Management of Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL)

Oliver G. Ottmann[1] and Heike Pfeifer[1]

[1]Medizinische Klinik II, Department of Hematology and Oncology, Goethe University, Frankfurt, Germany

The tyrosine kinase inhibitor (TKI) imatinib has become an integral part of front-line therapy for Ph+ ALL, with remission rates exceeding 90% irrespective of whether imatinib is given alone or combined with chemotherapy. Treatment outcome with imatinib-based regimens has improved compared with historic controls, but most patients who do not undergo allogeneic stem cell transplantation (SCT) eventually relapse. Acquired resistance on TKI treatment is associated with mutations in the bcr-abl tyrosine kinase domain in the majority of patients, and may be detected at low frequency prior to TKI treatment in a subset of patients. Second generation TKIs, eg, dasatinib and nilotinib, show activity against most of the bcr-abl tyrosine kinase domain (TKD) mutations involved in acquired imatinib resistance, but clinical benefit is generally short-lived. Accordingly, SCT in first complete remission (CR) is considered to be the best curative option. Molecular monitoring of minimal residual disease levels appears to have prognostic relevance and should be used to guide treatment. International standardization and quality control efforts are ongoing to ensure comparability of results. Mutation analysis during treatment relies increasingly on highly sensitive PCR techniques or denaturing HPLC and may assist in treatment decisions, eg, in case of molecular relapse. Results from current studies of second-generation TKI as front-line treatment for Ph+ ALL are promising and show high molecular response rates, but follow-up is still too short to determine their impact on remission duration and long-term survival. Strategies to improve outcome after SCT include the pre-emptive use of imatinib, which appears to reduce the relapse rate. In patients ineligible for transplantation, novel concepts for maintenance therapy are needed. These could involve novel immunotherapeutic interventions and combinations of TKI.

Philadelphia chromosome (Ph)/BCR-ABL–positive acute lympoblastic leukemia (ALL) is the largest genetically defined subtype in adult ALL, and until recently the one with the most unfavorable prognosis. Introduction of the tyrosine kinase inhibitor (TKI) imatinib in combination chemotherapy has led to a marked improvement in treatment outcome of this leukemia; survival now ranges from 40% to 50%. Remarkably, patients with Ph+ ALL now have a better prognosis than patients with bcr-abl–negative high-risk B-precursor ALL.[1] It has become clear that these improvements are not attributable to TKI alone, but depend on the implementation of an integrated strategy incorporating chemotherapy, stem cell transplantation (SCT), second-generation TKIs and molecular monitoring to guide therapeutic decisions.[2] Despite these advances, substantial obstacles remain. Ph+ ALL is notorious for its ability to rapidly develop resistance to TKI, with bcr-abl tyrosine kinase domain mutations being a major, but not the only, culprit.[3-5] Furthermore, the incidence of Ph+ ALL increases with age, limiting the option of allogeneic SCT in a significant proportion of patients. This article will examine the evidence base for the current management of Ph+ ALL as well as comment on areas of therapeutic uncertainty and upon promising approaches under development.

Induction and Consolidation Therapy

Several strategies have been tested to optimize the combination of imatinib and chemotherapy. Initial studies were based on schedules alternating imatinib and chemotherapy cycles, followed by clinical trials that investigated schedules in which imatinib and chemotherapy were given concomitantly (**Table 1**). The question of whether minimization of therapy-related toxicity by combining imatinib with less intensive chemotherapy or administering it alone yielded equivalent or superior results were also addressed. As far as can be determined in the absence of randomized studies, the results of induction therapy using these different strategies are comparable, with CR rates exceeding 90% to 95%.

Table 1. Studies combining imatinib with chemotherapy for de novo Philadelphia chromosome–positive (Ph$^+$) ALL.

