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Chronic Myeloid Leukemia, BCR-ABL1 Positive

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Synonyms

Chronic myelogenous leukemia

Definition

Chronic myeloid leukemia (CML) represents the clonal and neoplastic proliferation of a hematopoietic stem cell with a chromosomal translocation t(9;22) and junction of the BCR-gene and ABL-gene resulting in a BCR-ABL fusion protein of 210 kD or 190 kD, and leading to growth factor independent proliferation and leucocytosis. Non-neoplastic stem cells are vergrown but differentiation and maturation are retained by neoplastic cells with sufficient production of blood cells. In untreated patients, the steady state phase (chronic phase) with sufficient production of mature blood cells usually progresses to an accelerated phase with deterioration of hematologic blood parameters and/or organomegaly. Differentiation of the transformed hemaopoietic stem cells gets lost after a period of about 3 years (median) resulting in the blast phase. Transition from chronic to accelerated and blast phase, respectively, is defined by a number of parameters, which according to WHO (Vardiman et al. 2017) are summarized in Table 1 of chapter "▶ Chronic Myeloid Leukemia and Polcythemia Vera Progression."

Clinical Features

- **Incidence**

  Incidence of CML in Europe is about 1.2 to 1.5 per 100,000 inhabitants per year. In Germany, about 1200 cases are newly diagnosed each year. Presentation most frequently takes place in the chronic phase of disease with mild anemia, thrombocytopenia, and leucocytosis. Abnormal peripheral blood values may be accompanied by mild B symptoms and splenomegaly. The incidence of progression in CML has changed dramatically since the introduction of tyrosine kinase inhibitors (TKI) into therapy. The chronic phase in CML has historically lasted for 3–4 years with a progression rate to blast crisis in the first 2 years of 5–10% and thereafter of 20–25% per year. Untreated patients will invariably develop progression mostly within 3–4 years after diagnosis (Kantarjian et al. 1988). In the era of TKI treatment, the 5-year progression-free survival is 80–95%. Disease progression to advanced phase (accelerated or blast phase) has been reduced to 1–1.5% per

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Chronic Myeloid Leukemia, BCR-ABL1 Positive, Table 1 Response to TKI treatment in CML (Melo and Barnes 2007)

Time of treatment (months)	Failure	Optimal response
3	Philadelphia chromosome: >95% BCR-ABL RNA: >10%	Philadelphia chromosome: <35% BCR-ABL RNA: <10%
6	Philadelphia chromosome: >35% BCR-ABL RNA: >10%	Philadelphia chromosome: 0% BCR-ABL RNA: ≤1%
12	Philadelphia chromosome: >1% BCR-ABL RNA: >1%	BCR-ABL RNA: ≤0.1%
>18		BCR-ABL RNA: ≤0.01%
Any time period	Loss of major response with BCR-ABL RNA increase ≥5 fold	

year from more than 20% per year in the pre-TKI era (Mukherjee and Kalaycio 2016).

The highest incidence of CML is in the fifth and sixth decade of living, but every age can be affected. Very rarely, CML occurs in childhood (Hijiya et al. 2016).

- **Sex**

  In CML, there is male predominance.

- **Site**

  The bone marrow is the primary site of CML and is almost always affected. Neoplastic stem cells and precursor cells may colonize other organs, most frequently the spleen and liver, less frequently lymph nodes. Principally every organ can be affected.

- **Treatment**

  Treatment in CML is directed against the underlying tyrosine kinase activation of the BCR-ABL fusion protein. Since the first TKI, imatinib, had proven its potency to cure CML, other more effective agents became available (Dasatinib, Nilotinib, Bosutinib). Therapy is guided by depth of molecular response in the peripheral blood as depicted in Table 1.

  In case of therapy failure, increase of dosage of TKI or change of drug is recommended. Measurements between indicated thresholds require short-term control and in case of persistence are considered as indicators of increased risk for therapy failure. TKI-treated patients in the chronic phase who have achieved major molecular response enjoy durable responses with virtually no current progression to accelerated phase or blast crisis (Steegmann et al. 2016). Patients who have achieved stable complete molecular remission may experience in approximately 40% of cases complete continued remission in the absence of maintenance treatment (Steegmann et al. 2016). In the accelerated phase, dosage increase of TKI may be successful (Deininger 2015).

