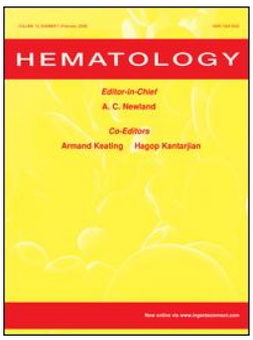

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Philadelphia chromosome-positive Acute Lymphoblastic Leukemia

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous malignancy characterized by the accumulation of immature lymphoid cells in bone marrow (BM), peripheral blood (PB) and other organs. ALL is the most common cancer in children, but approximately one third of cases occur in adults, with an estimated annual incidence of about one in 100,000 persons.

Philadelphia (Ph) chromosome is the most common cytogenetic abnormality found in adult B-cell lineage ALL. The incidence of Ph+ ALL increases with age, from less than 5% in younger children to 20-30% in older adults, with a peak incidence in patients aged 35-50 years. The Ph chromosome is a translocation, t(9;22), between ABL-1 oncogene on the long arm of chromosome 9 and a breakpoint cluster region (BCR) on the long arm of chromosome 22, resulting in the fusion gene transcript BCR-ABL, which encodes an oncogenic protein with constitutively active tyrosine kinase activity, leading to alteration of multiple intracellular signalling pathways, self-renewal, proliferation and tumor growth. The p190 BCR-ABL transcript may be documented in 50-80% of adults with Ph+ ALL, whereas the p210 transcript, commonly observed in chronic myeloid leukemia (CML), is found in the remaining Ph+ ALL population. Co-presence of both p190 and p210 BCR-ABL transcripts may also be found.

Symptoms and signs

The clinical presentation of Ph+ ALL, similarly to other forms of ALL, is largely non-specific and may include fatigue and dyspnea, dizziness, infections, constitutional symptoms (fever, night sweats, weight loss) and bleeding. Neurologic symptoms, secondary to leukemia central nervous system involvement, are more frequent at relapse. Lymphadenopathy, splenomegaly and/or hepatomegaly may be observed on physical examination in approximately 20% of the patients.

Tests

Upon laboratory suspicion of leukemia, based on clinical presentation and complete blood count with differentials, BM aspirate and trephine biopsy should be performed. The diagnosis of ALL requires the demonstration of 20% or greater BM lymphoblasts on morphologic and immunophenotypic examinations. Identification of specific recurrent either cytogenetic or molecular abnormalities is critical for disease evaluation, optimal risk stratification and treatment planning. The presence of Ph chromosome/BCR-ABL fusion transcript should urgently be investigated using conventional cytogenetics, interphase fluorescence in situ hybridization (FISH) and molecular assays on PB and BM samples. Quantitative polymerase chain reaction (RQ-PCR) should also be performed to document, at diagnosis, the absolute number of p190 or p210 fusion transcripts, relative to a housekeeping gene. The presence of additional cytogenetic abnormalities is also commonly observed.

Prognosis and treatment

Until recently, Ph+ ALL adults, undergoing standard chemotherapy, had a dismal prognosis with long-term survival rates of approximately 10-20%. Allogeneic hematopoietic stem cell transplantation (alloHSCT) from a HLA-matched donor, performed in few selected patients in complete remission (CR), significantly decreased the relapse rate, leading to a long-term survival ranging from 40% to 60%. The development of tyrosine kinase inhibitors (TKIs), which inhibit BCR-ABL and other constitutively activated aberrant tyrosine kinases, has revolutionized therapy and outcomes of patients with CML and Ph+ ALL. However, imatinib, the first BCR-ABL inhibitor which obtained clinical approval, produced only modest and short-lasting responses in patients with previously treated, relapsed Ph+ ALL. Conversely, imatinib, either alone or combined with steroids/chemotherapy, may induce CR in >90% adults with newly diagnosed Ph+ ALL, with minimal toxicity. It is widely recommended to use a TKI in all newly diagnosed Ph+ ALL patients to increase CR rate, prolong time to relapse, improve alloHSCT eligibility and improve leukemia-free survival. Upon achievement of CR, treatment should be continued until disease progression or alloHSCT. There is no clinical

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evidence to support intermittent drug administration or drug holidays. These recommendations apply to both transplant eligible and non-transplant eligible patients, including elderly subjects. The clinical outcome of Ph+ ALL has significantly improved over the last 10 years, with up to 60% 5-year overall survival rates in patients undergoing alloHSCT, from matched related or unrelated donor, in first CR after TKIs-based remission induction/consolidation treatments.

Unfortunately, resistance to one or more TKIs may emerge because of BCR-ABL-dependent and BCR-ABL-independent mechanisms. Of note, BCR-ABL-dependent mechanisms include gene amplifications and tyrosine-kinase domain mutations, disrupting binding to the drug target. One third of patients presents, at diagnosis, with small subpopulations containing BCR-ABL mutations, whereas mutations may also be acquired or emerge under selection pressure during TKIs treatment. For patients with relapsed/refractory Ph+ ALL, while receiving imatinib, a second- or subsequent-generation TKI (dasatinib, nilotinib, bosutinib and ponatinib), with or without further additional chemotherapy should be administered, according to the results of mutational analysis of BCR-ABL transcript. Of note, ponatinib has activity against the highly-resistant T315I mutation and is effective in treating patients with resistant or progressive disease after multiple TKIs. For patients with disease relapsing after alloHSCT, donor lymphocyte infusion (DLI) and/or a second alloHSCT may be therapeutic options. Furthermore, experimental immunotherapeutic approaches with blinatumomab, an antibody BiTE anti-CD19, or chimeric antigen receptor (CAR) T cells may be considered.

Quantitative assessment of BCR-ABL transcript levels by molecular assays to monitor minimal residual disease (MRD) in patients achieving hematologic CR has strong prognostic significance. For patients not candidate to receive alloHSCT, serial monitoring during initial therapy is relevant because it may prompt a switch of TKI treatment before morphologic relapse. Moreover, BCR-ABL monitoring may have immediate impact after alloHSCT to guide specific approaches, such as immunosuppression reduction, re-starting of TKIs administration or DLI. Of interest, BCR-ABL-specific T-cells may emerge in patients with Ph+ ALL under TKIs treatment and synergize with TKIs for remission maintenance because they are associated with lower MRD values and can directly mediate specific lysis of Ph+ blasts.

The use of the aforementioned newer generations TKIs, with or without additional chemotherapy, has been explored in clinical trials for patient with newly diagnosed Ph + ALL, obtaining CR with minimal toxicity. However, the choice of optimal TKI for remission induction/consolidation treatments remains to be elucidated. Although molecular CR may be obtained in some patients with TKIs alone, long-term outcome without intensive chemotherapy and alloHSCT is currently unknown. To date, available information cannot support the omission of alloHSCT in younger fit patients, regardless of MRD status.

In conclusion, the wide clinical use of TKIs has significantly improved remission duration and prognosis of Ph+ ALL patients, but further clinical investigations are warranted to clarify some therapeutic issues.

Resources

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