Management of adult patients with Philadelphia positive acute lymphoblastic leukemia

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Introduction

For decades Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) has been considered as the ALL subgroup with the worse prognosis. It occurs in 20 to 40% of adult ALL and in about 3% of pediatric patients; the frequency of the Ph chromosome increases with age and is present in over 50% of patients aged 50 years or older. The main reason for the poor clinical outcome of BCR-ABL1+ ALL is genetic instability.

The outcome for adult Ph+ ALL patients has improved considerably with the current treatment approaches that include tyrosine kinase inhibitors (TKI) and which allow to achieve complete hematological remissions (CHR) in 98−100% of patients. Indeed, treatment with a TKI, with or without chemotherapy, represents today the gold standard first line approach for patients with Ph+ ALL, both in terms of CHR and of disease-free survival (DFS), and can also act as a "bridge" to stem cell transplantation (SCT) for eligible patients. Low levels of minimal residual disease (MRD) at the time of transplantation are likely be of great importance in this setting; therefore, a correct MRD screening by means of real-time reverse transcriptase polymerase chain reaction (RT-PCR) and BCR-ABL1 quantification is recommended, although a worldwide consensus on MRD data interpretation has not been yet reached.

All patients with a diagnosis of ALL, regardless of age, should be rapidly tested for the presence of the BCR-ABL1 rearrangement; this is particularly true in the elderly, since the majority of patients are not eligible for intensive chemotherapy, while virtually all can achieve a CHR with a TKI, including patients in their eighties. Molecular diagnosis is strongly advisable, since the marker can be used to monitor MRD during the course of the disease. It should be recalled that the BCR-ABL1 protein can be detected at diagnosis also by flow cytometry with a 100% accuracy. This may allow a rapid diagnostic work-up of Ph+ ALL in geographic regions where PCR-based technologies are not available.

Clinical features

Ph+ ALL is usually characterized by a slightly higher initial white blood cell (WBC) count compared to Ph− ALL, while other symptoms or clinical signs do not differ from those of Ph− ALL patients. A central nervous system (CNS) involvement is infrequent (5%) at initial presentation, but there is a significant risk of developing meningeal leukemia during the course of treatment. For this reason, CNS-directed prophylactic therapy should be considered mandatory in patients with Ph+ ALL.

Diagnostic work-up

While in the past the diagnosis of Ph+ ALL was made by conventional cytogenetics, nowadays these cases are better identified by RT-PCR. The molecular screening identifies the fusion product of the t(9;22) chromosome translocation, i.e. the BCR-ABL1 fusion gene. RT-PCR is much more rapid and has a higher sensitivity than cytogenetics. Quantitative RT-PCR (Q-RT-PCR) assay also allows to quantify the levels of the BCR-ABL1 rearrange-
ment and permits an adequate MRD screening. This framework is nowadays essential for an optimal diagnostic work-up and management of ALL patients of all ages and is also crucial for a uniform monitoring of MRD during the course of the disease\textsuperscript{11, 12}.

Cytogenetic analyses have improved over time and fluorescence in situ hybridization (FISH) can provide results in a very short time. However, the sensitivity of FISH is inferior to that of RT-PCR.

From a research standpoint, conventional cytogenetics remains valuable in order to identify the presence of additional chromosomal abnormalities. The prognostic importance of the latter within \( Ph^+ \) ALL is starting to emerge.

**Biologic acquisitions**

The Ph chromosome results from a reciprocal translocation fusing the abelson (ABL1) proto-oncogene on chromosome 9 with the breakpoint cluster region (BCR) sequences on chromosome 22, creating the BCR-ABL1 fusion protein, a constitutively activated form of the ABL TK. Depending on the breakpoint of the BCR region, two types of fusion transcripts can be distinguished: the major BCR-ABL, which accounts for approximately one-third of \( Ph^+ \) ALL and encodes the larger p210 protein, and the minor BCR-ABL (found in two-thirds of \( Ph^+ \) ALL) that encodes the smaller p190 protein\textsuperscript{13, 14}. Both proteins constitutively enhance TK activity, recruit and activate multiple pathways that transduce oncogenic signals, thus leading to increased cell survival and proliferation, impaired migration and adhesion, an arrested differentiation of hematopoietic progenitors and impaired apoptosis\textsuperscript{8, 15}. The reason for the aggressive nature of BCR-ABL1-induced ALL is not fully understood and it is likely that factors other than BCR-ABL1 are involved in its development and progression.