Reference	N (evaluated)	Age. y (range)	Imatinib, mg/d	ChThx regimen	Schedule of TKI and ChThx	CR, %	PCR negative, %	Induction death, n (&)	Relapse, %	Outcome
Lee KH 2005 [6]	20	37 (15-67)	600 (IND) 400 (C+M)	Modified from Linker	Concurrent	95	NR	1 (5)	32	OS (2y): 59% EFS (2y): 62%
Yanada M 2006 [7]	80	48 (15-63)	600	JALSG ALL202	Concurrent/ sequential	96	71	2 (2.5)	25	OS (1y): 76% EFS (1y): 60%
Wassmann B 2006 [8]	92 (47+45)	46 (21-65) 41 (19-63)	400 / 600	GMALL 06/99 and 07/03 alloSCT (77%)	Sequential/ concurrent	95	19 vs 52	0	NA	OS (2y): 36% (sequential) 43% (concurrent) DFS (2y): 52% (sequential) 61% (concurrent)
De Labarthe A 2007 [9]	45	45 (16-59)	600	GRAAPH-2003	Concurrent	96	38	2 (4)	19	OS (1.5y): 65% DFS (1.5y): 51%
Thomas, DA 2008 [10]	45*	51 (17-84)	600	HyperCVAD alloSCT (33%)	D1-14 of each cycle	93	52	1 (2)	22	OS (3y): 66% with SCT 49% without SCT
Chalandon, 2008 [11]	83 (42+41)	42	800	VCR+DEX vs HyperCVAD; alloSCT (n = 41)	D1-28 D1-14	100 vs 95	48 vs 72	1 (1.2)	22	OS (2y): 62% DFS (2y): 43%
Delannoy A 2006 [17]	30	–	600	GRAALL AFR09	Concurrent Alternating	72	–	–	60	OS (1y): 58% DFS (1y): 66%
Rea D 2006 [15]	31	–	600	GRAALL AFR07 (pilot)	Concurrent	90	–	–	NR	OS (1y): 60% DFS (1y): 48%
Ottmann OG 2007 [16]	55 (28+27)		600	IM (induction) GMALL-elderly	Concurrent	96 50	–	–	41 54	

DFS indicates disease-free survival; EFS, event free survival; OS, overall survival; CR, complete remission; ChThx, chemotherapy; TKI, tyrosine kinase inhibitor; IND, induction; c, consolidation; M, alternating; VCR, vincristine; DEX, dexamethasone; hyper-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; C, concurrent; A, alternating; NR, not reported; na, not applicable; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multi-Centre Acute Lymphoblastic Leukemia; GRAALL, Group for Research in Adult Acute Lymphoblastic Leukemia; JALSG, Japan Adult Leukemia Study Group; GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia.

*39 patients with de novo Ph+ALL, 6 pts. refractory to one prior treatment cycle

Table 2. Studies with dasatinib for de novo Philadelphia chromosome–positive (Ph⁺) ALL.

Reference	N (evaluated)	Age. y (range)	Dasatinib, mg/d	ChThx regimen	Schedule of TKI and ChThx	CR, %	PCR negative, %	Induction death, n (%)	Relapse, n (%)	Outcome
Ravandi F 2008 [18]	28*	52 (21-79)	100 QD	HyperCVAD	D1-14 of each cycle	93	50	2 (7)	5 (18)	CR (10 mo): 18 (64%) OS (10 mo): 21 (75%)
Rousselot P 2008 [19]	22	71 (61-83)	140 QD 100 QD	EWALL elderly	IND: parallel, then alternating	95	28	1 (4.5)	1 (4.5)	na
Foa R 2008 [20]	48 (34)	54 (24-76)	70 BID	Steroid prephase, then 12 wk dasatinib	Post-induction therapy not defined	100	na	0	9 (27)	OS (10 mo): 81%

*22 patients with de novo Ph⁺ALL, 6 pts. with one prior treatment cycle

OS indicates overall survival; CR, complete remission; ChThx, chemotherapy; hyper-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; IND, induction; na, not applicable; EWALL: European Working Group for Adult ALL of the European LeukemiaNet

Imatinib in Combination with Chemotherapy in Younger Patients

The current standard approach for young patients is the combination of a chemotherapy protocol employing four to five cytotoxic agents typically used for ALL with imatinib at a daily dose of 400 mg to 800 mg (**Table 1**).[6,-11] Complete remission rates in these studies consistently exceeded 90%; the profile and incidence of severe toxicity were not different from those associated with the historic chemotherapy-alone regimens.[7,12] Estimated overall survival (OS) in the different studies ranged from 36% to 76%, although follow-up is short (1 to 3 years). While the superiority of adding imatinib to conventional chemotherapy was strongly suggested by historical comparisons between the outcome of the patients using similar chemotherapeutic schedules with or without imatinib,[6,12] the impact of imatinib-based regimens on long-term outcome is difficult to assess due to the higher rate of patients undergoing SCT in CR1, which became possible due to a lower incidence of early relapses.[6,9,11,13]