- **Outcome**

  Without treatment, most patients will progress to acceleration and blast crisis after a median duration of 3 years of the chronic phase (see chapter "▶ Progression"). The prognosis of CML patients in the blast phase is dismal with median survival ranging from 7 to 11 months (Hehlmann et al. 2016). This has dramatically changed with the introduction of TKI. Five year overall survival ranges from >90% to 99% with modern TKI (Hochhaus et al. 2017; Cortes et al. 2018.

Macroscopy

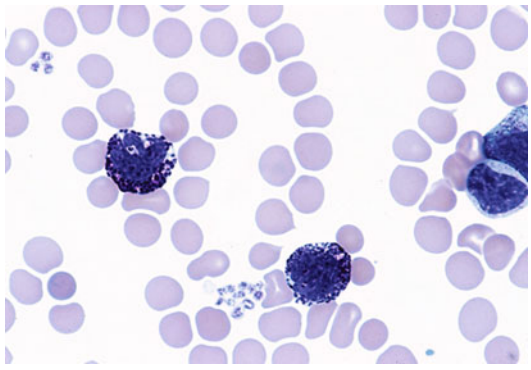
Usually there is mild splenomegaly with diffuse organ enlargement; in addition, hepatomegaly and lymph node tumors may be observed. In the accelerated phase, there may be considerable splenomegaly.

Microscopy

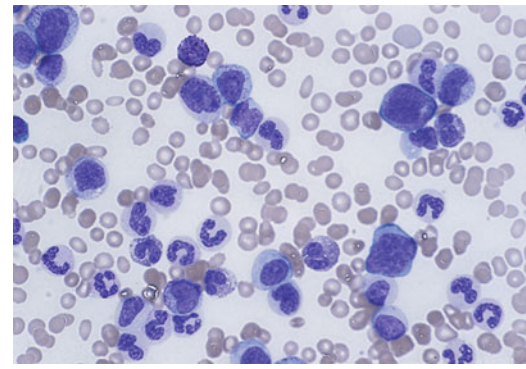
Microscopic presentation of CML is dependent of the phase of disease, either chronic phase or acceleration phase or blast crisis.

In the chronic phase, granulocyte numbers are increased in the peripheral blood accounting predominantly for leucocytosis. Median leucocyte counts are about 100 × 10^3/μl ranging from 12–1000 × 10^3/μl. Regularly, there is an increase of basophil counts absolutely and in most cases also relatively with more than 1% of blood leucocytes (Fig. 1). Likewise, eosinophils display higher blood cell counts. Diagnostic hallmark are immature cells of granulopoiesis encompassing all stages of maturation from promyelocytes to myelocytes (Fig. 2). Monocytes are absolutely increased in number (>1.000/μl) but usually the percentage is below 5%. Whereas thrombocytopenia is uncommon, increased thrombocyte counts are frequently encountered, in some cases amounting up to 1 × 10^6/μl.

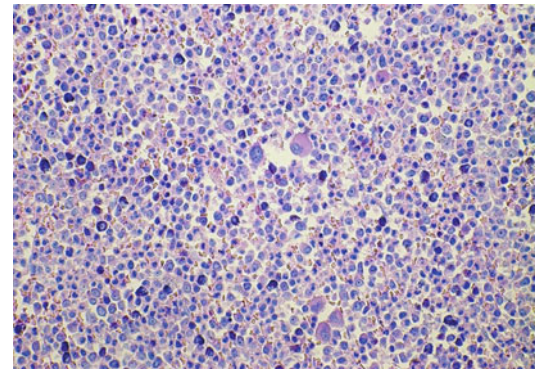
Besides highly characteristic peripheral blood cell findings, bone marrow histology reveals typical but not specific changes. Cellularity is exaggerated and usually fatty cells are not visible any more (Fig. 3). Dominating and left-shifted granulopoiesis displays peritrabecular rims of promyelocytes with maturation towards the center of the intertrabecular spaces. In addition, there is prominent proliferation of eosinophils and eosinophilic precursor cells (Fig. 4). In some, but not all cases, megakaryocytes are increased in number and reveal formation of clusters. Regularly, megakaryocytes are small and show round, hypo-lobulated nuclei (Fig. 5). Erythropoietic nests are smaller than usual and reduced in number. In the chronic phase, immature blasts may be increased but do not exceed 5% of all bone marrow cells. As a correlate of increased intramedullary cell turnover, sea-blue histiocytes and pseudo Gaucher cells can be found (Fig. 6) whereas hemosiderin macrophages are reduced or even completely missing. About a



