Published in final edited form as:

Leuk Lymphoma. 2011 February ; 52(Suppl 1): 81–91. doi:10.3109/10428194.2010.546917.

New developments in the treatment of chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia

AMBER FULLMER, HAGOP KANTARJIAN, JORGE CORTES, and ELIAS JABBOUR

M. D. Anderson Cancer Center, The University of Texas, Houston, TX, USA

Abstract

Although imatinib revolutionized the management of chronic myeloid leukemia (CML), recent data indicate a transformation in the treatment approach likely in the near future. The superiority of second-generation tyrosine kinase inhibitors (TKIs) over imatinib in newly diagnosed disease has been recognized. Several investigational agents specific for those patients with the T315I mutation remain under evaluation. In Philadelphia-positive (Ph-positive) acute lymphoblastic leukemia (ALL), the addition of imatinib improved response rates. However, short remission durations with single agent therapy limit the benefit on survival. Early molecular remissions achieved with dasatinib will enable more patients to proceed to stem cell transplant (SCT), with increased likelihood of positive outcomes post-SCT.

Keywords

Lymphoid leukemia; myeloid leukemias and dysplasias; chemotherapeutic approaches

Chronic myeloid leukemia

The most remarkable advancement in chronic myeloid leukemia (CML) was the development of imatinib, a tyrosine kinase inhibitor (TKI) that inhibits BCR–ABL. Imatinib was proved superior to the previous standard of care regimen in the International Randomized Study of Interferon and STI571 (IRIS). Patients with chronic phase CML (CML-CP) were randomized to receive treatment with imatinib 400 mg daily ($n=553$) or interferon- α in combination with low dose cytarabine ($n=553$) [1]. Treatment with imatinib resulted in higher rates of hematologic and cytogenetic responses, less progression to advanced forms of CML (accelerated phase [CML-AP] and blast phase [CML-BP]), and improved tolerability. The most recent report of the IRIS trial confirms sustained treatment responses and durable remissions through 8 years of follow-up, with a low likelihood of disease progression. Imatinib is currently approved for newly diagnosed patients with CML-CP, CML-AP, CML-BP, CML-CP after failure of interferon- α therapy, and Philadelphia-positive acute lymphoblastic leukemia (Ph-positive ALL) [2].

Imatinib resistance

Despite the results with imatinib, some patients will have resistance or intolerance to the drug. Approximately 33% of patients are refractory to treatment with imatinib [3]. Primary resistance, defined as failure to achieve response, has been classified as primary hematologic resistance, reported in 2–4% of cases, and primary cytogenetic resistance, reported in 15–25% of cases [4]. Primary resistance has not been attributed to mutations in BCR–ABL, but associations have been suggested with increased transcript levels of prostaglandin-endoperoxide synthase 1/cyclooxygenase 1 (PTGS/COX1). Thus, elevated levels of this gene may identify patients with primary resistance to imatinib [5,6]. Secondary resistance is described as achievement of response followed by loss of the hematologic or cytogenetic response. Over half of the resistance displayed following treatment with imatinib occurs as a result of mutations in the BCR–ABL kinase domain [7–9]. Further treatment can be tailored to the mutation that is detected. For example, the T315I mutation, reported to occur in 4–15% of imatinib resistance, confers additional resistance to dasatinib, nilotinib, and bosutinib [10,11]. In the case that this mutation becomes present, further treatment should include clinical trials with investigational agents or hematopoietic stem cell transplant (HSCT). However, not all BCR–ABL point mutations confer resistance to the available TKIs. Decreased sensitivity to nilotinib is apparent for mutants Y253H, E255K/V, and F359C/V, whereas mutants E255K/V, V299L, and F317L are insensitive to dasatinib [12]. Additional treatment should incorporate the TKI that retains sensitivity to the particular mutation. In some cases, the above mutations are not present, and therapy should be guided by patient comorbidities as well as adverse effects associated with the drug.

Baseline mutational assessment for newly diagnosed patients is currently not recommended. The identification of mutations has not correlated with sensitivity of imatinib or response [13,14]. However, in the case of suboptimal response or failure of a particular therapy, mutational analysis is recommended [15,16].