Imatinib-based Therapy in Elderly Patients

To avoid the toxicity of intensive chemotherapy in elderly patients with Ph⁺ ALL, the GIMEMA conducted a study in which patients older than 60 years received a 45-day induction treatment with imatinib (800 mg/day) in combination with prednisone, followed by imatinib maintenance until disease relapse or excessive toxicity.[14] All patients achieved complete remission, and there were no deaths in CR. Median remission duration was only 8 months, however, and median survival from diagnosis was 20 months. Imatinib in combination with chemotherapy of varying intensity was also tested by several groups. A study examining a low intensity chemotherapy schedule with vincristine and dexamethasone in combination with high-dose imatinib (800 mg/d) in patients older than 55 years (DIV regimen) is ongoing, following promising results of a pilot study in relapsing and refractory Ph⁺ ALL, in which more than 90% of patients achieved a CR (**Table 1**).[15]

In a prospective, randomized trial comparing imatinib with multi-agent chemotherapy as induction therapy followed by combined intensive consolidation chemotherapy and imatinib in elderly patients with *de novo* Ph⁺ ALL, the CR rate with imatinib induction was 96% with no induction deaths, and severe adverse events (SAE) were significantly less frequent than with chemotherapy. Estimated OS in both cohorts was 42% at 24 months.[16] Encouraging results were also reported for the delayed start of imatinib in conjunction with consolidation chemotherapy, rather than during induction, although a number of patients entered remission only after consolidation with imatinib.[17]

Thus, imatinib is now accepted as an essential element of induction therapy due to its pronounced anti-leukemic efficacy and good tolerability when used as front-line therapy for Ph⁺ ALL in elderly patients, but acquired imatinib resistance and the toxicity of postremission chemotherapy are major clinical problems.

Dasatinib in Combination with Chemotherapy

The combination of dasatinib with a variety of cytotoxic chemotherapy regimens both in younger and elderly patients with *de novo* or minimally pretreated Ph⁺ ALL was explored in recent phase II trials (**Table 2**).[18,19] CR rates exceeded 90%, independent of the regimen used; molecular remission rates ranged from 28% to 72%. No formal comparison of studies regarding toxicity of treatment is possible, but SAE particularly during induction were frequent in both younger and older patients, although in general manageable. Response duration and survival in the different studies are encouraging, but follow-up is still short.

Dasatinib Monotherapy

Induction therapy with dasatinib, administered at 70 mg BID for 12 weeks and combined with corticosteroids during the first 4 weeks of treatment, in patients 18 years or older, induced complete remission in all evaluable patients.[20] Follow-up is still short (median 11.2 months), and analysis of outcome is confounded by the heterogeneous therapy given subsequent to the first 12 weeks of dasatinib treatment. The degree of minimal residual disease (MRD) response had prognostic relevance. Relapse was associated with bcr-abl mutations in 6 of 8 patients examined, 5 of whom showed the T315I mutation.

Maintenance Therapy

To date, there is no consensus on what constitutes the most effective maintenance therapy in patients in whom allogenic SCT is not possible. Usually, imatinib is given either alone or in combination with classical ALL maintenance such as low-dose methotrexate and 6-mercaptopurine, although published data on the efficacy of these strategies are scarce.[17] In a small group of 7 patients with Ph$^+$ ALL who were in first complete remission and received maintenance therapy with imatinib alone, 2-year progression-free survival was 75%. Persisting molecular complete response by quantitative polymerase-chain-reaction (qPCR) of BCR-ABL was associated with long-lasting CR. Surprisingly, molecular relapse did not invariably lead to leukemic relapse, which was predicted only by rapid and/or substantial increments of BCR-ABL transcripts.[21] However, larger studies show less favorable results with imatinib-based maintenance. More intensive maintenance therapy is being employed by the M D Anderson Cancer Center (MDACC): imatinib 800 mg for 24 months with monthly vincristine and prednisone interrupted by 2 intensifications with hyper-CVAD and imatinib, then imatinib indefinitely.[10]