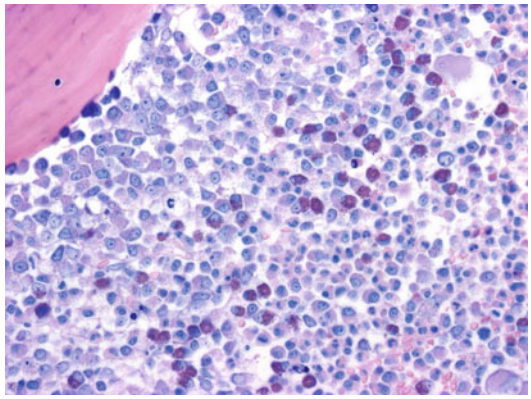
Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 1 BCR-ABL positive CML typically reveals increase of basophilic granulocytes (absolutely and relatively >1%) which is missing in most reactive leucocytoses and atypical CML (May Grünwald Giemsa)



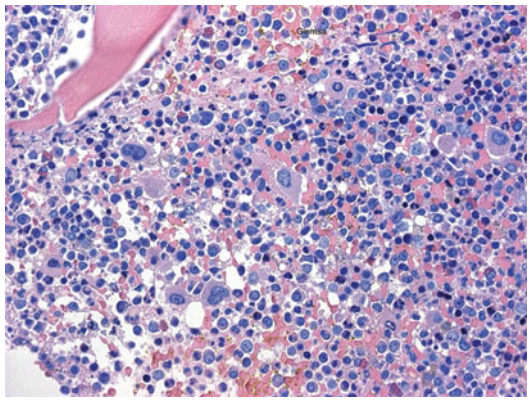
Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 2 In the peripheral blood there is an increase of leucocytes and shift to the left with all precursor stages of granulopoiesis ranging from immature blasts (right lower corner) to promyelocytes, metamyelocytes to mature granulocytes (May Grünwald Giemsa)



Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 3 Histology shows exaggerated cellularity with almost complete loss of fatty tissue with prominent proliferation of the eosinophilic lineage besides predominant neutrophilic differentiation (Giemsa)



Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 4 A typical features are broad peritrabecular rims of promyelocytes exhibiting maturation to granulcytes towards the centers of intertrabecular spaces with prominent participation of the eosinophilic lineage (Giemsa)



Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 5 The majority of megakaryocytes are small with unsegmented small hypolobulated round nuclei (Giemsa)

third of cases display mild to moderate myelofibrosis which is associated with reduced therapy response.

Besides bone marrow, which is affected in every case of CML, other organs may show infiltration of other organs by clonal hematopoietic cells. Most frequently the spleen is involved and immature and mature cells of granulocytic lineage are found as diffuse and focal not clearly demarcated infiltrates in the red pulp. The liver ranks second and when affected reveals intrasinusoidal infiltration. Lymph nodes usually demonstrate involvement of the interfollicular T-cell area. Besides granulopoietic cells, megakaryocytes may be seen in organs which are infiltrated by neoplastic hematopoiesis whereas erythroid colonies are only rarely encountered.

During acceleration, more organs may show involvement and the proportion of precursor cells and blasts is increasing (see chapter on "▶ Progression").