High dose imatinib

The dose of imatinib in newly diagnosed patients with CML-CP is 400 mg daily. In the case of suboptimal response or failure, imatinib dose escalation is likely to be successful in patients who had previously achieved a cytogenetic response and have not developed any mutations conferring resistance to imatinib. Some mutations display sensitivity with increased concentrations of imatinib [17–19]. In addition, dose escalation can potentially overcome resistance resulting from subtherapeutic levels of imatinib [15,20]. In the IRIS trial, dose escalation to 600 mg or 800 mg daily was permitted for failure to achieve complete hematological response (CHR) at 3 months or at least a minor cytogenetic response (CyR) by 12 months, loss of a major cytogenetic response (MCyR) at any time, disease progression including increase in white blood cell count, development of CML-AP or CML-BP, and loss of CHR or MCyR. Thirty-nine patients randomized to the imatinib arm of the study had an imatinib dose escalation due to the above mentioned criteria [21]. After 12 months of treatment with the escalated dose per the IRIS protocol, approximately half of the patients had positive results. Of those patients without CHR at 3 months ($n=7$), six (86%) demonstrated CHR at 12 months post-dose-escalation. Two of the eight patients without at least a minor CyR achieved a MCyR within 12 months, and MCyR was observed

in an additional two patients within 24 months of treatment. For those patients with loss of MCyR ($n=18$), nine had reached MCyR after 12.5 months of treatment with escalated imatinib dosing. Complete CyR (CCyR) occurred in three patients by 30 months of treatment. Forty-eight patients had dose escalation of imatinib according to the European LeukemiaNet (ELN) recommendations [15]. Improvements were reported as follows: CHR was achieved in 6/7 patients with escalated dose, 6/11 patients with failure achieved MCyR after 12 months of increased-dose imatinib, and CCyR was achieved in 2/10 patients with previous failure at 18 months. Three years following dose escalation per either IRIS or ELN criteria, the estimated progression-free survival (PFS) was 89% and overall survival (OS) was 84%.

In a separate evaluation of patients with CML-CP who developed hematologic or cytogenetic failure, dose escalation proved effective for patients with a previous cytogenetic response. Eighty-four patients failing imatinib had dose escalation from 400 mg daily to 800 mg daily, or from 300 mg daily to 600 mg daily in those patients with prior dose reduction due to toxicity [22]. Cytogenetic response was achieved in 47 patients (75%) with previous cytogenetic failure, of whom 34 (40%) attained CCyR. In contrast, three patients with hematologic failure had a cytogenetic response, with CCyR achieved in only one patient (5%). Of those patients who had never achieved a cytogenetic response, rates of 2- and 3-year event-free survival (EFS), transformation-free survival (TFS), and OS were significantly lower than in patients with previous cytogenetic response. While myelosuppression requiring dose reduction was apparent, the majority of patients received the full escalated dose throughout 12 months of therapy.

Though imatinib 400 mg daily is the approved Food and Drug Administration (FDA) dose for CML-CP, several investigations have suggested that initial treatment with a higher dose may improve response. In CML-AP and CML-BP, escalated dosing improves response rates, time to progression, and overall survival [23]. In the Rationale and Insight for Gleevec High-Dose Therapy (RIGHT) trial, 115 patients with newly diagnosed CML-CP treated with imatinib 400 mg twice daily attained high rates and early occurrence of molecular and cytogenetic responses [24]. Major molecular response (MMR) increased over time, with 48% in MMR at 6 months, 54% at 12 months, and 63% at 18 months, with a median time to MMR of 8.3 months. MCyR was 90% at 12 months and 96% at 18 months, with CCyR 85% at 12 months and 83% at 18 months. In comparison with previous investigations of standard dose imatinib, patients treated according to the RIGHT trial experienced higher and faster rates of molecular and cytogenetic responses. However, a randomized evaluation of imatinib 400 mg daily versus 800 mg daily in 476 newly diagnosed patients with CML-CP did not show a difference in MMR at 12 months [25]. Treatment discontinuation was similar in patients treated with imatinib 400 mg daily (15.9%) and imatinib 800 mg daily (19.7%). At 24 months, high dose imatinib was not associated with any significant improvement in MMR, CCyR, EFS, PFS, or OS as compared to standard dose imatinib in the TKI optimization and selectivity study (TOPS) [26]. In both treatment arms, patients who experienced one or less interruption during imatinib therapy achieved higher rates and shorter time to MMR and increased rates of CCyR. Dose interruptions longer than 5 days occurred in 71% of patients treated with high dose imatinib and 44% of patients who received the standard dose. The occurrence of adverse events including grade 3–4

