

Diagnostic and treatment of adult Philadelphia chromosome-positive acute lymphoblastic leukemia

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Practice points

- Tyrosine kinase inhibitors (TKIs) have become an integral part of front-line therapy for Philadelphia chromosome-positive (Ph⁺) acute lymphoblastic leukemia (ALL). Ph⁺ ALL serves as the first model system for truly targeted treatment.
- Although the choice of the most effective TKI is not yet settled, the best results are shown with TKIs incorporated early, daily and continuously with chemotherapy. Current complete remission rates reach 90% and long-term survival rates attain 50–60%.
- Real time-PCR breakpoint cluster region–Abelson leukemia viral proto-oncogene quantification is used to monitor minimal residual disease in patients with Ph⁺ ALL. *BCR–ABL* transcript levels have been correlated with response.
- Development of resistance during treatment remains a major problem in Ph⁺ ALL, especially with a T315I clone. Novel TKIs as well as monoclonal antibodies and the novel approach based on chimeric antigen receptor T-cells targeting CD19 have already been tested with encouraging first results.

The outcome of adult patients with Philadelphia chromosome-positive (Ph⁺) acute lymphoblastic leukemia (ALL) has improved substantially with the introduction of tyrosine kinase inhibitors (TKIs). TKIs are now integral components of therapy for Ph⁺ ALL. The current consensus is that they improve patient outcomes compared with historical control patients treated with chemotherapy alone, and increase the number of patients able to receive stem cell transplant. New challenges have emerged with respect to induction of resistance mainly via Abelson tyrosine kinase mutations. Several novel kinase inhibitors with significantly more potent antileukemic activity are currently being developed. Furthermore novel immune therapies, which recruit or modify patient's own T cells to fight leukemic cells, are being developed and could find an important place in Ph⁺ ALL therapy by few years. In this article, we reviewed treatment approaches in adults with Ph⁺ ALL with a focus on TKIs and combined chemotherapy regimens.

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Acute lymphoblastic leukemia (ALL) is a malignant neoplasm of the lymphocyte precursor cells. ALL is characterized by aberrations in proliferation and differentiation of lymphoblasts, leading to failure of normal immune response and decreased production of normal hematopoiesis responsible for anemia, thrombocytopenia and neutropenia. ALL represents a heterogeneous group with distinct morphologic, cytogenetics and molecular groupings, some of which have important clinical implications. The Philadelphia chromosome (Philadelphia chromosome-positive; Ph⁺), a reciprocal translocation between chromosomes 9 and 22 (t[9;22] [q34;q11]), is the most frequent cytogenetic

KEYWORDS

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abnormality in human leukemia [1,2]. It produces a fusion gene on chromosome 22, namely, the *BCR-ABL*.

How common is Ph⁺ ALL?

ALL represents <1% of adult cancers, while it represents 25% of all childhood cancers. Incidence of Ph⁺ ALL increases with age [2]. The Philadelphia chromosome can be detected in a range of 2–5% of children with ALL [3], and 20–40% of younger adults with ALL [4]. The proportion of Ph⁺ ALL cases increases with age up to 50% with no sex difference [5], but in very old persons the proportion decreases again [4]. The overwhelming majority of patients are diagnosed with *de novo* Ph⁺ ALL, although occasional cases of secondary Ph⁺ ALL have been reported following chemotherapy or radiation therapy.

How do we diagnose Ph⁺ ALL?

The defining feature of Ph⁺ ALL is a reciprocal translocation t(9;22) (q34;q11). The t(9;22) translocation leads to a head-to-tail fusion of the *ABL* proto-oncogene from chromosome 9 with a 5' half of the *BCR* sequences on chromosome 22 [6]. By standard cytogenetic analysis this becomes apparent as a shortened chromosome 22 referred to as the Philadelphia chromosome, which can also be visualized by FISH analysis. Transcription of *BCR-ABL* results either in a 8.5-kb mRNA that codes for a 210-kb protein when *ABL* moves to the major *BCR* or in a 7.5-kb RNA encoding a 190-kb protein when it moves to the minor *BCR* [7]. Both possible chimeric mRNAs (p210 and p190) can be sensitively and specifically detected by the real-time PCR (RT-PCR) [8]. *BCR-ABL* proteins demonstrate enhanced tyrosine kinase activity compared with the normal *ABL* gene product. *BCR-ABL* fusion proteins can alter multiple signaling pathways, contributing to tumor growth and proliferation. P190 exhibits a higher transforming potential than p210 in animal models [9]. The p190 protein is usually found in two out of three adults with *de novo* Ph⁺ ALL [10,11]. It has been associated with a significant increase in the risk of relapse [10]. The p210 protein constitutes the rest of the Ph⁺ ALL population. However, a rare p230 *BCR-ABL* mutation has also been described and is associated with Ph⁺ chronic neutrophilic leukemia [12]. *BCR-ABL* expression in hematopoietic cells is known to induce resistance to apoptosis, growth factor independence,