Recent works\textsuperscript{16, 17} have described a deletion on 7p12 of \( IKZF1 \), which encodes the transcription factor Ikaros, in most \( Ph^+ \) ALL cases, suggesting that loss of Ikaros may contribute to the leukemia initiation by blocking B-lymphoid maturation. SRC-family kinases (SFK) may also contribute to the pathogenesis of \( Ph^+ \) leukemias, since they have been implicated in BCR-ABL1 signaling and, consequently, in disease progression\textsuperscript{18}. Gene expression profiling has shown that \( Ph^+ \) ALL displays a very heterogenous profile and is not characterized by a distinctive molecular signature; however, it is worth noting that a small set of additional protein kinases and several genes that regulate cell cycle progression have been found highly expressed in this subset of patients\textsuperscript{19—21}.

**Treatment**

The management of \( Ph^+ \) ALL patients can be divided into a pre- and post-TKI era. The advent of TKI has completely changed the treatment and prognosis of \( Ph^+ \) ALL.

Prior to the advent of the TKI, after an initial response to conventional chemotherapy, with rates of CHR ranging from 60 to 70\% and long-term survivals in the order of 35–40\% in children and less than 20\% in adults\textsuperscript{22—24}, thus lower than in \( Ph^+ \) ALL, resistance to therapy and chemoresistant relapse occurred\textsuperscript{25}. Virtually no adult patients (<5\%) could be cured with standard chemotherapy; the median survival was 8–10 months in the absence of an allogeneic SCT, which was the only potentially curative therapy\textsuperscript{26—29}. Since the disease occurs more frequently in patients over the age of 60, the curative potential of allogeneic SCT has not been fully analyzed because relatively few elderly patients have undergone the procedure in a clinical-trial setting.

The whole scenario has changed in the last decade following the development of targeted therapies aimed at interfering with the molecular abnormality of the leukemic clone. The most prominent example of targeted therapy in oncology is indeed represented by the specific inhibitor of the BCR-ABL1 TK imatinib mesylate (Gleevec)\textsuperscript{30}, which has radically modified our treatment strategy for \( Ph^+ \) ALL\textsuperscript{31}. The potential of imatinib in \( Ph^+ \) ALL was first investigated in monotherapy studies for patients with relapsed or refractory disease. In a pilot study, 20 patients with \( Ph^+ \) ALL or lymphoid blast phase of CML were treated with imatinib and, of these, 20\% achieved a CHR\textsuperscript{32}. In a subsequent phase II study that recruited patients with \( Ph^+ \) ALL experiencing a lack of response or relapse to standard chemotherapy or SCT, 19\% of patients achieved a CHR\textsuperscript{33}. Thereafter, in several studies it could be documented that the addition of imatinib to frontline induction therapy resulted in much higher rates of CHR than with conventional chemotherapy\textsuperscript{34—41}. Moreover, DFS proved to be significantly longer with imatinib-based therapy than with standard chemotherapy.

In older adults with \( Ph^+ \) ALL, imatinib has been administered alone or in combination with only low-dose...
steroids, and it has resulted in very high CHR rates. It should be underlined that prior to the advent of the TKI, the management of elderly patients with Ph+ ALL was very often palliative in view of the dismal prognosis and of the frail conditions that prevented the use of chemotherapy regimens. The results of the GIMEMA study in patients over the age of 60, who were tested for the presence of the BCR-ABL1 aberration within one week during which they underwent a steroid pre-phase, and were then treated only with imatinib has represented a major advancement in the management of Ph+ ALL. The possibility of achieving a CHR with a well-tolerated oral non-chemotherapy treatment in virtually all elderly Ph+ ALL patients has been an important step forward.