neutropenia, thrombocytopenia, rash, diarrhea, and myalgia was more frequent with imatinib 800 mg daily compared with imatinib 400 mg daily. To improve outcomes, interruption of therapy should be avoided, and dose intensity should be maintained throughout treatment. In the standard dose arm, median dose intensity was 400 mg, while in the high dose arm, median dose intensity was 728 mg. Of patients in the high dose arm who maintained a dose of 600–800 mg daily versus those who received less than 600 mg daily, significant improvements were noted in achievements of MMR at 12 months (62.4% vs. 34.1%), MMR at 18 months (75.2% vs. 40.3%), time to and duration of MMR, and CCyR at 12 months (89.6% vs. 70.3%) in patients continuing on a higher daily dose. Though 800 mg daily appeared tolerable, frequent dose interruptions limit the ability to maintain dose intensity, and therefore 400 mg daily remains the recommended dose for initial treatment of CML-CP. Furthermore, 800 mg daily has been reported in some studies to shorten the time to MMR and CCyR when compared to imatinib 400 mg daily with or without the addition of interferon; however, longer duration of follow-up is necessary to determine a correlation with survival [27].

Dasatinib

Dasatinib is an orally available TKI approved for treatment of all phases of CML with resistance or intolerance to imatinib and Ph-positive ALL [28]. Dasatinib has multiple advantages over imatinib and can overcome several mechanisms of resistance, proving beneficial in patients who have secondary resistance to imatinib [29]. For example, dasatinib binds to BCR–ABL in both the open and closed conformation, whereas imatinib binds only in the closed conformation [30]. For dasatinib this results in an increased affinity to BCR–ABL, and it has a potency that is approximately 325-fold greater than that of imatinib [31,32]. In addition, dasatinib also has the ability to inhibit *src* activity, which blocks BCR–ABL activity through a separate mechanism.

The efficacy of dasatinib following imatinib failure has been reported. In the Src/ABL tyrosine kinase inhibition activity research trials of dasatinib (START)-C, dasatinib 70 mg twice daily demonstrated efficacy in 387 patients with CML-CP, resistant or intolerant to imatinib [33,34]. At 24 months' follow-up, MCyR was achieved in 62% of patients, with CCyR in 53% of patients [35]. PFS was 80% and OS 94%. Neutropenia and thrombocytopenia were reported to be of grade 3–4 in 50% and 49% of patients, respectively. Notable non-hematologic grade 3–4 adverse effects included pleural effusion (9%), dyspnea (6%), bleeding (4%), diarrhea (3%), and fatigue (3%).

START-R further evaluated dasatinib in comparison with imatinib 800 mg daily in patients with CML-CP who had failed therapy with imatinib 400–600 mg daily [36]. Patients were randomized to receive therapy with dasatinib 70 mg twice daily ($n=101$) or imatinib 800 mg daily ($n=49$). Greater cytogenetic responses were achieved with dasatinib, as reported rates of MCyR were 53% for dasatinib and 33% for imatinib, and CCyR rates were 40% for dasatinib and 16% for imatinib. MMR was also significantly improved with dasatinib (16%) compared with imatinib (4%). In addition, dasatinib appeared better tolerated, as significantly fewer patients discontinued therapy with dasatinib versus imatinib. Pleural

effusions were common in the dasatinib group (17%); however, only 3% were reported as grade 3, and none were reported as grade 4.

Though initial investigations studied dasatinib dosed twice daily, once-daily dosing has proved to be as effective, with better tolerability [37–40]. Four dasatinib dosing regimens were evaluated in CML-CP: 100 mg daily ($n=167$), 50 mg twice daily ($n=168$), 140 mg daily ($n=167$), and 70 mg twice daily ($n=168$). After 24 months of follow-up, dasatinib 100 mg daily demonstrated MCyR and CCyR rates similar to the other investigated dosing schemes [38]. Estimates for PFS were reported as follows: 80% for 100 mg daily, 76% for 50 mg twice daily, 75% for 140 mg daily, and 76% for 70 mg twice daily. Overall survival estimates were 91% for dasatinib 100 mg daily, 90% for 50 mg twice daily, 94% for 140 mg daily, and 88% for 70 mg twice daily. Reported PFS and OS at 36-months of follow-up continue to favor 100 mg daily as the optimal dose [39]. Dasatinib 100 mg daily was associated with significantly fewer pleural effusions of any grade (14%) in comparison to the other dasatinib treatment regimens (23–25%). Of those reported, only 2% of pleural effusions in the 100 mg daily group were classified as grade 3–4 versus 4–5% in the other investigated regimens. In a separate dose optimization study of dasatinib in CML-AP and CML-BP, 140 mg daily displayed comparable response rates and lower rates of adverse effects, particularly pleural effusions, compared with 70 mg twice daily [40]. As a result of these studies, 100 mg daily has been approved for patients with CML-CP and 140 mg daily for patients with advanced phase disease [28].

