
Acute Lymphoblastic Leukemia (ALL) Philadelphia Positive (Ph1) (Incidence Classifications, Prognostic Factor in ALL Principles of ALL Therapy)

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<http://dx.doi.org/10.5772/55095>

1. Introduction

ALL is a malignancy of lymphoid cells occurring at any age. Almost 5000 cases are diagnosed annually in the USA. Cell-B subtypes account for 85–90% of cases in children and 75–80% of cases in adults; T-lineage ALL accounts for a small proportion of cases. It has a bimodal incidence occurring at 2–4 years of age followed by a gradual increase after the age of 50.

In the last years much progress has been made in understanding the biology of acute lymphoblastic leukemia which is now recognized as an expanding group of heterogeneous entities. Recognition of distinct gene expression patterns may identify patient subgroup with unique response to therapy and prognosis. Accurate definition of prognostic subgroups based on cytogenetic molecular marker has allowed institution of risk oriented therapies. [2] The Philadelphia (Ph1+) chromosome was first described in 1960 in a patient with chronic myeloid leukemia (CML). This is the product of the fusion of chromosomes 9 and 22, t (9;22), which results in a BCR-ABL hybrid gene. [2]

The incidence is approximately 20-30 % of adult patients with ALL who present the Philadelphia (Ph) Chromosome. Whereas Ph+ ALL is rare in children, comprising less than 5% of acute lymphoblastic leukemia, its incidence increases to approximately 40% in adults 40 years of age, with a 10% increment for every further decade of life with no sex difference. The majority of patients are diagnosed with de novo Ph+ ALL, although occasional cases of secondary Ph1+, ALL have been reported following chemotherapy or radiation therapy. [3, 4]. There are no known risk factors for Ph+ ALL. The associations with environmental socioeconomic infections and genetic events are being studied extensively in ALL. Few causal links have been established and the etiology of ALL remains obscure in most cases. The strongest associations to

date exist with genetic factors and the role of Epstein Barr virus (EBV) and human immunodeficiency virus (HIV) in patients with mature B cell ALL [2].

2. Diagnosis

The characteristic findings of Ph1+ ALL is a reciprocal translocation t(9,22) (q34;q11) that fuses the BCR gene from chromosome 22 to the ABL gene from chromosome 9. By standard cytogenetic analysis this becomes apparent as a shortened chromosome 22 referred to as the Philadelphia chromosome, which can also be visualized by fluorescent in situ hybridization (FISH) analysis. At the molecular level, the bcr/abl fusion transcript can be detected by RT-PCR. The location of the breakpoint within the BCR gene results in either the p190^{BCR/ABL} protein observed in Ph+ ALL (66.3% of the cases) or the p210^{BCR/ABL} protein common to patients with Ph+ CML which is present in ALL Ph+ (31,2%) The remaining cases are associated either with both transcript type or with atypical transcripts. [4]

Other additional chromosome aberrations were present in up to 79% of the cases in a large study of 209 patients (Moorman et al). Yanada et al. study involving 77 Ph+ ALL patients, additional aberrations with a frequency of greater than 10% included a second Ph chromosome (+der(22) t (9,22)) abnormalities involving the short arm of chromosome 9, monosomy 7, and trisomy 8. The presence of additional aberrations was associated with significantly shorter relapse free survival (RFS) and higher relapse rate. This was particularly pronounced for the +der (22)t(9,22) and abnormalities involving the short arm chromosome 9. In reference to this, standard karyotyping is mandatory to establish the initial diagnosis while FISH analysis may be used as a confirmatory technique. The major role of PCR analysis at diagnosis is determination of the type of fusion transcript, which becomes relevant during follow up studies of MDR. Using only PCR to establish the diagnosis is not acceptable, even more so as occasional patients harbor an aberrant fusion transcript that is not detected by standard primer combination [5,6.]

The white blood cell count is variable at diagnosis, hyperleukocytosis and/or splenomegaly may be present. Ph+ ALL is a B-precursor ALL which typically expresses the CD19 and CD10 antigens, and the CD34 antigen is expressed in 89% of cases. The most frequent immunologic subtypes are common ALL (78.2%) and pre-B ALL (19.9%), whereas only 1.9% of patients display the pro – B immunophenotype. Except for few case reports, the chromosome is not found in T lineage ALL. Myeloid markers are frequently expressed, most notably the CD13 antigen (20%) and CD33 antigen (15%). CNS leukemia is infrequent (5%) at initial presentation, but there is an increased risk of developing meningeal leukemia during the course of treatment when compared with other B lineage ALL. [7]

The main differential diagnosis at the begime,of the disease is chronic myelogenous leukemia (CML) lymphoblastic blast crisis (LBC). In the absence of a history of CML, myeloid hyperplasia, bone marrow basophilia, eosinophilia or excessive splenomegaly are suggestive of LBC-CML. While identification of the e1a2 fusion product (p190^{BCR-ABL}) essentially rules out CML, the major BCR fusion transcript (p210^{BCR-ABL}) is found in both Ph+ ALL and LBC-CML. This

distinction is usually of no clinical significance. However, as newly diagnosed LBC-CML without a prior history of CML is generally treated in the same way as Ph+ ALL. [8]

3. Treatment of Ph 1+ ALL: The result with Imatinib and chemotherapy

Chemotherapy alone for adult with ALL Ph1+ is poor, with less than 10% probability. Long term survival. The development of tyrosin kinase inhibitor, imatinib and its use with chemotherapy for the induction obtained complete remission in ranged from 60-70%, moderately lower than 70-90 % achieved in Ph1+ negative ALL. The median CR duration was considerably inferior, however ranging from 9-16 month in patients treated only with chemotherapy with almost no long term survivor. Because of the poor outcome with chemotherapy, the allogeneic stem cell transplantation (SCT) is considered to be the treatment of choice in adult Ph+ ALL. [9]

Imatinib Mesylate (STI571 Glivec[®]) (IM) was the first Tyrosin Kinase inhibitor for CML treatment and now is the gold standard for the treatment of de novo CML in chronic phase. The BCR/ABL fusion gene encodes the chimeric BCR/ABL oncoprotein which has constitutively active tyrosine kinase activity. This results in dysregulated activity of additional signal transduction pathways located downstream of BCR/ABL. The strong pathophysiological similarity between Ph+ ALL and CML provided the rationale for exploring the clinical efficacy of IM. [10].

