |
|                   | absence of BCR-ABL or rearrangements of PDGFRα, PDGFRβ, or FGFR1 | absence of basophilia (< 2%) | no rearrangements of PDGFRα, PDGFRβ, FGFR1 or PCM1-JAK2 |
|                   | absence of BCR-ABL or rearrangements of PDGFRα, PDGFRβ, or FGFR1 | absence of basophilia (< 2%) | WHO criteria for BCR-ABL1 positive chronic myeloid leukaemia, primary myelofibrosis, polycythaemia 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:        | –               | 53%                | 90%               | –                    | 16%               | 50%               |
| Erythroid line                   | 53%             | 49%                | 89%               | 100%                 | 20%               | 22%               |
| Megakaryocytic line             | 32% (severe)    | 54%                | 50%               | 75%                  | 52%               | 61%               |
| Granulocytic line               | –               | 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), leucocyte 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 hepatosplenomegaly (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 = 0.03), 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 g/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 Brecchia 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 allo-HSCT in aCML 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%)

| 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]   |
| TET1             | 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 Gravtow 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 alloH SCT 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.

References
1. Galton DA. Haematological differences between chronic granulocytic leukaemia, atypical chronic myeloid leukaemia, and chronic myelomonocytic leukaemia. Leuk Lymphoma 1992; 7: 343-50.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391-405.
3. Orazi A, Bennett JM, Bain BJ, et al. Atypical chronic myeloid leukaemia, BCR-ABL1-negative. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues Revised. Swerdlow SH, Campo E, Harris NL, et al. (eds.). 4th Edition. IARC 2017; 87-9.
4. Wang SA, Hasserjian RR, Fox PS, et al. Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. Blood 2014; 123: 2645-51.
5. Vardiman JW, Bennett JM, Bain BJ, et al. Atypical chronic myeloid leukaemia, BCR-ABL-negative. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, Campo E, Lee Harris N, et al. (eds). IARC Press, Lyon 2008; 80-1.
6. Breccia M, Biondo F, Latagliata R, et al. Identification of risk factors in atypical chronic myeloid leukaemia. Haematologica 2006; 91: 1566-8.
7. Patnaik MM, Barraco D, Laslo TL, et al. Targeted next generation sequencing and identification of risk factors in World Health Organization defined atypical chronic myeloid leukaemia. Am J Hematol 2017; 92: 542-548.
8. Hernandez JM, del Canizo MC, Cuneo A, Garcia JL, Gutierrez NC, Gonzalez M, Castoldi G, San Miguel JF. Clinical, hematological and cytogenetic characteristics of atypical chronic myeloid leukaemia. Ann Oncol 2000; 11: 441-4.
9. Kurzrock R, Bueso-Ramos CE, Kantarjian H, Freireich E, Tucker SL, Siciliano M, Pilat S, Talpaz M. BCR rearrangement-negative chronic myelogenous leukaemia revisited. J Clin Oncol 2001; 19: 2915-26.
10. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, Sultivan C, Cox C. The chronic myeloid leukaemia: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Groups. Br J Haematol 1994; 87: 746-54.
11. Onida F, Ball G, Kantarjian HM, et al. Characteristics and outcome of patients with Philadelphia chromosome negative, bcr/abl negative chronic myelogenous leukaemia. Cancer 2002; 95: 1673-84.
12. Maxson JE, Gottlib J, Poliyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med 2013; 368: 1781-90.
13. Pardanani A, Laslo TL, Laborde RR, et al. CSF3R T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. Leukemia 2013; 27: 1870-3.
14. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. Blood 2015; 125: 499-503.
15. Meggendorfer M, Haferlach T, Alpermann T, et al. Specific molecular mutation patterns delineate chronic neutrophilic leukemia, atypical chronic myeloid leukemia, and chronic myelomonocytic leukemia. Haematologica 2014; 99: e244-e.
16. Piazza R, Valletta S, Winkelmann N, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. Nat Genet 2013; 45: 18-24.
17. Meggendorfer M, Bacher U, Alpermann T, et al. SETBP1 mutations occur in 9% of MDS/MPN and in 4% of MPN cases and are strongly associated with atypical CML, monosomy 7, isochromosome i(17) (q10), ASXL1 and CBL mutations. Leukemia 2013; 27: 1852-1860.
18. Laslo TL, Finke CM, Zblewski D, et al. Novel recurrent mutations in ethanamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosinophilia and chronic myelomonocytic leukemia. Blood Cancer J 2015; 5: e275.
19. Hausmann H, Bhatt VR, Yuan J, Maness LJ, Ganti AK. Activity of single-agent decitabine in atypical chronic myeloid leukemia. J Oncol Pract 2015.
20. Ammatuna E, Eefting M, van Lom K, Kavelaars FG, Valk PJ, Touw IP. Atypical chronic myeloid leukemia with concomitant CSF3R T618I and SETBP1 mutations unresponsive to the JAK inhibitor ruxolitinib. Ann Hematol 2015; 94: 879-880.
21. Dao KH, Solti MB, Maxson JE, Winton EF, Press RD, Drueker BJ, Tyner JW. Significant clinical response to JAK1/2 inhibition in a patient with CSF3R T618I-positive atypical chronic myeloid leukaemia. Leuk Res Rep 2014; 3: 67-69.
22. Koldehoff M, Beelen DW, Trenschel R, Steckel NK, Peceny R, Dietzchold M, Ottinger H, Elmaagacli AH. Outcome of haematopoietic stem cell transplantation in patients with atypical chronic myeloid leukemia. Bone Marrow Transplant 2004; 34: 1047-1050.
Atypical chronic myeloid leukaemia – a rare subtype of myelodysplastic/myeloproliferative neoplasm