Concomitant administration of imatinib and interferon-alpha (IFNα) is an interesting approach based on experimental data suggesting that IFNα may enhance the antileukemic activity of imatinib, and on clinical experience with combined imatinib and low-dose conventional IFNα or Pegasys® in patients with Ph$^+$ ALL who were ineligible for stem cell transplantation. Results are encouraging, but longer follow-up is needed to determine whether this strategy will translate into better relapse-free survival.[22,23]

CNS-directed Treatment

Central nervous system (CNS) leukemia is infrequent (5%) at initial presentation, but there is a significant risk of developing meningeal leukemia during the course of treatment.[24] Imatinib levels in the cerebrospinal fluid have been shown to reach only 1% to 2% of serum levels.[25-29] Accordingly, CNS-directed prophylactic therapy should be considered mandatory in patients with Ph$^+$ ALL. Both repeated intrathecal injection of chemotherapy, eg, methotrexate, alone or in combination with cytarabine and corticosteroids, and prophylactic cranial irradiation have been used successfully.

Dasatinib shows better penetration 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.[30] It remains to be determined whether the current approach to CNS-directed prophylaxis can be modified in the context of dasatinib-based treatment.

Stem Cell Transplantation

The proportion of patients able to undergo SCT in CR1 has increased with imatinib-based induction and early postremission therapy, and there is currently no evidence that imatinib has an adverse effect on transplant-related morbidity or mortality.[1,7,13,31] In addition, donor availability has benefitted from results showing equivalence of sibling and matched unrelated donors in terms of remission duration, non-relapse mortality and overall survival.

Several studies have shown improved post-transplant outcome of patients previously receiving imatinib-based treatment when compared with historic control groups.[7,13] As a consequence, most ALL study groups currently consider imatinib-based treatment, followed by matched related or unrelated allogeneic SCT in CR1, to be the gold standard of first-line therapy for Ph$^+$ ALL, and as the only treatment unequivocally accepted as having curative potential in adult patients with Ph$^+$ ALL.[32,33] On the other hand. imatinib-based treatment not followed by SCT has been suggested to achieve OS and DFS similar to that obtained after SCT in one study,[7] and a recently updated MDACC study showed only a trend towards better OS in transplanted patients.[9] Future studies will have to determine whether therapy based on second generation TKI may be equivalent or superior to SCT in a subset of patients, particularly those at high risk of transplant-related mortality (TRM).

Allogeneic Stem Cell Transplantation with Myeloablative Conditioning

Attempts to improve outcome of Ph$^+$ ALL included intensified conditioning regimens in order to reduce the relapse rate. An intensified preparatory regimen consisting of SCT after fractionated total body irradiation and etoposide with or without cyclophosphamide was explored by Kröger et al[34] and Laport et al.[35] TRM was mainly due to infections or GVHD, and was higher in patients with more advanced disease.[35,36] Factors affecting event-free and overall survival likewise included disease status (CR1 vs > CR1) and higher age, with a cutoff at approximately 30 years, at the time of transplantation.[32-35]

Thus, while these intensified preparatory regimens confer long-term survival in a subset of patients with Ph^+ ALL, relapse and TRM remain important causes of treatment failure, making success unlikely in patients with more advanced disease. Interestingly, comparable survival data were reported for patients with high-risk ALL with the Philadelphia chromosome and those with normal cytogenetics; actuarial disease-free survival (DFS) at 5 years was 43% for patients in first remission.[37]

Chronic GVHD appears to reduce the risk of relapse without increasing the risk of TRM, whereas severe acute GVHD increases the risk of TRM without diminishing the risk of relapse. Thus, patients who developed extensive chronic GVHD had better survivals ($P = .0217$), and those who developed grade III-IV acute GVHD had worse survivals ($P = .0023$) than did the others.[36] Immunotherapy with donor lymphocyte infusion (DLI) and imatinib appears to be well tolerated but is rarely and in general only transiently effective. A rationale for the combined use of DLI and second-generation TKIs such as nilotinib is suggested by case reports, but prospectively collected data are as yet not available.[38,39]