as well as alterations in cell–cell and cell–matrix interactions [13]. Ph⁺ ALL has an aggressive clinical course. Patients present with a variable white blood cell count, and have an increased risk of developing meningeal leukemia during the course of treatment, although CNS leukemia was not significantly more frequent (5%) at diagnosis [5,14]. Splenomegaly may be present. Ph⁺ ALL are found almost exclusively among B-cell lineage ALL. The most frequent immunologic subtypes are common ALL (78%), and pre-B ALL (20%), whereas only few percentages of patients display the pro-B immunophenotype [15]. Except for few case reports, the Ph chromosome is not found in T-cell lineage ALL. Leukemic cells often present surface expression of CD34 antigen (89%), and frequent expression of myeloid markers (15–20%) [10]. Additional chromosome abnormalities have been observed in 70% of Ph⁺ ALL patients [16], including mainly 9p abnormalities, monosomy 7 or hyperdiploid karyotypes >50. The main differential diagnosis at diagnostic is chronic myeloid leukemia in lymphoid blast crisis.

What are the treatment options for adult patients with Ph⁺ ALL?

• Historic regimens (pretyrosine kinase inhibitor era)

Most of adults with Ph⁺ ALL have an extremely poor prognosis when treated with chemotherapy alone [10,16–22]. Chemotherapy regimens induce complete remissions (CRs) in >70% (moderately lower than the 70–90% achieved in Ph-negative ALL), but most patients relapse within 6–11 months of treatment and die of the disease. During this pre-tyrosine kinase inhibitor (TKI) period, the 5-year overall survival (OS) rates for those treated with intensive chemotherapy alone were <10%. Only, the hyper-CVAD chemotherapy (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine) from the MD Anderson Cancer Center reported higher CR rate (91%) with median event-free survival (EFS) and OS of 43 and 42 months, respectively [23]. However, although reported results were significantly higher than those from historical control, survival curves converged after 3 years. Only allogeneic stem cell transplantation (SCT) performed early during remission was potentially curative and has permitted long-term survival (35–65%) [10,24–28]. Nevertheless, approximately

30% of allografted patients experienced relapse, making this the most frequent cause of failure next to treatment-related mortality [29]. Younger age, conditioning with total body irradiation, HLA-identical sibling donor [30], disease status at the time of SCT [30,31] and the occurrence of acute graft-versus-host disease (GvHD) [32] were factors associated with improved survival. Regarding autologous SCT, 3-year survival rates have been shown to be inferior to those of allogeneic SCT as well as to those of continued chemotherapy [33]. Long-term disease-free survival (DFS) was noted in 22% of cases with a median of 52 months when using purged bone marrow or peripheral blood stem cells [34]. However, no long-term surviving patients were observed among those transplanted beyond the first CR. Because the results of SCT correlate with the pre-transplant leukemia burden, improved treatment strategies have clearly been warranted to ensure molecular CR at the time of SCT for patients with Ph⁺ ALL [31]. Chemotherapy in elderly Ph⁺ ALL patients was also associated with a very poor prognosis. In contrast with younger adults, the presence of Ph chromosome showed here no specific impact on the OS, probably because of the overall poor outcome of the other ALL subtypes in this patient population [35].

• Imatinib in the treatment of Ph⁺ ALL

Imatinib mesylate, a TKI that targets BCR–ABL, is now an integral component of therapy for Ph⁺ ALL. It partially blocks the ATP-binding site of BCR–ABL [36]. Following initial studies showing that use of imatinib mesylate as a single agent in Ph⁺ ALL yielded potential responses, but was unlikely to be sufficient for long-term disease control [37], the efficacy of imatinib was explored as front-line treatment combined with chemotherapy, either concurrently (simultaneous administration) or sequentially (alternating administration) [28,38–45]. CRs can be obtained in almost 95% of cases with newly diagnosed Ph⁺ ALL. In younger adults, imatinib-based regimens used imatinib at 400–800 mg/day. Efficacy analyses based on BCR–ABL transcript levels showed a clear advantage of the simultaneous over the alternating schedule [43]. The current consensus is that imatinib improves patient outcomes compared with historical control patients treated with chemotherapy alone. The number of patients able to receive SCT, as the outcome of SCT, has improved [39,40,43,46,47]. It also appeared important to maintain imatinib