23. Mittal P, Saliba RM, Giralt SA, et al. Allogeneic transplantation: a therapeutic option for myelofibrosis, chronic myelomonocytic leukemia and Philadelphia-negative/BCR-ABL-negative chronic myelogenous leukemia. Bone Marrow Transplant 2004; 33: 1005-1009.

24. Cahu X, Chevalier P, Clavert A, et al. Allo-SCT for Philadelphia-negative myeloproliferative neoplasms in blast phase: a study from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SF-GM-TC). Bone Marrow Transplant 2014; 49: 756-60.

25. Langabeer SE, McCarron SL, Haslam K, O’Donovan MT, Connolly E. The CSF3R T618I mutation as a disease-specific marker of atypical CML post allo-SCT. Bone Marrow Transplant 2014; 49: 943-4.

26. Lim SN, Lee JH, Lee JH, et al. Allogeneic hematopoietic cell transplantation in adult patients with myelodysplastic/myeloproliferative neoplasms. Blood Res 2013; 48: 178-84.

27. Onida E, de Wreede LC, van Biezen A, et al. Allogeneic stem cell transplantation in patients with atypical chronic myeloid leukaemia: a retrospective study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. Br J Haematol 2017; 177: 759-65.

28. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 1998; 352: 1087-92.

29. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood 2013; 122: 1707-11.

30. Vardiman JW, Imbert M. Atypical chronic myeloid leukemia. In: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Jaffe ES, Harris NL, Stein H, JWV (eds.). World Health Organization Classification of Tumours. Lyon IARC Press 2001; 53-54.

31. Drozd-Sokolowska J, Madry K, Waszczuk-Gajda A, et al. Atypical chronic myeloid leukaemia: A case of an orphan disease-A multicenter report by the Polish Adult Leukemia Group. Hematol Oncol 2013; 36: 2391-2405.

32. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med 2013; 369: 2391-2405.

33. Grand FH, Hidalgo-Curtis CE, Ernst T, et al. Frequent CBL mutations associated with 11q acquired uniparental disomy in myeloproliferative neoplasms. Blood 2009; 113: 6182-92.

Address for correspondence
Joanna E. Drozd-Sokołowska
Department of Hematology, Oncology and Internal Diseases
Medical University of Warsaw
Banacha 1a
02-097 Warsaw, Poland
e-mail: johna.dr@poczta.fm

Submitted: 31.01.2018
Accepted: 11.03.2018