Reduced-intensity Conditioning alloSCT

In order to decrease the high TRM associated with myeloablative alloSCT but still generate a graft-versus-leukemia effect, reduced-intensity conditioning (RIC) regimens were developed for patients unlikely to tolerate the toxicities of intensive preparative regimens. Overall, several retrospective analyses and a single prospective study suggest that alloSCT following RIC is feasible in adult patients with high-risk ALL but associated with a high probability of treatment failure in patients transplanted beyond CR1.[40-44] The incidence of TRM and disease progression in these studies was still substantial, however, particularly in patients transplanted beyond first CR. The incidence of acute (grades II-IV) and chronic GVHD (43.2% and 65.6%, respectively) was high, but the significantly lower frequency of disease progression in patients with chronic GVHD highlights the antileukemic activity of chronic GVHD.

Autologous Stem Cell Transplantation

The role of autologous stem cell transplantation (ASCT) was studied most extensively in the pre-imatinib era and has attracted little interest since then. While there are no prospective, randomized trials comparing autologous and allogeneic SCT, treatment outcome with conventional ASCT procedures has consistently been inferior to alloSCT in several retrospective analyses due to a high relapse rate.[45-47] More recently, some investigators have reevaluated the therapeutic potential of ASCT when given in conjunction with TKI. Shin et al describe an approach in which Ph^+ ALL patients receive imatinib as interim therapy between chemotherapeutic cycles and prior to autologous SCT, followed by maintenance therapy.[48] Small patient numbers and as yet limited duration of follow-up preclude a definite assessment of this strategy, which can be expanded to include the more potent second-generation TKI.

Clinical Implications of MRD

High levels of bcr-abl transcripts at different treatment stages indicate poor responsiveness to chemotherapy and to TKI, and intuitively could be considered a risk factor for disease recurrence. However, published data are not consistent. MRD levels determined at different timepoints prior to alloSCT were found to have prognostic relevance, with an early reduction in BCR-ABL transcript levels of at least 3 log appearing as the most powerful predictor of lower relapse rate and better DFS.[49] Stratification based upon MRD levels was also the principal prognostic parameter in two studies with 154 and 45 Ph^+ ALL patients, respectively.[47,50]

In contrast, prospective MRD monitoring in 100 adult patients with Ph^+ ALL treated with uniform imatinib-combined chemotherapy failed to establish an association between PCR negativity at the end of induction therapy and either relapse rate or relapse-free survival, although an increase in bcr-abl transcripts during hematologic CR was predictive of relapse in non-transplanted patients.[51]

Despite these discrepancies, these studies demonstrate that prospective monitoring of MRD has the potential to identify patients at risk of relapse, although the implication of different transcript levels and increments require validation within each therapeutic context or clinical study. These issues highlight the need for standardization and harmonization of methodologies used for bcr-abl quantification in Ph^+ ALL. To achieve this aim at an international level, regular quality control rounds are jointly conducted by the European Working Group for Adult ALL (EWALL) of the European LeukemiaNet and the European Study Group for MRD Analysis in Acute Lymphoblastic Leukemia.

Prophylactic and Interventional Administration of Imatinib after SCT

The high risk of relapse in patients who are MRD positive after SCT[52] makes administration of an ABL-directed TKI conceptually attractive as a measure to prevent relapse and reestablish molecular negativity. The feasibility of giving imatinib after SCT was tested in a prospective study involving patients with Ph+ ALL (n = 15) or high-risk chronic myeloid leukemia (n = 7) who received imatinib from the time of engraftment until 365 days after hematopoietic cell transplantation (HCT). Grade 1-3 nausea, emesis, and serum transaminase elevations were the most common adverse events related to imatinib administration.[53] The median daily imatinib dose that was tolerated before day 90 was 400 mg/d in adults (n = 19) and 265 mg/m^2/d in children (n = 3).