dose intensity during the initial phase of treatment [48]. Furthermore, an induction regimen combining reduced-intensity chemotherapy and imatinib was recently validated in a randomized study in which it was compared with a standard imatinib/chemotherapy treatment [47]. The rate of molecular remission increased from 5% to >50%, and the 5-year survival to 50% or more. The number of patients able to receive SCT, as the outcome of SCT, has improved [47]. However, imatinib is ineffective at preventing or treating CNS involvement [49]. Several approaches using imatinib-based induction therapy have been explored for elderly patients. With relatively minimal use of imatinib (600 mg/day for three blocks of 60 days) alternating with chemotherapy, a significant improvement in the 1-year survival was observed compared with historical controls [44]. Similar results were reported with continuous administration of imatinib (800 mg) only combined with prednisone [41]. In a randomized study comparing induction therapy with single-agent imatinib with standard induction chemotherapy [42], response rate was better with single-agent imatinib. In addition to hematologic and cytogenetic monitoring, monitoring of minimal residual disease (MRD) by flow cytometry and/or quantitative RT-PCR may be useful in detecting impending imatinib failure [50]. Achievement of molecular remission was associated with longer DFS. The detection of MRD may allow for targeted therapy before the occurrence of a frank relapse [51]. Unfortunately, imatinib resistance may develop rapidly and lead to disease progression. Multiple mechanisms of resistance have been implicated, of which mainly the acquisition of point mutations within the tyrosine kinase domain [52,53]. The T315I mutation leads to an extreme insensitivity to imatinib. Its presence is associated to shorter survival [54]. Mutations have also been reported to exist before the initiation of imatinib treatment in >40% of patients, and may be responsible for relapse during therapy [14,55]. The other mechanisms of resistance include amplification of the *BCR–ABL* gene, decreased drug efflux and involvement of secondary downstream pathways such as SRC family kinases [56,57]. One recently identified mechanism of resistance involves the expression of spliced isoforms of *IKZF1*, a critical regulator of normal lymphocyte development [58]. The presence of genetic deletions affecting *PAX5* (a transcription factor expressed throughout B-cell maturation) and the *CDKN2A/B* (a negative regulator of p53)

locus has also been identified in Ph⁺ ALL patients by genome-wide single nucleotide polymorphism array analysis [58]. Because of the development of potential resistance, the combination of imatinib with chemotherapy has not supplanted allogeneic SCT as treatment of choice in patients with Ph⁺ ALL.

• Second-generation TKIs in the treatment of Ph⁺ ALL

Faster and deeper molecular responses can be achieved with second-generation TKIs. Dasatinib is a dual SRC/ABL inhibitor with 30–50-fold more *in vivo* potency than imatinib against BCR–ABL. It can bind to both the active and inactive conformations of the ABL kinase domain. It also inhibits the c-KIT, PDGFR and ephrin A receptor kinases. Mutations that show a high degree of insensitivity to imatinib are sensitive to dasatinib, with the exception of T315I [59]. In a Phase I trial, a hematologic response rate of 80% has been observed in patients with imatinib-resistant Ph⁺ ALL [60]. In a Phase II program using single-agent dasatinib (70 mg two-times a day [b.i.d.]) in imatinib-resistant Ph⁺ ALL patients, a major cytogenetic response was observed in 57% of cases after a median time of 6.9 months [61,62]. The activity of twice daily for dasatinib was confirmed by other studies in this indication [63], but a randomized Phase III dose-optimization study changed the approval dosage to 140 mg once daily (q.d.) [64]. Consequently, safety profile was improved with the once-daily arm. Responses were observed in the presence of ABL tyrosine kinase domain (TKD) mutations other than T315I and E355G.

In the final results of the Gruppo Italiano Malattie Ematologiche dell'Adulto protocol LAL1205, in which dasatinib (70 mg b.i.d.) was combined with steroids in adults with Ph⁺ ALL, all patients achieved CR with a very marked clearance of blasts already at day 22, irrespective of age, with limited toxicities and no fatalities [65]. A Phase II study combining the hyper-CVAD regimen with dasatinib (50 mg b.i.d.) for the first 14 days of each cycles showed CR achievement in 93% of newly diagnosed Ph⁺ ALL [66]. Molecular remissions were observed even after the first cycle with 94% of patients achieving MRD negativity assessed by flow cytometry at a median of 3 weeks. A recent long-term follow-up of this study showed that the median DFS and OS were 31 and 47 months, respectively [67]. A high activity of dasatinib as first-line therapy was also demonstrated

in patients older than 55 years [68]. After a steroid prephase, dasatinib (100–140 mg q.d.) was combined with four weekly cycles of vincristine and dexamethasone. Induction was followed by alternating blocks of dasatinib, methotrexate plus asparaginase and cytarabine; then maintenance therapy with alternating blocks of dasatinib, mercaptopurine plus methotrexate and dexamethasone plus vincristine. Dasatinib plus chemotherapy gave 96% of CR, and EFS was 41% at 3 years. A third of patients achieved undetectable levels of BCR–ABL transcripts [68]. Dasatinib-based treatment may be used in patient unable to receive SCT. It has also been shown to facilitate SCT, without increasing toxicity [69].

Nilotinib, a second-generation TKI, is an aminopyrimidine derivative of imatinib. While dasatinib has a pan-TKI profile, nilotinib has a profile close to that of imatinib and inhibits BCR–ABL, c-KIT and PDGFR. It is 20–50-fold more potent than imatinib as an ABL kinase inhibitor [70]. Until now, it has not been approved for the treatment of patients with Ph⁺ ALL. In a Phase I dose-escalation study in imatinib-resistant Ph⁺ ALL, hematologic responses were observed in 33% of the patients [71]. In a Phase II study, nilotinib, as monotherapy at 400 mg b.i.d. in patients with relapsed or refractory Ph⁺ ALL, gave CR in 24% of cases [72]. The use of nilotinib in combination with chemotherapy is currently under investigations. First results showed achievement of high cumulative complete molecular remission and hematologic relapse-free survival rates [73]. Mutagenesis-resistance screening indicates the selection of T315I and P-loop mutations Y253H and E255K during nilotinib treatment [52,74].