Overall, these studies indicate that first-line treatment of Ph+ ALL with imatinib administered alone or in combination with chemotherapy is associated with improved responses and outcomes, and that the greatest benefits are reported when imatinib treatment is initiated during the induction phase and is used continuously alone or in combination with chemotherapy. It should, however, be noted that the combined use of imatinib and chemotherapy in adult Ph+ ALL is always associated with important toxicities and deaths in induction.

The use of imatinib may improve the chance of eligibility for an allogeneic SCT by increasing the proportion of patients achieving a CHR compared with historical controls. In addition, the longer remission duration allows extra time for donor search and for allogeneic SCT. One prospective phase II study has reported that first-line imatinib, in combination with chemotherapy, improves the curative potential of a subsequent allogeneic SCT. Recently, another phase II study compared the clinical outcome of patients who received imatinib plus chemotherapy followed by allogeneic SCT in their first CHR (imatinib cohort) with the historical control patients in the pre-imatinib era, showing a significant increase of OS, DFS and relapse-free survival (RFS) for the imatinib cohort. Moreover, data suggest that Ph+ ALL patients who are MRD+ post-transplant may benefit from receiving imatinib post-SCT.

Furthermore, elevated values of MRD are predictive of a subsequent relapse and allogeneic SCT can override its adverse effect. Despite the clear benefits offered by imatinib, many patients with Ph+ ALL do not experience durable remissions and resistance frequently occurs. Resistance can be classified as primary (failure to achieve CHR) or acquired/secondary (relapse despite continued treatment).

Second generation TKI have shown good results for these patients. Dasatinib (Sprycel) is a potent, oral inhibitor of the BCR-ABL1, c-KIT and SRC kinase family, which has proven to be a more active inhibitor of BCR-ABL1 and c-KIT than imatinib. Clinically, it has been shown to be effective in Ph+ ALL patients resistant or intolerant to imatinib and is currently approved by the Food and Drug Administration (FDA) for these patients. Following encouraging phase I results, an international phase II study (START-L) confirmed that dasatinib is associated with marked hematological and cytogenetic response rates in relapsed/resistant Ph+ ALL. The clinical responses observed with second-line dasatinib in Ph+ ALL post-imatinib failure provided a rationale for the evaluation of dasatinib as a first-line therapy. Recent phase II studies report the experience of dasatinib administered either as monotherapy with prednisolone only or in combination with hyper-CVAD chemotherapy. In the GIMEMA first line study virtually all adult Ph+ ALL patients irrespective of age achieved a CHR with dasatinib alone (plus steroids); treatment was associated with a very favorable tolerability and safety profile, partly administrable at home, and with no deaths in induction.

The results obtained first in the elderly with imatinib alone and then in all adult patients with dasatinib alone question the role of chemotherapy in combination with a TKI as induction treatment in Ph+ ALL. In the French-German EWALL protocol, patients with Ph+ ALL aged 55 years or more were treated with dasatinib combined with chemotherapy. This strategy resulted in notable toxicities, deaths during induction and treatment discontinuation in 35% of patients. Similarly, in the phase II studies combining hyper-CVAD with dasatinib as frontline therapy, three deaths due to infections were recorded during induction and grade 3–4 side effects, including several bleeding episodes as well as pleural effusions occurred. In addition, a pilot first line GIMEMA study of imatinib plus chemotherapy was emended because of toxicity (personal data) into a sequential scheme.

Nilotinib (Tasigna) is a selective BCR-ABL1 inhibitor. It binds to the BCR-ABL1 kinase domain and it can overcome resistance in the BCR-ABL1 kinase domain related to mutations. Only few studies have been performed with nilotinib in patients with Ph+ ALL post-imatinib failure; the results do not appear very
promising (2/13 patients and 24% of 41 obtained a CHR, respectively) and a longer follow-up is required to assess response durability. A recent pilot study reported the results of nilotinib in combination with hyper-CVAD as first-line treatment; all 5 patients treated achieved a CHR. The results are encouraging, but must be extended to a larger number of patients. A phase II study tested nilotinib plus chemotherapy in 50 newly diagnosed patients obtaining a 90% CHR rate (with 4 patients who died during induction), with DFS, event-free survival (EFS) and OS at 2 years of 71.1%, 49.4% and 66.2%, respectively.