In a prospective, multicenter study, adult patients with Ph+ ALL (n = 27) received imatinib upon appearance of bcr-abl transcripts after SCT. Bcr-abl transcripts became undetectable in 52% of patients; median time to PCR negativity was 1.5 months (range: 0.9-3.7 months). All patients who achieved an early molecular response remained in remission for the duration of imatinib treatment; 3 patients relapsed after imatinib was discontinued. In contrast, 12 of the 13 patients (92%) who did not promptly achieve PCR negativity after imatinib initiation relapsed; median time to relapse was only 3 months. Thus, in the post-transplant setting, the molecular response to imatinib discriminates between patients with long-term DFS and patients likely to experience relapse and who therefore should receive additional or alternative antileukemic therapy.[31]

These data are consistent with a single-center analysis of 32 patients with Ph+ ALL, including pediatric patients, who underwent allo-HCT and received imatinib in either the pre- or post-transplant period. There was a trend towards improved OS, relapse-free survival and relapse at 2 years (61%, 67% and 13%) for the imatinib group (n = 15) as compared with the 41%, 35% and 35% for the non-imatinib group (n = 17), respectively. Cardiac toxicity and TRM at 2 years were similar between the groups.[54] Overall, further data are needed to define the optimal use and impact of imatinib in the peri-transplant management of patients with Ph+ ALL.

Treatment of Children with Ph+ ALL

The Philadelphia/bcr-abl translocation is uncommon among pediatric ALL patients, with a frequency of less than 5%, but it is classified as high or very high risk. The potential of BCR-ABL kinase inhibitors to improve outcome prompted studies in which imatinib has been combined with conventional chemotherapy in children and adolescents with Ph+ ALL. The COG AALL0031 protocol gave imatinib at 340 mg/m^2 for an increasing number of days (ranging from 42 days to 280 continuous days) in combination with an intensive chemotherapy backbone prior to maintenance therapy. In 83 evaluable patients, the addition of imatinib to consolidation blocks 1 and 2 resulted in a significantly lower rate of MRD positivity (P = .0002 and P = .007, respectively) compared with chemotherapy alone. Early EFS at 1 year improved with increasing imatinib exposure, from 71% to 95% (P= .02). Patients who underwent related BMT and received imatinib for a 6-month period, starting 4 to 6 months post BMT had a higher 1 year EFS compared with a comparable historical BMT group receiving no Imatinib. Interestingly, there was no statistically significant difference in early outcome between those patients with the longest imatinib exposure treated without sibling donor BMT compared with patients who received a matched sibling donor BMT (P = .26). Longer observation will be required to determine whether long-term outcome with intensive imatinib and chemotherapy is indeed equivalent to that of patients treated with allogeneic related or alternative donor BMT.[55] Reports on the use of second-generation bcr-abl kinase inhibitors in children with Ph+ ALL are scarce. The feasibility and clinical benefit of using dasatinib as salvage therapy enabling HSC transplantation is indicated by a few case reports.[56] More extensive data from clinical trials is needed to determine whether the administration of second-generation TKI in children and adults is comparable.

Mechanisms of Resistance to Kinase Inhibitors

Approximately 80% to 90% of patients with Ph+ ALL who relapse while on imatinib are found to have bcr-abl mutations, with predominance of P-loop and T315I mutations.[57-59] With dasatinib, relapse is most frequently associated with the T315I mutation, whereas P-loop mutations are less common.[57] It has become of central interest whether mutations are already present in TKI-naïve patients, and this frequently appears to be the case. Pfeifer et al detected low-level TKD mutations in pre-therapeutic leukemic samples in approximately 40% of patients with Ph+ ALL.[59] At relapse, the dominant cell clone harbored an identical mutation in the majority of cases. Soverini et al likewise reported a high rate of BCR-ABL mutations, several of which have been recognized in resistant patients with Ph+ ALL.[60]

In all these patients additional but as yet largely unknown mechanisms of resistance to TKI therapy have been suggested. Cytogenetic abnormalities in addition to Ph chromosome are present in approximately one third of cases of adult leukemias and have been associated with inferior outcome. Members of the SRC family of kinases have been implicated in leukemogenesis and development of imatinib-resistance in bcr-abl–positive ALL, suggesting that simultaneous inhibition of Src and Bcr-Abl kinases may benefit individuals with Ph+ acute leukemia.[61,62]