Bosutinib is a novel dual SRC/ABL inhibitor in early clinical development for Ph⁺ ALL. Biochemical assays have shown it to be up to 200-fold more potent than imatinib as an inhibitor of BCR–ABL phosphorylation. Bosutinib does not exhibit significant inhibition of c-KIT or PDGFR, which may result in a relatively favorable safety profile. Preliminary data with bosutinib at 500 mg/day in patients who experienced failure on previous imatinib therapy indicate complete hematological response and major molecular response in Ph⁺ ALL [75].

• Third-generation TKI in the treatment of Ph⁺ ALL

Ponatinib, a third-generation TKI, which targets the T315I mutation, a common cause of

relapse in patients with Ph⁺ ALL, is currently in development. Ponatinib is a pan-*BCR-ABL* inhibitor. It also showed potent activity against other kinases including VEGFR, FGFR, ephrin, SRC kinases, KIT (mast/stem-cell growth factor receptor), RET (rearranged during transfection) and FLT3. Ponatinib is 520-times more potent than imatinib for the native *BCR-ABL* mutation [76]. At a dose of 45 mg orally, responses were observed in patients whose disease was resistant to imatinib or dasatinib [77]. The PACE trial was a pivotal Phase II trial evaluating the efficacy of ponatinib in patients who are resistant or intolerant to dasatinib or nilotinib or had a T315I mutation [78]. Higher response rates were demonstrated in patients previously treated with fewer TKIs. Combinations of chemotherapy regimens and ponatinib may be associated with better response rates and higher likelihood of eradication of MRD. The combination of chemotherapy (hyper-CVAD) with ponatinib is effective in achieving early sustained remissions with major molecular response in 95% [79]. The 2-year EFS rate was 81%. OS was similar with or without censoring for allogeneic SCT. The combination was safe and highly effective in achieving molecular remissions. New strategies, including dosing titration of ponatinib and optimized control of vascular risk factors, might further improve outcomes.

• Monoclonal antibodies & immunotherapy

Monoclonal antibodies represent a new approach for the treatment of B-cell lineage ALL [80]. Ph⁺ ALL blast cells can express a variety of specific antigens, such as CD19, CD20 and CD22. Hyper-CVAD plus the anti-CD20 monoclonal antibody rituximab combined with TKI gave results better than those observed with historical cohorts [79]. Monoclonal antibodies directed against CD22, such as inotuzumab ozogamicin, are being explored in ALL. In relapsing patients with Ph⁺ ALL, first results on a small series showed an advantage for inotuzumab compared with standard therapy, but the difference was not significant [81]. Blinatumomab, a bispecific T-cell-engaging antibody binding CD19 and CD3, has showed promising results in patients with high-risk ALL [82]. Activity has been demonstrated in Ph-ALL with T315I mutation [83]. CR was achieved in 36% of case and in 40% of patients with mutation T315I. Preliminary results indicate that treatment with blinatumomab is able to convert MRD-positive ALL

into an MRD-negative status. A total of 88% of patients achieved a complete MRD response [83]. Monoclonal antibody development could, however, be challenged by the novel approach based on chimeric antigen receptor (CAR) T cells targeting CD19, which has already been tested with encouraging first results [84].

SCT in the TKI era

• Allogeneic SCT

Allogeneic SCT remains the standard of care for adult Ph⁺ ALL [85]. All TKIs can increase the feasibility of allogeneic SCT by increasing remission rates and extending remission duration [86–88]. Furthermore, reducing *BCR-ABL* transcript levels has resulted in a lower pre-SCT leukemia burden [2]. However, the 3-year outcome in children treated with imatinib and chemotherapy compared favorably to those treated with allogeneic SCT, suggesting that patients with Ph⁺ ALL can be treated successfully without allogeneic SCT [89]. Allogeneic SCT with myeloablative conditioning regimen overcomes MRD prior to SCT in some but not all studies. It is superior to allogeneic SCT after nonmyeloablative conditioning regimen if MRD is not considered, but may be equivalent with complete molecular response. Nonmyeloablative allogeneic SCT approaches are therefore promising in patients with ALL [90]. No particular conditioning regimen was deduced to be optimal. Treatment-related toxicity in Ph⁺ ALL in first CR has been reported in 20–30% of cases with high rates of chronic graft-versus-host disease [91–95]. Prophylactic TKI given after engraftment may improve outcomes by preventing a resurgence of the leukemic clone [96]. However, the optimal duration of this treatment has not already been established. In MRD-positive patients after SCT, imatinib at 400 mg/day has been shown to prevent relapse and to achieve molecular remission in 52% of cases after 1.5 months of treatment [97]. However, imatinib is sometimes poorly tolerated after allogeneic SCT and many patients require discontinuation or dose reduction [98]. Overall, recent studies showed a trend toward improved outcome in patients who could be treated with imatinib after allogeneic SCT [46,91]. Alternative therapy based on other TKIs or on monoclonal antibody therapy should be proposed to patients who remain positive for *BCR-ABL* transcripts >2 months after starting imatinib therapy after transplant.