In comparison with standard dose imatinib, dasatinib 100 mg daily in CML-CP was associated with significantly higher and faster rates of CCyR and MMR [41]. Patients with newly diagnosed CML were randomized to receive dasatinib 100 mg daily ($n=259$) or imatinib 400 mg daily ($n=260$) in the Dasatinib versus Imatinib Study in Treatment-Naive CML Patients (DASISION) (Table I). At 12 months, CCyR was significantly higher among patients treated with dasatinib versus imatinib (77% vs. 66%, $p=0.007$) as well as the rate of MMR (46% vs. 28%, $p=0.002$). Shorter time to achievement of CCyR was evident with dasatinib. After 3, 6, and 9 months of treatment with dasatinib, the rates of CCyR were 54%, 73%, and 78%, while rates of CCyR with imatinib were only 31%, 59%, and 67% at the same time points. Time to achievement of MMR was also reduced with dasatinib. The rates of MMR achieved after 3, 6, and 9 months of dasatinib were 8%, 27%, and 39% versus 0.4%, 8%, and 18% with imatinib. Progression to more advanced forms of CML occurred less frequently in patients receiving dasatinib (1.9%) versus imatinib (3.5%). Both drugs were well tolerated, and adverse events were similar between groups. Pleural effusion was only reported for patients taking dasatinib (10%), with all events reported as grade 1 (2%) or grade 2 (8%). Drug discontinuation was infrequent among both groups, with 84% of patients receiving dasatinib and 81% of patients receiving imatinib throughout the duration of study. Achieving CCyR and MMR quickly is associated with more favorable long-term outcomes. The ability of dasatinib to rapidly induce high rates of response suggests the potential role of this agent in newly diagnosed patients.

Nilotinib

Nilotinib, similar to imatinib, binds to the inactive conformation of BCR–ABL and has no ability to inhibit *scr* activity, but is a more potent and selective inhibitor [42–44]. It is approved for the treatment of patients with newly diagnosed CML-CP, (before CML-CP) CML-CP and CML-AP who are resistant or intolerant to imatinib [45]. At 24-months of follow-up, nilotinib 400 mg twice daily administered to 321 patients with CML-CP led to MMR in 28% and CCyR in 46% of those treated [46]. MCyR and CCyR were maintained for 77% and 84% of patients at 24 months. Of note, patients with complete hematologic response at initiation of nilotinib had more favorable responses and outcomes than those patients who had lost their hematologic response. Common grade 3–4 laboratory abnormalities and adverse effects included elevated lipase (17%), hypophosphatemia (16%), hyperglycemia (12%), elevated bilirubin (8%), neutropenia (31%), thrombocytopenia (31%), and anemia (10%). In 137 heavily pretreated patients with CML-AP, nilotinib led to durable responses and favorable outcomes [47]. The rate of MCyR was 32%, with CCyR achieved in 20% of patients. At 24 months, the estimated OS was 67%.

Nilotinib has displayed favorable outcomes in the front-line setting (Table I). Patients at the M. D. Anderson Cancer Center with newly diagnosed CML-CP received treatment with nilotinib 400 mg twice daily ($n=51$) [48]. Within 6 months of therapy, almost all patients reached CCyR (98%) and 76% achieved a MMR. In a separate phase II evaluation of newly diagnosed patients with CML-CP, nilotinib led 96% of patients to achieve CCyR and 85% reached MMR within 1 year of therapy [49]. Nilotinib 300 mg twice daily also produced high rates of CCyR and MMR in a study conducted by the All-Ireland Cooperative Oncology Research Group [50]. The high response rates and favorable toxicity profile associated with nilotinib warrant further investigation of front-line therapy for CML-CP. In the phase III randomized trial of nilotinib 300 or 400 mg twice daily versus imatinib 400 mg daily in newly diagnosed patients with CML-CP (EN-ESTnd; Evaluating Nilotinib Efficacy in Clinical Trials of Newly Diagnosed Ph+CML Patients), both regimens of nilotinib were associated with higher rates of MMR and CCyR at 12 months [51]. Patients were randomized to nilotinib 300 mg twice daily ($n=282$), nilotinib 400 mg twice daily ($n=281$), or imatinib 400 mg daily ($n=283$). At 12 months, MMR and CCyR were significantly higher for those patients treated with nilotinib. The MMR was 44% for nilotinib 300 mg, 43% for nilotinib 400 mg, and 22% for imatinib ($p<0.001$). Time to achievement of MMR was shorter for both nilotinib 300 mg (8.6 months) and nilotinib 400 mg (11 months) compared with imatinib (median not yet achieved). CCyR reported for nilotinib 300 mg, nilotinib 400 mg, and imatinib was 80%, 78%, and 65%, respectively ($p<0.001$). In addition, rate of progression to advanced disease was lower for those patients receiving nilotinib 300 mg and nilotinib 400 mg versus imatinib (<1% and <1% vs. 4%). Dose intensity was maintained for each treatment group with the median dose reported as 592 mg daily for nilotinib 300 mg twice daily, 779 mg for nilotinib 400 mg twice daily, and 400 mg daily for imatinib. Rates of adverse events necessitating drug discontinuation were comparable between all study arms (5% nilotinib 300 mg, 9% nilotinib 400 mg, 7% imatinib). There were no occurrences of QT interval above 500 ms in either the nilotinib group or the imatinib group. In a subset analysis of Japanese patients ($n=79$), the rate of MMR at 12 months was twice as high with nilotinib 300 mg and nilotinib 400 mg versus imatinib (57% and 50% vs. 24%) [52]. CCyR rates