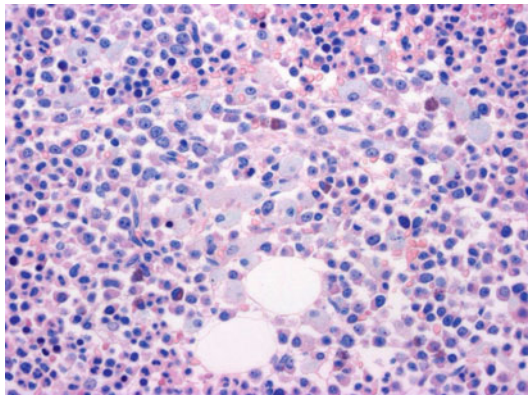
Immunophenotype

Immunophenotyping does not play a major role in diagnosis of CML in the chronic phase. CD34 and CD117 can be applied to get a rough estimate of the blast content. However, leukemic blasts may be partly or completely negative for these markers in up to 30% of cases. Hence, in order to avoid underestimation, immunohistochemically determined blast cell content cannot be equalled with counts in bone marrow smears which is still representing the gold standard.

In blast crisis which may be manifest in the first presentation, immunophenotyping is mandatory as indicated in the chapter on "▶ Progression."

Molecular Features

CML is defined by the presence of *BCR-ABL* fusion gene. *BCR-ABL* fusion represents the molecular basis of the Philadelphia chromosome generated by translocation t(9;22). The reciprocal translocation between chromosomes 9 and 22 is detectable by routine cytogenetic karyotyping in more than 90% of cases. In a small subset of cases, the translocation may be complex with involvement of more than two chromosomes or it may be hidden and demonstrable only by molecular studies of the *BCR-ABL* fusion. There is evidence that translocation t(9;22) is not the first event in clonal evolution of the neoplasm but rather a secondary event (Fialkow et al. 1981). The break on chromosome 22 occurs within a comparably small region of 5.5 kilo bases (kb) which accordingly has been labeled as break point cluster region (BCR). The break on chromosome 9 affects the *ABL* proto-oncogene and is located in the huge



Chronic Myeloid Leukemia, BCR-ABL1 Positive, Fig. 6 In many but not all cases of CML pseudo-Gaucher cells with broad lightly stained cytoplasm may be found. These sphingolipid rich macrophages are not specific for CML but also may be encountered in other stages with increased turnover of granulocytic cells (Giemsa)

first intron (>100 kb) between ABL exon 1a and 1b. The split within the *BCR* gene affects exons 12–16 and in most cases takes place between exons 13 and 14 or 14 and 15, respectively. Rarely, exons 17–20 may be involved. These cases are characterized by marked neutrophilia or thrombocytosis (Pane et al. 1996). As a consequence of the variability in break point location in the large intron 1 of the *ABL* gene, DNA-based PCR is not suited to detect the gene fusion but reversely transcribed mRNA has to be utilized. The fused mRNA is also exploited to evaluate depth of molecular remission (Table 1). As alternative approach, fluorescence in-situ hybridization can be applied to detect the *BCR-ABL* gene fusion. In most systems, red and green dyes produce a yellow colored spot of the fusion gene. The fusion gene is translated into a 210 kilo Dalton (kDa) protein. Due to alternative splicing also, a 190 kDa variant of the BCR-ABL fusion protein may be found (Melo 1996; van Rhee et al. 1996) which in a minority of cases represents the dominating protein. These cases are characterized by marked monocytosis and have to be differentiated from chronic myelomonocytic leukemia (Melo et al. 1994). In cases with predominant 190 kDa variant of the BCR-ABL fusion protein, the break in the *BCR* gene is located upstream of exons 12–16 (major break point region) within the so-called minor break point region. The latter is affected in Philadelphia-chromosome positive acute lymphoblastic leukemia. Immunohistochemical detection of BCR-ABL fusion protein is not used. In blastic progression, the Philadelphia chromosome (Ph) is retained in most instances but additional changes occur (see chapter "▶ Progression"). Additional aberrations may occur in the chronic phase (+Ph, +8, +19, iso(17), −7, 3q−, complex aberrant karyotype) and indicate an increased risk of progression. As a consequence and in order to detect advanced stages, guidelines request karyotypic analysis of CML at initial diagnosis, which cannot be replaced by molecular analysis alone (Vardiman et al. 2017).