- **Haploidentical SCT**

Alternative donors may be considered for patients lacking a matched-related or matched-unrelated donor. Haploidentical SCT represents an encouraging treatment option [99]. The incidence of nonrelapse mortality was similar between the patients who received HLA-matched donor cells and those who received haploidentical donor cells. The incidence of cytomegalovirus infection was, however, significantly higher in the last group. Haploidentical SCT reduced the relapse rate.

- **Cord blood transplantation**

The status of umbilical cord blood transplantation in adults with Ph ALL is not well established. Recent analyses showed that MRD-positivity before umbilical cord blood transplantation was associated with increased relapses [100].

- **Autologous SCT**

Although autologous SCT has never been considered a standard of care in the setting of Ph⁺ ALL, it remains a possible therapeutic option when MRD is not present before the procedure [47]. Results of autologous SCT have significantly improved in the era of TKIs [101,102]. There are no data on how best to use TKIs after autologous SCT.

How we currently treat adult Ph⁺ ALL at Lyon-University Hospital?

Many trials using TKIs in combination with chemotherapy have been developed for the treatment of adult Ph⁺ ALL (Table 1). Currently most groups keep testing approved or not approved TKIs in combination with chemotherapy. In our previous study about younger adults with Ph⁺ ALL, we carried out an initial randomized comparison of imatinib combined with hyper-CVAD against imatinib with dexamethasone and vincristine. Almost all patients in the imatinib-based arm achieved CR versus only 92% in the chemotherapy-based arm, with toxicity being responsible for the difference [47]. However, long-term survival did not differ between the two arms. Molecular response rate was also similar. Our current trial in younger adults is testing nilotinib in combination with chemotherapy (Figure 1). Although not extensively studied in Ph⁺ ALL, this TKI of second generation is known for a faster efficacy than imatinib [70,71]. Because survival curves after allogeneic SCT (despite improvements since

the use of TKIs) did not demonstrate any plateau [42] and encouraging results were observed with autologous SCT [101], patients demonstrating a major molecular response could receive either allogeneic SCT or autologous SCT as continuation therapy. In older adults, dasatinib combined with only vincristine and dexamethasone showed a 90% CR rate. The median OS was 27 months and most relapses were associated with T315I *BCR-ABL* mutation [68]. Dasatinib, offering inhibition of both tyrosine and SRC kinases, may theoretically hold out more promise of benefit than imatinib. However, studies from the MD Anderson group did not show any significant differences between both TKIs when combined with the hyper-CVAD regimen [38,66]. Our current study in older adults is testing nilotinib at 400 mg b.i.d. from day one throughout induction, consolidation and maintenance according to the backbone schedule of the European Working Group on Adult ALL, in which induction combines vincristine and dexamethasone. This is followed by six cycles of consolidation therapy altering methotrexate-asparaginase and high-dose cytarabine courses, then by a 2-year maintenance therapy with 6-mercaptopurine, methotrexate, dexamethasone and vincristine.

In relapsed Ph⁺ ALL and in patients with T315I mutation, ponatinib could be given at 45 mg per os (p.o.) daily for the first 14 days of cycle one of hyper-CVAD [79].

'Ph-like' ALL: a new entity with specific therapeutic implications

Last decade has been marked by a dramatic improvement in molecular and cytogenetic characterization in ALL, thus providing robust surrogate markers for risk assessment and therapeutic intensification. However, leukemic cells from many patients with B-cell lineage-ALL lack known chromosomal alterations [1]. A new entity of high-risk B-cell precursor ALL has been recently described, namely 'Ph-like' ALL or '*BCR-ABL1*-like' ALL, defined by a similar gene signature than Ph⁺ ALL without *BCR-ABL* translocation [107]. This subtype represents up to 15 and 25% in pediatrics and adolescent/young adult ALL respectively and is associated with a poor outcome [108]. Comparative genomic hybridization arrays and molecular cytogenetics are necessary for the diagnosis. However, validation of a robust gene expression classifier is still warranted for

Table 1. Main clinical trials using tyrosine kinase inhibitors in combination with chemotherapy in the treatment of adult Philadelphia chromosome-positive acute lymphoblastic leukemia.