Finally, in 2 Ph+ ALL patients refractory to treatment with chemotherapy and TKI the efficacy of clofarabine could be documented: in fact, both patients obtained a CHR and a molecular response with no significant side effects.

Minimal residual disease

Monitoring of MRD is routinely utilized in clinical trials to evaluate the response to treatment in ALL patients, including Ph+ ALL. The level of BCR-ABL1 reduction achieved early during therapy is a good parameter of subsequent response, while high levels of BCR-ABL1 transcripts at different treatment stages indicate poor responsiveness to chemotherapy and to TKI, and intuitively could be considered a risk factor for disease recurrence. A retrospective study based on the stratification of MRD levels after induction and consolidation chemotherapy showed that the reduction of the BCR-ABL1 transcript was the main prognostic parameter to predict outcome. In contrast, prospective MRD monitoring in 100 adult patients with Ph+ ALL uniformly treated with imatinib and chemotherapy failed to establish an association between PCR negativity at the end of induction therapy, relapse rate or RFS, although increased levels of BCR-ABL1 transcripts during hematologic CHR were predictive of relapse in non-transplanted patients. Lee et al were able to demonstrate that a 3-log reduction in BCR-ABL1 transcripts after 1 month of imatinib treatment strongly predicted a reduced relapse risk: this finding was confirmed in a subsequent study. In contrast, Yanada et al observed no association between rapid achievement of BCR-ABL1 negativity and long-term outcome after an initial imatinib/chemotherapy induction regimen and also the GRAAL group showed that early MRD evaluation did not significantly influence patients’ outcome, both in terms of OS and DFS. Two studies analyzing the outcome of patients with Ph+ ALL who underwent a transplant showed that the persistent expression of BCR-ABL1 during the first 100 days post-transplant was associated with a higher incidence of relapse and a lower DFS. Both studies argue in favor of a maintenance therapy with imatinib after transplantation in patients with a positive MRD evaluation, and the same is suggested in recent studies. Moreover, Pfeifer et al support the prophylactic administration of imatinib after allogeneic SCT regardless of the MRD status. Finally, in the GIMEMA study based on dasatinib administration BCR-ABL1 levels < 10^-3 at the end of the TKI induction correlated with DFS. These studies demonstrate that prospective monitoring of MRD has the potential to identify patients at risk of relapse. Open issues remain the definition of precise cut-off levels for the quantification of the disease and its increment. These issues highlight the need for standardization and harmonization of the methodologies used for BCR-ABL1 quantification in Ph+ ALL and the indications suggested by White et al lead to a uniform international assessment of BCR-ABL1 levels.

Relapse and mutations

Relapse still remains a problem for patients with Ph+ ALL and the emergence of resistant clones is quite common in ALL as the cause of relapse. In Ph+ ALL patients treated with TKI, the relapse is an expected event and it is most often accompanied by selection of point mutations in the BCR-ABL1 kinase domain. The occurrence of BCR-ABL1 mutations is a key element in managing leukemic patients during TKI therapy, because of the greater genetic instability occurring in patients with Ph+ ALL. Other causes have pharmacokinetic or pharmacodynamic bases, like disruptions in drug uptake and efflux, or are due to the development of other secondary genetic abnormalities and activation of alternative signaling pathways. Cytogenetic abnormalities, in addition to the Ph chromosome, are present in about one third of adult cases and have been associated with an inferior outcome. Members of the SRC family of kinases have been implicated in leukemogenesis and development of imatinib-resistance in BCR-ABL1+ ALL, suggesting that the simultaneous inhibition of SRC and BCR-ABL1 kinases may benefit individuals with Ph+ leukemia. About 80–90% of patients with Ph+ ALL who relapse while on imatinib are found to have BCR-ABL1 mutations, with a
predominance of P-loop and T315I mutations; with dasatinib, relapse is most often associated with the T315I mutation, whereas P-loop mutations are less common. It has become of central interest whether mutations are already present in TKI-naïve patients, and this frequently appears to be the case. Our group and a previous study have found that BCR-ABL1 mutations, including T315I, can be detected in a proportion of patients at diagnosis. In our series, low levels of T315I mutations could also be found at diagnosis, but this does not seem to correlate with a subsequent relapse or persistence of remission. Further prospective studies will conclusively clarify the implications of finding a mutation prior to treatment, which may involve only a minor subclone depending on the sensitivity of the test utilized. CNS relapses are also common with imatinib, which does not penetrate the CNS; in fact, imatinib levels in the cerebrospinal fluid have been shown to reach only 1 to 2% of serum levels. Thus, aggressive CNS prophylaxis is needed. Dasatinib shows a better infiltration of the CSF and achieves clinically active concentrations, as shown in small series of patients in whom stabilization and regression of CNS disease were achieved.