Differential Diagnosis

The most relevant differential diagnoses to be considered are (Bennett et al. 1994):

- Reactive leucocytosis (leukemoid reaction)
- BCR-ABL negative atypical CML
- Chronic myelomonocytic leukemia
- Other types of myeloproliferative neoplasms

Exceptionally, a left-shifted blood picture with immature cells up to promyelocytes may represent a reactive change in infectious or other inflammatory conditions. In these cases, basophilia is regularly lacking. Bone marrow histology reveals normally sized megakaryocytes without the atypical features of small and mononuclear megakaryocytes in CML. Usually, hypercellularity in reactive lesions leaves more residual fatty tissue than CML bone marrow. In cases which remain questionable are encountered only very infrequently. In doubtful cases, detection of *BCR-ABL* fusion mRNA will enable definite discrimination.

A more difficult discrimination is provided by the differentiation of atypical CML from *BCR-ABL* positive CML. Left-shifted blood picture is present in both diseases. Basophilia is rare in atypical CML but it may be observed.

Megakaryocytic atypia is variable in atypical CML, usually the number is reduced and preponderence of micromegakaryocytes as in BCR-ABL positive is lacking. A feature which is generally not found in atypical CML by contrast to *BCR-ABL* positive CML is prominent proliferation of eosinophilic precursors. Myelofibrosis can occur in both diseases but it is more frequent in *BCR-ABL* positive CML. Analysis of *BCR-ABL* is mandatory in order to achieve an adequate classification.

Some *BCR-ABL* negative myeloproliferative neoplasms, in particular primary myelofibrosis, may present with left-shifted leucocytosis and basophilia like in CML. Bone marrow histology usually allows differentiation because small mononuclear megakaryocytes which are typical for CML are not found but instead large, cluster-forming megakaryocytes are encountered. In addition, molecular studies will be helpful (*BCR-ABL* fusion transcripts and mutations of *JAK2*, *MPL*, or *calreticulin*). In rare cases, however, the BCR-ABL junction may be combined with *JAK2* mutation (Hussein et al. 2007). In these cases, the size of megakaryocytes resembles that of *JAK2* mutated myeloproliferative neoplasms and small megakaryocytes are usually missing. Sometimes, the combined JAK2 mutated neoplasm is not evident at primary diagnosis and becomes evident only after successful treatment of the *BCR-ABL* positive clone by TKI, usually mistaken as developing therapy resistance (see chapter on "► Progression," Fig. 4) (Hussein et al. 2007).

References and Further Reading

Baccarani, M., Cortes, J., Pane, F., Niederwieser, D., Saglio, G., Apperley, J., Cervantes, F., Deininger, M., Gratwohl, A., Guilhot, F., Hochhaus, A., Horowitz, M., Hughes, T., Kantarjian, H., Larson, R., Radich, J., Simonsson, B., Silver, R. T., Goldman, J., Hehlmann, R., & European LeukemiaNet. (2009). Chronic myeloid leukemia: An update of concepts and management recommendations of European LeukemiaNet. *Journal of Clinical Oncology, 27*, 6041–6051.

Baccarani, M., Castagnetti, F., Gugliotta, G., Palandri, F., & Rosti, G. (2014). Definition and treatment of resistance to tyrosine kinase inhibitors in chronic myeloid leukemia. *Expert Review of Hematology, 7*, 397–406.

Barosi, G., Mesa, R. A., Thiele, J., Cervantes, F., Campbell, P. J., Verstovsek, S., Dupriez, B., Levine, R. L., Passamonti, F., Gotlib, J., Reilly, J. T., Vannucchi, A. M., Hanson, C. A., Solberg, L. A., Orazi, A., Tefferi, A., & International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). (2008). Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. *Leukemia, 22*, 437–438.

Bartels, S., Lehmann, U., Büsche, G., Schlue, J., Mozer, M., Stadler, J., Triviai, I., Alchalby, H., Kröger, N., & Kreipe, H. (2015). SRSF2 and U2AF1 mutations in primary myelofibrosis are associated with JAK2 and MPL but not calreticulin mutation and may independently reoccur after allogeneic stem cell transplantation. *Leukemia, 29*, 253–255.

Bartels, S., Faisal, M., Büsche, G., Schlue, J., Kreipe, H., & Lehmann, U. (2018). Fibrotic progression in polycythemia vera is associated with early concomitant driver-mutations besides JAK2. *Leukemia, 32*, 556–558.