Study (year)	Regimen	Patients/age (years)	Response to therapy	Survival	Ref.
Lee <i>et al.</i> (2005)	Ima + chemo	20/≥15	95% CR	2-year DFS: 62% 2-year OS: 59%	[40]
Delannoy <i>et al.</i> (2006)	Ima + chemo (GRAALL-AFR09)	30/≥55	90% CR	1-year RFS: 58% 1-year OS: 66%	[44]
Wassmann <i>et al.</i> (2006)	Ima + chemo (GMALL)	45/≥18	96% CR 52% CMR	2-year OS: 43%	[43]
De Labarthe <i>et al.</i> (2007)	Ima + chemo (GRAAPH)	45/15–59	96% CR 38% CMR	1.5-year DFS: 51% 1.5-year OS: 65%	[45]
Ottmann <i>et al.</i> (2007)	Ima + chemo (GMALL)	28/≥55	96% CR	1.5-year DFS: 30% 1.5-year OS: 57%	[42]
Vignetti <i>et al.</i> (2007)	Ima + steroids	30/>60	100% CR 4% CMR	1-year OS: 74%	[41]
Thomas <i>et al.</i> (2010)	Ima + chemo (Hyper-CVAD)	54/≥15	93% CR 52% CMR	3-year DFS: 62% 3-year OS: 55%	[88]
Yanada <i>et al.</i> (2008)	Ima + chemo (JALSG ALL202)	80/15–64	96% CR 71% CMR	2-year EFS: 49% 2-year OS: 58%	[103]
Bassan <i>et al.</i> (2010)	Ima + chemo (NILG)	59/19–66	92% CR	5-year DFS: 39% 5-year OS: 38%	[104]
Foa <i>et al.</i> (2011)	Dasa (70 mg daily)	53/>18	100% CR	1.7-year DFS: 51% 1.7-year OS: 69%	[65]
Fielding <i>et al.</i> (2014)	Ima + chemo (MRC UKALL XII/ECOG 2993)	175/16–64	92% CR	4-year OS: 38%	[105]
Jabbour <i>et al.</i> (2015)	Pona + chemo (Hyper-CVAD)	37/≥18	94% CCR	2-year EFS: 81% 2-year OS: 80%	[79]
Kim <i>et al.</i> (2015)	Nilo + chemo	90/17–71	91% CR	2-year RFS: 72% 2-year OS: 72%	[73]
Ravandi <i>et al.</i> (2015)	Dasa + chemo	72/21–80	96% CR 83% CCR	Median OS: 47 months	[67]
Sartor <i>et al.</i> (2015)	Nilo (400 mg) and Ima (300 mg) alternating every 6 weeks	34/>65	94% CR	2-year OS: 64%	[106]
Chalandon <i>et al.</i> (2015)	Ima + chemo (low intensity) or chemo (Hyper-CVAD)	268/18–59	99 vs 91% CR	5-year EFS: 42 vs 32% 5-year OS: 48 vs 43%	[47]
Rousselot <i>et al.</i> (2016)	Dasa + chemo (EWALL-Ph-01)	71/>55	96% CR	5-year OS: 36%	[68]

CCR: Complete cytogenetic remission; Chemo: Chemotherapy; CMR: Complete molecular remission; CR: Complete remission; Dasa: Dasatinib; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EWALL: European Working Group on Adult Acute Lymphoblastic Leukemia; GMALL: German Multicenter study group for adult Acute Lymphoblastic Leukemia; GRAALL: Group for Research in Adult Acute Lymphoblastic Leukemia; GRAAPH: Group for Research in Adult Philadelphia chromosome-positive Acute Lymphoblastic Leukemia; Hyper-CVAD: Fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine; Ima: Imatinib; JALSG: Japan Adult Leukemia Study Group; MRC: Medical Research Council leukemia trial; NILG: Northern Italy Leukemia Group; Nilo: Nilotinib; OS: Overall survival; Pona: Ponatinib; RFS: Relapse-free survival; UKALL XII: UK Acute Lymphoblastic Leukemia XII.

a routine clinical use [109]. More than 80% of 'Ph-like' ALL cases have abnormalities in genes involved in B-cell development (i.e., *IKZF1* deletions in about 40% of cases), which facilitate leukemia transformation by inducing constitutive kinase activation and signaling through the activation of *ABL1* and/or *JAK/STAT* pathways, but also *CLRF2* overexpression and tyrosine kinase-activating rearrangements involving *ABL1*, *JAK2*, *PDGFRB* and several other genes [110]. Preclinical results of 'Ph-like' ALL pointed out potent role of a targeted therapeutic

strategy according to the molecular profile of leukemia cells [111,112]. Recently, several cases have been reported with responses to TKIs (mostly imatinib) [113–115]. 50% of 'Ph-like' ALL show activation of *JAK-STAT* and *PI3K/mTOR* pathways and should also be sensitive to *JAK* and *mTOR* inhibitors [100,112].

Conclusion: what is the prognosis of adult Ph⁺ALL? Future perspectives?