Treatment of Relapse

Since point mutations of the ABL TK domain appear to be major contributors to imatinib resistance in Ph+ leukemias, different drugs active on mutant Bcr-Abl or on its signal transduction pathway have been developed. Several second-generation ABL TKIs possess significant activity against imatinib-resistant BCR/ABL mutants, although their specificities vary.[63] Of these compounds, dasatinib has been tested most extensively in Ph+ ALL and has been approved as second-line treatment of bcr-abl–positive leukemias. Dasatinib (Sprycel, formerly BMS-354825) is a multitarget kinase inhibitor of Bcr-Abl, SRC family kinases, ephrin receptor kinases, PDGFR and KIT, among others. In a phase II study, dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Ph+ ALL with resistance or intolerance to imatinib.[64] Non-hematological side effects include diarrhea, nausea, headache, peripheral edema and pleural effusion. However, remission duration and PFS were short, due to resistance that was often associated with appearance of the T315I mutation. To enhance efficacy, dasatinib was combined with the hyperCVAD chemotherapy regimen in a small phase II study with 14 patients, 3 of whom had CNS involvement.[65] All patients responded; 71% achieved a CR, 64% achieved a major molecular response. With a median follow-up of 6 months, 7 patients remained in CR/CRp. Although toxicity was significant, with several episodes of gastrointestinal and subdural hemorrhage and pleural effusions, these preliminary results suggest that combination therapy should be preferred over single-agent therapy; alloSCT should be the goal if at all possible. To achieve a CR, mutation analysis should precede salvage therapy, and experimental treatment should be considered if the T315I mutation is detected, as this mutation confers resistance to all second generation ABL TKI.

Small-molecule inhibitors developed to target Aurora kinases (AK), a family of serine-threonine kinases involved in control of chromosome assembly and segregation during mitosis, have been found to possess activity against the T315I mutation. Several of these novel AK inhibitors have recently entered preclinical or clinical testing.[66,67] Another novel chemical class of compounds that bind to distinct structural pockets that the ABL kinase uses to switch between the inactive and active conformations have recently been developed using structure-based drug design. Compounds have emerged that potently inhibit purified ABL in both the unphosphorylated and phosphorylated states via a non-ATP-competitive mechanism and impair proliferation and induce apoptosis of cells expressing a wide variety of BCR-ABL TKI-resistant mutants, including the T315I mutant, many P-loop mutants, and the dasatinib-resistant mutant F317L.[70]

Future Treatment Concepts

Ongoing and future clinical trials will establish whether front-line therapy with second-generation ABL kinase inhibitors, ie, dasatinib, nilotinib, bosutinib and Inno-406, are superior to imatinib. Results may differ depending on their use as single-agents or as components for combination therapy. SCT-independent immunotherapeutic approaches are also evolving. Bispecific T cell–engager (BiTE) antibodies that transiently engage cytotoxic T cells for lysis of selected target cells are among the most interesting agents for immunotherapy of Ph+ ALL. The bispecific antibody construct called blinatumomab links T cells with CD19-expressing target cells, resulting in a non-restricted cytotoxic T-cell response and T-cell activation. A phase II dose-escalating study investigating the efficacy and safety of blinatumomab in ALL patients who are in complete hematological remission but remain MRD-positive is ongoing. Preliminary results indicate that treatment with blinatumomab is well tolerated and able to convert MRD-positive ALL into an MRD negative status.[69]

In conclusion, our armamentarium of drugs that hold promise as active agents for treating Ph+ ALL is expanding substantially. Studies will need to focus on drug combinations, with specific attention to sequence and dosing of these agents. In designing trials, treatment algorithms should increasingly be based on molecular markers of disease and utilize quantitative assessment of MRD, and highly sensitive detection of mutations.

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Correspondence

Oliver G. Ottmann, MD, Medizinische Klinik II, Abteilung Hämatologie und Onkologie, Johann Wolfgang Goethe University, Frankfurt, Theodor Stern-Kai 7, 60590 Frankfurt, Germany; Phone: +49-69-6301-3947; Fax: +49-69-6301-4170; e-mail: ottmann@em.uni-frankfurt.de

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