Bennett, J. M., Catovsky, D., Daniel, M. T., Flandrin, G., Galton, D. A., Gralnick, H., Sultan, C., & Cox, C. (1994). The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French–American–British co-operative leukaemia group. *British Journal of Haematology, 87*, 746–754.

Cortes, J. E., Gambacorti-Passerini, C., Deininger, M. W., Mauro, M. J., Chuah, C., Kim, D. W., Dyagil, I., Glushko, N., Milojkovic, D., le Coutre, P., Garcia-Gutierrez, V., Reilly, L., Jeynes-Ellis, A., Leip, E., Bardy-Bouxin, N., Hochhaus, A., & Brümmendorf, T. H. (2018). Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: Results from the randomized BFORE trial. *Journal of Clinical Oncology, 36*, 231–237. https://doi.org/10.1200/JCO.2017.74.7162.

Deininger, M. W. (2015). Diagnosing and managing advanced chronic myeloid leukemia. *American Society of Clinical Oncology Educational Book*, e381–388.

Fialkow, P. J., Martin, P. J., Najfeld, V., Penfold, G. K., Jacobson, R. J., & Hansen, J. A. (1981). Evidence for a multistep pathogenesis of chronic myelogenous leukemia. *Blood, 58*, 158–163.

Hehlmann, R., Saußele, S., Voskanyan, A., & Silver, R. T. (2016). Management of CML-blast crisis. *Best Practice & Research. Clinical Haematology, 29*, 295–307.

Hijiya, N., Schultz, K. R., Metzler, M., Millot, F., & Suttorp, M. (2016). Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood, 127*, 392–399.

Hochhaus, A., Larson, R. A., Guilhot, F., Radich, J. P., Branford, S., Hughes, T. P., Baccarani, M., Deininger, M. W., Cervantes, F., Fujihara, S., Ortmann, C. E., Menssen, H. D., Kantarjian, H., O'Brien, S. G., Druker, B. J., & IRIS Investigators. (2017). Long-term outcomes of Imatinib treatment for chronic myeloid leukemia. *The New England Journal of Medicine, 376*(10), 917–927. https://doi.org/10.1056/NEJMoa1609324.

Hussein, K., Bock, O., Seegers, A., Flasshove, M., Henneke, F., Buesche, G., & Kreipe, H. H. (2007). Myelofibrosis evolving during imatinib treatment of a chronic myeloproliferative disease with coexisting BCR-ABL translocation and JAK2V617F mutation. *Blood, 109*(9), 4106–4107.

Kantarjian, H. M., Dixon, D., Keating, M. J., Talpaz, M., Walters, R. S., McCredie, K. B., & Freireich, E. J. (1988). Characteristics of accelerated disease in chronic myelogenous leukemia. *Cancer, 61*, 1441–1446.

Khalidi, H. S., Brynes, R. K., Medeiros, L. J., Chang, K. L., Slovak, M. L., Snyder, D. S., & Arber, D. A. (1998). The immunophenotype of blast transformation of chronic myelogenous leukemia: a high frequency of mixed lineage phenotype in "lymphoid" blasts and A comparison of morphologic, immunophenotypic, and molecular findings. *Modern Pathology, 11*, 1211–1221.

Lehmann, U., Bartels, S., Hasemeier, B., Geffers, R., Schlue, J., Büsche, G., Hussein, K., & Kreipe, H. (2013). SRSF2 mutation is present in the hypercellular and prefibrotic stage of primary myelofibrosis. *Blood, 121*, 4011–4012.

Lundberg, P., Karow, A., Nienhold, R., Looser, R., Hao-Shen, H., Nissen, I., Girsberger, S., Lehmann, T., Passweg, J., Stern, M., Beisel, C., Kralovics, R., & Skoda, R. C. (2014). Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. *Blood, 123*, 2220–2228.

Melo, J. V. (1996). The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. *Blood, 88*, 2375–2384.

Melo, J. V., & Barnes, D. J. (2007). Chronic myeloid leukaemia as a model of disease evolution in human cancer. *Nature Reviews Cancer, 7*, 441–453. https://doi.org/10.1038/nrc2147.

Melo, J. V., Myint, H., Galton, D. A., & Goldman, J. M. (1994). P190BCR-ABL chronic myeloid leukaemia: the missing link with chronic myelomonocytic leukaemia. *Leukemia, 8*, 208–211.