The outcome of adult patients with Ph⁺ ALL has substantially improved since the introduction

of TKIs. The best results are shown with TKIs incorporated early, daily and continuously with chemotherapy. Current CR rates reach 90% and long-term survival rates attain 50–60%. Now, key challenges are the selection of appropriate pretransplantation therapy, the minimization of transplantation toxicity, the use of TKIs after transplantation and the appropriate use of BCR–ABL monitoring. Clinical trials with TKIs currently recruiting in adult Ph⁺ ALL are summarized in **Table 2**. Although recent data suggest that addition of chemotherapy to dasatinib might help to prevent the emergence of dasatinib-resistant mutation [116], this is now logical to ask whether there is a rationale for

reducing cytotoxic agents from initial induction [41,47,65]. Less chemotherapy intensity in induction prior to SCT was shown not inferior, while initial dose intensity of TKI was demonstrated as important. Second and third generation TKIs improved results in terms of MRD, but there are no prospective randomized trials on outcome. Furthermore, there is little evidence to date that allogeneic SCT is a dispensable part of therapy. In a Phase II trial combining dasatinib with chemotherapy, there was no difference in outcomes between patients in CR who did and did not undergo allogeneic SCT [117]. MRD monitoring by RT-PCR and multiparameter flow cytometry may identify patients

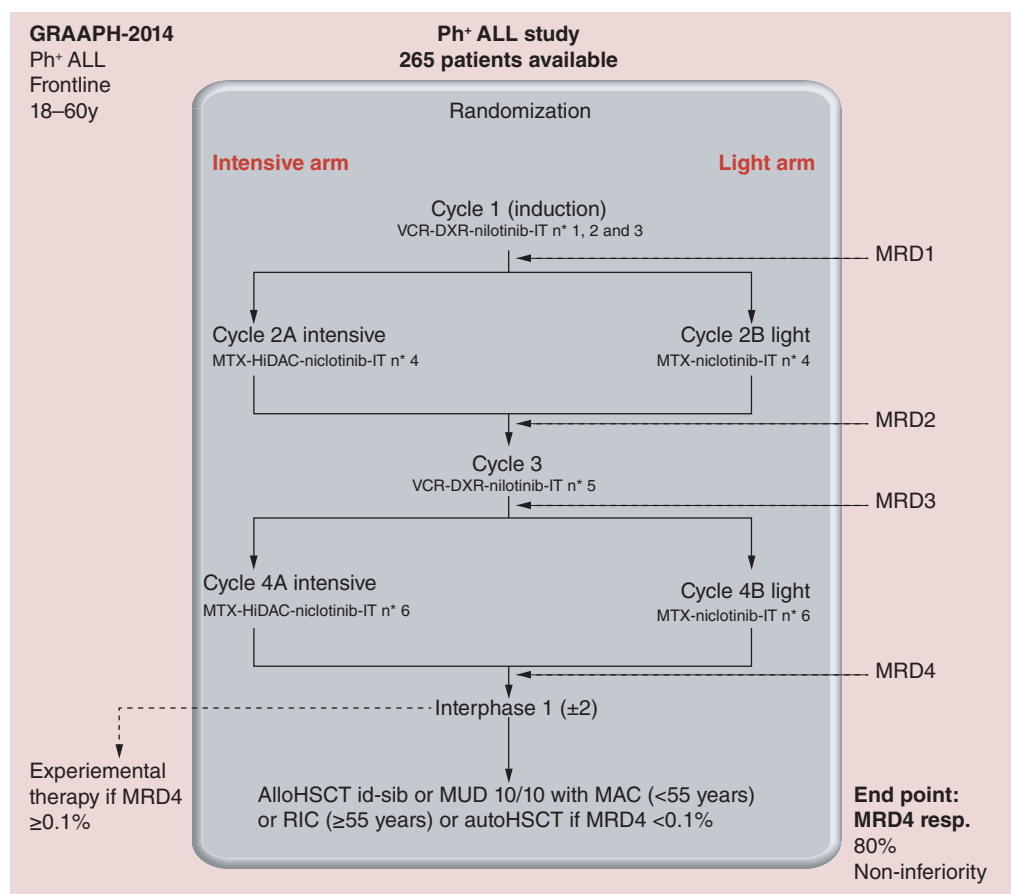


Figure 1. Schema of the Group for Research in Adult Philadelphia chromosome-positive Acute Lymphoblastic Leukemia-2014: treatment from the French Group for Research on Adult Acute Lymphoblastic Leukemia for young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia.

ALL: Acute lymphoblastic leukemia; AlloHSCT id-sib: Allogeneic hematopoietic stem cell transplantation from identical sibling; AutoHSCT: Autologous hematopoietic stem cell transplantation; DXR: Doxorubicin; HiDAC: High-dose cytarabine; IT: Intrathecal; MAC: Myeloablative conditioning; MRD: Minimal residual disease; MTX: Methotrexate; MUD: Matched unrelated donor; Ph⁺: Philadelphia chromosome-positive; RIC: Reduced intensity conditioning; VCR: Vincristine.

Table 2. Recruiting clinical trials with tyrosine kinase inhibitors in adult Philadelphia chromosome-positive acute lymphoblastic leukemia.