were similar between groups and were as follows: 77% for nilotinib 300 mg, 83% for nilotinib 400 mg, and 76% for imatinib. Though long-term follow up is lacking in the front-line setting, the superiority of nilotinib versus imatinib led to the FDA approval of nilotinib in newly diagnosed patients and suggests a modification of current treatment algorithms likely in the near future [53].

Investigational agents

Several agents with novel mechanisms are under evaluation for CML. Bosutinib (SKI-606), a dual Src/ABL inhibitor, has displayed activity in Ph-positive leukemias [54,55]. In a phase I/II study of 299 patients with CML-CP resistant or intolerant to imatinib, 58% of evaluable patients achieved a MCyR, with 46% reported as CCyR [55]. Grade 3–4 adverse effects and laboratory abnormalities included rash (9%), diarrhea (8%), hypermagnesemia (11%), and increased alanine transaminase (ALT) (10%). Grade 3–4 hematologic toxicity, including thrombocytopenia (23%), neutropenia (14%), and anemia (9%), was common. While bosutinib maintains activity in patients with various BCR–ABL mutations, it is not active against the T315I mutation.

Other investigational agents that do display activity against the T315I mutation include omacetaxine, AP24534, PHA-739358, and DCC-2036. Omacetaxine, semi-synthetic homoharringtonine available for subcutaneous administration, is a multitargeted protein synthase inhibitor that works through a mechanism independent of BCR–ABL inhibition and displays activity regardless of mutational status [56–58]. In adult patients with CML-CP, CML-AP, or CML-BP, subcutaneous omacetaxine was administered at 1.25 mg/m² twice daily for 14 days every 28 days until hematologic response, followed by maintenance dosing with 1.25 mg/m² twice daily for 7 days every 28 days [59]. Of 90 patients enrolled, analysis was possible for 66. All patients had failed prior therapy with imatinib and had the T315I mutation, and 79% had failed therapy with two or more TKIs. In CML-CP, 27.5% of patients had a cytogenetic response, of which 15% were MCyR sustained for 6 or more months, and 15% achieved MMR. Activity was maintained in advanced disease with one patient achieving CCyR. Myelosuppression was the most frequent adverse effect leading to treatment delays in 50% of patients. A separate analysis of two long-term phase II studies in CML confirmed the safety of omacetaxine [60].

AP24534 is an orally available multikinase inhibitor. In a phase I evaluation of 42 patients with CML, the maximum tolerated dose of 60 mg daily has been reached [61]. Of the evaluable patients with CML, MCyR has been achieved in 48%, and CCyR in 33%. Of the seven patients with T315I CML-CP evaluable for response, CCyR was reported for 57%. Eight patients with T315I CML-AP or CML-BP were evaluable, of whom 13% had CCyR. Commonly reported toxicities included nausea (20%), fatigue (15%), vomiting (15%), headache (13%), arthralgia (10%), hot flush (10%), increased glucose (10%), increased lipase (10%), muscle spasms (10%), and rash (10%). At the 60 mg dose, grade 3–4 elevations of amylase and lipase occurred in one-third of patients, with two patients experiencing pancreatitis.

Danuserib hydrochloride (PHA-739358) is an aurora kinase inhibitor currently under phase I evaluation in CML and Ph-positive ALL. Administration via intravenous infusion over 3 h

daily for 7 consecutive days represents the current dosing regimen under study [62]. Doses ranging from 90 mg/m² to 200 mg/m² have been tested; however, the maximum tolerated dose has not yet been established. Of 15 patients with documented T315I mutations, six have reported responses including cytogenetic, hematologic, and clinical improvement.