Mesa, R. A., Verstovsek, S., Cervantes, F., Barosi, G., Reilly, J. T., Dupriez, B., Levine, R., Le Bousse-Kerdiles, M. C., Wadleigh, M., Campbell, P. J., Silver, R. T., Vannucchi, A. M., Deeg, H. J., Gisslinger, H., Thomas, D., Odenike, O., Solberg, L. A., Gotlib, J., Hexner, E., Nimer, S. D., Kantarjian, H., Orazi, A., Vardiman, J. W., Thiele, J., Tefferi, A., & International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). (2007). Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leukemia Research, 31*, 737–740.

Mukherjee, S., & Kalaycio, M. (2016). Accelerated phase CML: Outcomes in newly diagnosed vs. progression from chronic phase. *Current Hematologic Malignancy Reports, 11*, 86–93. https://doi.org/10.1007/s11899-016-0304-7.

Ortmann, C. A., Kent, D. G., Nangalia, J., Silber, Y., Wedge, D. C., Grinfeld, J., Baxter, E. J., Massie, C. E., Papaemmanuil, E., Menon, S., Godfrey, A. L., Dimitropoulou, D., Guglielmelli, P., Bellosillo, B., Besses, C., Döhner, K., Harrison, C. N., Vassiliou, G. S., Vannucchi, A., Campbell, P. J., & Green, A. R. (2015). Effect of mutation order on myeloproliferative neoplasms. *The New England Journal of Medicine, 372*, 601–612.

Pane, F., Frigeri, F., Sindona, M., Luciano, L., Ferrara, F., Cimino, R., Meloni, G., Saglio, G., Salvatore, F., & Rotoli, B. (1996). Neutrophilic-chronic myeloid leukemia: A distinct disease with a specific molecular marker (BCR/ABL with C3/A2 junction). *Blood, 88*, 2410–2414.

Reid, A. G., De Melo, V. A., Elderfield, K., Clark, I., Marin, D., Apperley, J., & Naresh, K. N. (2009). Phenotype of blasts in chronic myeloid leukemia in blastic phase-analysis of bone marrow trephine biopsies and correlation with cytogenetics. *Leukemia Research, 33*, 418–425.

Silverstein, M. N. (1976). The evolution into and the treatment of late stage polycythemia vera. *Seminars in Hematology, 13*, 79–84.

Soverini, S., Hochhaus, A., Nicolini, F. E., Gruber, F., Lange, T., Saglio, G., Pane, F., Müller, M. C., Ernst, T., Rosti, G., Porkka, K., Baccarani, M., Cross, N. C., & Martinelli, G. (2011). BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood, 118*, 1208–1215.

Steegmann, J. L., Baccarani, M., Breccia, M., Casado, L. F., García-Gutiérrez, V., Hochhaus, A., Kim, D. W., Kim, T. D., Khoury, H. J., Le Coutre, P., Mayer, J., Milojkovic, D., Porkka, K., Rea, D., Rosti, G., Saussele, S., Hehlmann, R., & Clark, R. E. (2016). European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia, 30*, 1648–1671.

van Rhee, F., Hochhaus, A., Lin, F., Melo, J. V., Goldman, J. M., & Cross, N. C. (1996). p190 BCR-ABL mRNA is expressed at low levels in p210-positive chronic myeloid and acute lymphoblastic leukemias. *Blood, 87*, 5213–5217.

Vannucchi, A. M., & Harrison, C. N. (2017). Emerging treatments for classical myeloproliferative neoplasms. *Blood, 129*, 693–703.

Vardiman, J. W., Melo, J. V., Baccarani, M., Radich, J. P., & Kvasnicka, H. M. (2017). Chronic myelogenous leukemia, BCR-ABL1 positive. In S. H. Swerdlow, E. Campo, N. L. Harris, E. S. Jaffe, S. A. Pileri, H. Stein, J. Thiele, D. A. Arber, R. P. Hasserjian, L. B. MM, A. Orazi, & R. Siebert (Eds.), *WHO classification of haematopoietic and lymphoid tissues* (pp. 30–36). Lyon: IARC Press.