Study	Age (years)/status	Treatment	Identifier
Phase II NCI	≥65/newly diagnosed	Dasatinib + blinatumomab + prednisone	NCT02143414
Phase II MDACC	≥10/Ph-like ALL	Dasatinib + chemo (hyper-CVAD)	NCT02420717
Phase I MSKCC	≥40/newly diagnosed	Dasatinib + ruxolitinib + Dex	NCT02494882
Phase II University of California, San Diego	18–60/newly diagnosed	Dasatinib + rituximab [†] + chemo	NCT02043587
Phase I Novartis Pharmaceuticals	≥18/R/R to TKIs	ABL001 + dasatinib or imatinib or nilotinib	NCT02081378
Phase III PETHEMA	≥55/newly diagnosed	Dasatinib or imatinib + chemo	NCT01376427
Phase II MDACC	≥55/newly diagnosed	Dasatinib or imatinib + rituximab [†] + chemo (hyper-CVAD)	NCT01319981
Phase I and II University of Toronto	≥18/R/R to TKIs	Nilotinib + ruxolitinib	NCT01914484
Phase III GRAALL (GRAAPH 2014)	18–59/newly diagnosed	Nilotinib + chemo	NCT02611492
Phase II OHSU Knight Cancer Institute	21–70/relapsed	Nilotinib or ponatinib or dasatinib	NCT01620216
Phase I and II Novartis Pharmaceuticals	≥18/R/R	Nilotinib + ruxolitinib	NCT02253277
Phase II MDACC	≥18/R/R	Bosutinib + inotuzumab ozogamicin	NCT02311998
Phase II GIMEMA	≥18/newly diagnosed	Ponatinib	NCT01641107
Phase II MDACC	≥18/newly diagnosed	Ponatinib + chemo (hyper-CVAD)	NCT01424982
Phase IV PETHEMA	<55/newly diagnosed	Imatinib + chemo	NCT01491763
Phase II Asan Medical Center (RADICAL)	≥15/newly diagnosed	Imatinib + rituximab [†] + chemo	NCT01429610

[†]In patients expressing CD20.
 ABL001: A potent allosteric BCR–ABL inhibitor; Chemo: Chemotherapy; Dex: Dexamethasone; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; GRAALL: Group for Research in Adult Acute Lymphoblastic Leukemia; GRAAPH: Group for Research in Adult Philadelphia chromosome-positive Acute Lymphoblastic Leukemia; Hyper-CVAD: Fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine; MDACC: MD Anderson Cancer Center; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; PETHEMA: Programa para el Tratamiento de Hemopatías Malignas; Ph⁺ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; R/R: Relapsed/refractory; TKI: Tyrosine kinase inhibitor.

in first CR for whom further consolidation with allogeneic SCT may not be needed [117]. After molecular response achievement, autologous SCT or chemotherapy plus TKI yielded similar results than allogeneic SCT. However, the long-term outcome of chemotherapy-free induction strategies is currently not assessable.

RT-PCR BCR–ABL quantification is used to monitor MRD in patients with Ph⁺ ALL. BCR–ABL transcript levels have been correlated with response [61]. However, no consensus has been drawn on what represents an optimal response. A 3-log reduction in BCR–ABL transcripts after 1 month of imatinib therapy has been shown to predict a reduced relapse risk [118], as no rapid achievement of BCR–ABL negativity was described for achieving a long-term outcome [119]. However, MRD at 3 months has better discrimination for OS and relapse-free survival than did MRD status at CR. Patients who achieve complete molecular response at 3 months have superior survival compared with those with lesser molecular responses and have excellent long-term outcomes even when SCT is not performed [120]. However, currently BCR–ABL should be monitored after allogeneic SCT and re-emergence of BCR–ABL positivity should be a formal indication for intervention.

Many patients with Ph⁺ ALL relapse with a T315I clone, which is resistant to imatinib and second-generation TKIs. Novel molecules have shown interesting first results in Ph⁺ leukemias. Among them, ponatinib is a more potent third-generation BCR–ABL1 TKI that also suppresses the T315I clones. More recently, danusertib, a pan-aurora kinase inhibitor with potent activity against ABL kinase including the gatekeeper T315I mutant, has demonstrated an acceptable toxicity profile and is active in patients with BCR–ABL-associated advanced hematologic malignancies [121]. Axitinib is a VEGFR TKI that has also been shown as a selective and effective inhibitor for T315I mutant BCR–ABL1-driven leukemia [122]. New monoclonal antibodies are also going to change the landscape of ALL therapy. Monoclonal antibody development could, however, be challenged by the novel approach based on CAR T cells targeting CD19, which has already been tested with encouraging first results. CAR T cells targeting CD22 or CD19/CD22 are also under investigation. Further challenges should include: how to modulate immunotoxicity without losing efficacy; defining the optimal placement of monoclonal antibodies and CAR therapy either as bridge to SCT or alternative to SCT; defining the optimal therapeutic strategy

with administration in relapse or after remission achievement; and define when it should be given in relation to chemotherapy.

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