Another agent still in phase I studies is DCC-2036, which belongs to a new class called switch pocket inhibitors that bind to five structural pockets involved in the endogenous 'switch' mechanism used by the ABL kinase to conformationally control the state of activity [63]. DCC-2036 is selective for ABL, FLT3, and Src family kinases.

Philadelphia-positive acute lymphoblastic leukemia

Ph-positive ALL occurs in 20–30% of patients [64,65]. Long-term disease-free survival remains poor for patients treated with traditional chemotherapy; however, the addition of TKIs to the therapy of Ph-positive ALL has improved outcomes in this subset of leukemia. Allogeneic SCT (aSCT) represents the only curative option, and current recommendations support eligible patients to proceed to aSCT in first complete remission (CR). Single agent therapy with imatinib was first reported to induce high response rates; however, remission durations were short, likely due to mutations in the BCR–ABL kinase domain. Dasatinib has the ability to overcome several limitations with imatinib, and recent data have supported the use of this agent with or without intensive chemotherapy. Early molecular responses with dasatinib reduce the disease burden, allowing more patients to proceed to aSCT and lengthen survival.

Imatinib

The first evaluations with imatinib monotherapy focused on relapsed or refractory elderly patients, likely not eligible for future aSCT. In CML-BP and relapsed and refractory ALL, single agent imatinib displayed activity at doses ranging from 300 to 1000 mg per day [66]. Response rates of 70% were promising; however, only 20% of patients achieved CR. In 48 patients with relapsed Ph-positive ALL, imatinib 400–600 mg daily led 27% of patients to sustained hematologic response lasting 4 or more weeks in duration. Despite this, the median time to progression was 2.2 months, and overall survival was 4.9 months [67].

Data have suggested a benefit in response rates compared with intensive chemotherapy in newly diagnosed elderly patients [68]. In patients aged 55 years or older with *de novo* Ph-positive ALL or CML-BP, imatinib 600 mg daily (*n*=27) produced superior responses compared with multiagent chemotherapy (*n*=26). CR for patients receiving imatinib was 96%; 85% achieved CR, and 11% attained CR without peripheral blood count recovery. In the multiagent chemotherapy arm, CR was only achieved in 50% of patients, with the majority represented as CR without peripheral blood count recovery. In elderly patients, imatinib 800 mg daily in combination with prednisone led to CR in all patients evaluable for response (*n*=29) [69]. However, fewer than half of the patients evaluated were alive and in CR after 10 months (*n*=13). While single agent imatinib, or in combination with steroids, represents a feasible option for elderly patients to achieve CR, short durations of remission will unlikely lead to any improvements in survival.

In younger patients fit to tolerate intensive chemotherapy, imatinib in combination with chemotherapy produces high quality CR enabling eventual aSCT (Table II). Both concurrent (administration at the same time) and sequential administration (alternating administration) of imatinib are practical approaches. In early investigations, the M. D. Anderson Cancer Center included imatinib 400 mg daily for 14 days concurrently with HCVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) as induction and consolidation therapy [70]. Imatinib was also incorporated into maintenance therapy with vincristine and prednisone at a continuous dose of 600 mg daily. Modifications to the initial regimen dosed imatinib at 600 mg daily for 14 days during course one of induction, 600 mg daily administered continuously through consolidation, and 800 mg daily administered continuously through maintenance, followed by indefinite imatinib therapy [71]. In 54 patients with imatinib naive, *de novo*, or minimally treated Ph-positive ALL, 93% achieved CR. Of 47 patients with *de novo* disease, 14 proceeded to aSCT in first CR. Three-year OS was significantly improved in patients aged 40 years or less who proceeded to aSCT (90%) compared with those who did not (33%). In comparison with HCVAD, the addition of imatinib improved 3-year remission durations and survival.

The Japan Adult Leukemia Study Group (JALSG) ALL202 Ph-positive arm alternated imatinib 600 mg daily in combination with methotrexate and cytarabine with single agent imatinib in 24 newly diagnosed patients during remission induction therapy [72]. CR was achieved in 96% of patients, with 63% eventually proceeding to aSCT. In a separate study conducted by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL), chemotherapy alternated with imatinib and steroids produced 72% CR in 30 newly diagnosed patients [73]. In this evaluation, the addition of imatinib improved OS and relapse-free survival when compared with similar patients who did not receive imatinib.