It has been hypothesized that these effects, which are different from imatinib, are due to the dual specific SRC/BCR-ABL1 TK-inhibitory property of dasatinib. It remains to be determined whether the current approach to CNS-directed prophylaxis can be modified in the context of dasatinib-based treatment for Ph+ ALL patients.

**Future perspectives**

While our approach to the management of Ph+ ALL has greatly changed and the overall prognosis has improved, some very important questions are still open. The first is if the induction treatment should be based on a TKI alone (plus steroid and intrathecal treatment) or whether chemotherapy should be associated to the TKI. Based on the evidence that this association is invariably associated with marked toxicity and deaths in induction, the GIMEMA group prefers to induce all adult patients into CHR without systemic chemotherapy. With this approach almost 150 adult patients with Ph+ ALL - with no upper age limit - have so far been treated with imatinib or dasatinib and no chemotherapy. The CHR rate is 98.4% with no single death in induction. The OS and PFS results are not inferior to those reported with the TKI-chemotherapy association. While we feel that the strategy for obtaining a CHR in virtually all patients, including the elderly, may be solved, the key question today is how to manage patients after the induction phase. Since the majority of patients are MRD+, further treatment is required. In the current GIMEMA protocol, patients between 18 and 60 years are induced into CHR with dasatinib (and steroids) and then patients with a donor will undergo as soon as possible an allo-SCT. Alternatively, they are consolidated with clofarabine-based chemotherapy.

If a relapse occurs, the outcome is very poor. Even if a second remission can be achieved, there is no consensus on the most appropriate regimen in the setting of TKI-resistant Ph+ ALL. In these patients, there are emerging data with third generation TKI. Ponatinib is a potent BCR-ABL1 inhibitor active against TKI-resistant cells, including those harboring the T315I mutation. In a recent phase I study, this drug was tested in 34 CML patients and 3 Ph+ ALL refractory patients, obtaining 36% of major hematological responses. A phase II study is currently ongoing.

Blinatumomab, a bispecific, T-cell-engaging antibody binding CD19 and CD3 is a novel agent currently being tested in a phase II study for relapsed/refractory B-precursor ALL adults patients and for patients with detectable MRD. This compound has been associated with very encouraging responses, also in Ph+ ALL patients carrying a T315I mutation. Bosutinib is a dual SRC&ABL tyrosine kinase inhibitor which has shown significant activity in patients with resistant Ph+ leukemias, except for those harboring the T315I mutation.

Other agents, like the SRC/ABL inhibitors, aurora kinase inhibitors, RAF kinase inhibitors, etc are being evaluated in clinical trials. Overcoming resistance remains the therapeutic challenge; identification of a molecular signature, possibly comprehensive of specific cytogenetic abnormalities, might provide targets for new interventions in the future.

It is clear that the management of patients with Ph+ ALL has been revolutionized. The evidence that virtually all patients – including the very elderly – can obtain a CHR with a TKI alone (plus steroids) and without systemic chemotherapy would have been unthinkable only a few years ago. Now the primary challenge that the hematologic community is facing is how to eliminate or control MRD.
Robin Foà has received honoraria for advisory boards from Roche Co., Ltd., BMS Co., Ltd., GSK, Celgene Co., Ltd., and Takeda Pharmaceutical Co., Ltd., and has received consulting fees from Roche Co., Ltd., and payment for lectures including service on speakers bureaus from Roche Co., Ltd., BMS Co., Ltd., GSK, Celgene Co., Ltd., Janssen Co., Ltd., and Mundipharma Co., Ltd.

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