Though the incorporation of a TKI improved response rates, the exact point in treatment to include imatinib as well as the duration of therapy to maximize outcomes required further clarification. Different designs include imatinib during initial induction therapy, while others have reported benefit with initiation during consolidation treatment. In the German Multicenter Acute Lymphoblastic Leukemia trial, two separate cohorts were evaluated to determine which administration schedule of imatinib more greatly reduced BCR-ABL transcript levels [74]. The first cohort consisted of imatinib alternating with chemotherapy, while the second cohort administered imatinib concurrently with chemotherapy. Though the reduction in BCR-ABL transcripts did not correlate with survival outcomes, the transcript level became undetectable in more patients in the concurrent arm (52%) compared with the sequential arm (19%). In the GRAAPH-2003 study, good early responders, defined by corticosenitivity and chemosensitivity, were enrolled in the study during the first course of consolidation therapy, which consisted of mitoxantrone, cytarabine, intrathecal chemotherapy, and continuous imatinib 600 mg daily [75]. Those patients who did not display early corticosenitivity and chemosensitivity were administered induction consisting of imatinib 800 mg daily with vincristine and dexamethasone (DIV). For all patients enrolled ($n=45$), the CR rate was reported as 96%, indicating the benefit of imatinib at varying doses administered during induction or consolidation. The high CR rate achieved with imatinib in this study allowed all patients with a donor to proceed to aSCT ($n=22$). Imatinib 800 mg daily in combination with HCVAD was most recently compared to an

imatinib-based regimen including the TKI in combination with vincristine and dexamethasone [76]. At the time of reporting, 83 of the 118 newly diagnosed patients enrolled were evaluable. After two courses of induction/consolidation, a 100% CR rate was reported for the imatinib-based treatment group ($n=42$) versus 95% for imatinib-HCVAD ($n=41$). No significant difference between imatinib-based and imatinib-with-HCVAD treatments was apparent in survival at 2 years.

Imatinib therapy in Ph-positive ALL is limited by primary and secondary resistance. Approximately 25–30% of patients display primary resistance and secondary resistance occurs rapidly, with an estimated time to development of 2 months after treatment initiation [67,77]. The majority of mutations in the kinase domain in Ph-positive ALL are recognized after treatment with a TKI [78]. In patients not treated with imatinib, mutations were not detected at the time of relapse; however, 88% of patients who were treated with TKIs displayed BCR-ABL mutations at the time of relapse [79]. While these ideas require investigation, intermittent TKI therapy, dual TKI therapy, and combinations of TKIs with agents that suppress clonal evolution have been proposed to minimize resistance and eventual relapse. Despite historical data reporting disappointing responses with immunologic therapy in Ph-positive ALL, imatinib in combination with interferon- α displayed encouraging outcomes in a small series of patients [80].

Central nervous system (CNS) relapse will develop readily in the absence of prophylactic interventions [81,82]. TKIs alone offer limited prophylaxis for CNS disease [83,84]. Considering the lack of penetration into the CNS with TKIs, intrathecal chemotherapy should routinely be incorporated to reduce the likelihood of relapse in the CNS.

Dasatinib

Initial studies with dasatinib were in relapsed and refractory patients. The START-L trial included 36 heavily pretreated patients with Ph-positive ALL or CML-BP [85]. All patients had previously failed treatment with imatinib, and had persistent disease despite aSCT (42%), chemotherapy (89%), and interferon- α (8%). Dasatinib 70 mg twice daily enabled rapid disease control with major hematologic response achieved at a median of 1.8 months. CCyR was achieved by 58% of patients at 8 months of treatment. In the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL 1205 protocol, dasatinib 70 mg twice daily was combined with intrathecal chemotherapy in 48 patients, 34 of whom were evaluable for response [86]. All patients achieved CHR. Dose optimization studies of dasatinib in CML concluded that once-daily therapy was as effective, with fewer adverse effects, than twice-daily dosing [37–40]. Patients with Ph-positive ALL resistant or intolerant to imatinib were randomized to dasatinib 140 mg daily ($n=40$) or 70 mg twice daily ($n=44$) [87]. Though not statistically significant, major hematologic response and MCyR were higher in the once-daily (38% and 70%) versus the twice-daily (32% and 52%) group. In addition, PFS and OS were longer in the once-daily (3 and 9.1 months) versus the twice-daily (4 and 6.5 months) group. Toxicities between groups were similar, though the occurrence of pleural effusion was lower in the once-daily (18%) versus the twice-daily (32%) treatment group. These results confirm that dasatinib 140 mg once daily rapidly

induces remissions in heavily pretreated patients with Ph-positive ALL, and serves as the currently approved dose [28].

Several studies have evaluated dasatinib in combination with chemotherapy [88–90]. Dasatinib 140 mg daily in combination with vincristine and dexamethasone was evaluated in 22 newly diagnosed patients over 55 years of age [88]. Dasatinib was incorporated into consolidation and maintenance therapy. The complete hematologic response was 95%; however, doses reductions for patients over 70 years of age have been recommended due to a high rate of adverse events, including four deaths. At the M. D. Anderson Cancer Center, dasatinib in combination with the HCVAD regimen has been investigated in newly diagnosed ($n=39$) as well as relapsed and refractory patients ($n=23$) [89,90]. Dasatinib 100 mg daily was included for 14 days with each cycle of induction and consolidation, with continuous dasatinib administered during maintenance. In newly diagnosed patients, CR was reported for 95% of patients and CCyR was achieved in 79% of patients [89]. Complete molecular remission was reported in 56% and MMR in 21%. In relapsed and refractory patients with Ph-positive ALL or CML-BP, 65% achieved CR and 26% had CR without complete platelet recovery [90]. MCyR was achieved in 90% and MMR in 65% of patients. The addition of dasatinib to intensive chemotherapy provides sufficient control of leukemia to enable eligible patients to proceed to SCT. With dose reductions, intensive regimens in combination with dasatinib can be administered to elderly patients to improve response rates and potentially improve survival.

Conclusion

While imatinib drastically changed the management of CML, advanced-generation TKIs have the potential to transform the current approach to treatment. Resistance and intolerance to imatinib require alternative therapies. High-dose imatinib does not consistently demonstrate a benefit in newly diagnosed patients; however, in patients with previous cytogenetic response and lack of mutations, this strategy can overcome resistance due to subtherapeutic levels of the drug. A substantial amount of data confirm the safety and efficacy of dasatinib and nilotinib after imatinib failure. In newly diagnosed patients with CML, dasatinib and nilotinib demonstrate similar rates of response, and shorten the time to achievement of clinical milestones. Data for front-line therapy with these agents require additional follow-up before conclusive outcomes on survival can be assessed. Currently available TKIs provide no benefit for patients who harbor the T315I mutation; however, investigational therapies such as omacetaxine and AP24534 display encouraging results in this subset of patients.

Although Ph-positive ALL has traditionally been associated with a poor prognosis, the introduction of TKIs has led to improved response rates. High quality CR rates and early molecular responses achieved with TKIs increase the eligibility for SCT and likelihood of positive outcomes. Monotherapy should be reserved for patients unable to tolerate intensive chemotherapy. Dose reductions of multiagent chemotherapy for elderly patients with adequate performance status should further be explored. The management of Ph-positive ALL with advanced-generation TKIs as well as investigational agents will eventually lead to durable remissions and lengthened survival.

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Table I

Second-generation TKI front-line investigations.

TKI	Phase of study	Dose	CCyR (%)	MMR (%)	OS (%)
Dasatinib [41] (<i>n</i> =519)	III (vs. imatinib)	100 mg daily (<i>n</i> =259)	77	46	97 (12 months)
Nilotinib [48] (<i>n</i> =51)	II	400 mg twice daily	98	76	NR
Nilotinib [49] (<i>n</i> =73)	II	400 mg twice daily	96	85	NR
Nilotinib [50] (<i>n</i> =15)	II	300 mg twice daily	80	60	NR
Nilotinib [51] (<i>n</i> =846)	III (vs. imatinib)	300 mg twice daily (<i>n</i> =282)	80	44	NR
		400 mg twice daily (<i>n</i> =281)	78	43	NR

TKI, tyrosine kinase inhibitor; CCyR, complete cytogenetic response; MMR, major molecular response; NR, not reported.

Table II

Imatinib-based combination chemotherapy in Ph-positive ALL.

Investigator	Regimen	Number of patients	CR (%)	OS (%)
MDACC [71]	Hyper-CVAD	54	93	54 (36 months)
JALSG [72]	ALL202	24	96	89 (12 months)
GRAALL [73]	AFR09	30	90	66 (12 months)
GRAALL [75]	GRAAPH-2003	45	96	65 (18 months)
GRAALL [76]	Vincristine + dexamethasone	42	100	68 (24 months)
	Hyper-CVAD	41	95	54 (24 months)

Ph-positive ALL, Philadelphia-positive acute lymphoblastic leukemia; MDACC, M. D. Anderson Cancer Center; JALSG, Japan Adult Leukemia Study Group; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CR, complete remission; OS, overall survival.