Druker et al. in one of the first evidence of clinical activity from a phase I study in 2001, in relapsed or refractory patients with Ph+ ALL which showed a significant number of hematological responses (70%) although only 20 % of the patients achieved a complete remission (CR). Later in 2002 these results were confirmed in phase II studies in which imatinib at daily doses of 400 mg to 600 mg induced a CR in 19% of the patients. These responses were not sustained however, and the estimated median survival in these studies was only 4.9 months. As a consequence, subsequent studies focused on the use of imatinib during front line therapy of Ph+ ALL, both as a single agent therapy and in combination with various chemotherapy regimens. A major goal of studies performed in younger patients was to increase the CR rate and improve the quality of response prior to hematopoietic stem cell transplantation (HSTC) in patients with a suitable donor. [12,13]. Several strategies have been evaluated 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. The question of whether minimization of chemotherapy related toxicity by combining imatinib with less intensive chemotherapy or administering it alone yielded equivalent or superior results was also addressed. [11]

The current standard approach for patients in 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). 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. The overall survival (OS) in the different studies

ranged from 36 to 76 %, although follow up is short (1-3 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 the impact of imatinib based regimen 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. [10]

Subtype	Chemotherapy regimen	Imatinib dosing				Results(%)			
		Induction (mg/d)	Consolidation (mg/d)	Maintenance (mg/d)	No	CR	Relapse	DFS (at y)	Survival (at y)
Adults									
Thomas et al	Hyper-CVAD	C(400)	C(400)	C(400)	39	92	14	83(3)	55 (3)
Yanada et al	JALSG ALL202	C(600)	A (600)	C(600)	80	96	26	60 (1) 51 (2)	76 (1) 58 (2)
Lee et al	Modified from Linker	C(600)	C(400)	C(400)	20	95	32	62 (2)	59 (2)
Wassmann et al	GMALL Alternating Concurrent	None	A (400/600)	NR	47	NA	NR	52 (2)	36 (2)
		None	C(600)	NR	45	NA	NR	61 (2)	43 (2)
de Labarthe et al	GRAAPH-2003	None	C(600)	NR	45	96	19	51 (1.5)	65 (1.5)
Ottmann et al	GMALL Chemotherapy Imatinib	None	C(600)	C(600)	28	96	41	29 (1.5)	35 (1.5)
		Only (600)	C(600)	C(600)	27	50	54	57 (1.5)	41 (1.5)

C= concurrent; A= alternating; NR= not reported; NA= not applicable; JALSG = Japan Adult Leukemia Study Group; GMALL= German Multi-Centre Acute Lymphoblastic Leukemia; hyper-CVAD= fractionated cyclophosphamide, vincristine, doxorubicine, dexamethasone; GRAAPH= Group for Research on Adult Acute Lymphoblastic Leukemia; GIMEMA= Gruppo Italiano Malattie Ematologiche dell'Adulto; GRAALL=Group for Research in Adult Acute Lymphoblastic Leukemia; Pred= prednisone

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Table 1. Studies combining imatinib with chemotherapy for de novo Philadelphia chromosome positive (Ph+) ALL [10]

4. Approach in young patients

4.1. Imatinib in combination with chemotherapy in younger patients

The current standard approach for young patients is the combination of chemotherapy protocol employing four to five cytotoxic agent typically used for ALL with imatinib at a daily dose of 400 to 600 mg. Such an approach was pioneered by the MD Anderson Group. They combined sequential imatinib at 400 mg with 8 alternate hyper-CVAD and HD-MTX/AraC cycles (fractionated Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone alternating with cycles of high dose Methotrexate and Cytarabine) followed by imatinib maintenance at 600 mg/d. In this trial the CR rate was 93% with about 2 years of DFS rate of 75%. The molecular remission rate or negativity for bcr/abl transcript by RT-PCR and nested PCR approach 60%. [14]

Yanada et al. have likewise reported results in complete remission (CR) in 77 patient (96.2%), as well as polymerase chain reaction negativity of bone marrow in 71,3 % with the use a multidrug protocol plus imatinib. The authors described that the profile and incidence of severe toxicity were not different from those associated with our historic chemotherapy-alone regimen. Relapse occurred in 20 patient after median CR duration of 5,2 months. 49 patients underwent the allogeneic hematopoietic stem cell transplantation (HSCT), 39 of whom underwent transplantation during their first CR. The 1 year-event-free and overall survival (OS) rates were estimated to be 60.0% and 76.1%, respectively, which were significantly better than ourfortheir historic controls treated with chemotherapy alone. The probability of OS for this group of patients described by the author at 1 year was 73.3 % for those who underwent allogeneic HSCT and 84.8% for those who did not. [15]

Lee K-H et al. evaluated 20 patients with Ph+ ALL who were administered with induction chemotherapy daunorubicin, vincristine prednisolone and L asparaginase along with imatinib 600 mg /day during remission induction and 400 mg /day during consolidation courses. 19 patients achieved complete remission (CR). In this trials, 15 underwent allogeneic hematopoietic cell transplantation (HCT) during first CR. After median follow up period of 799 days, 6 patients experienced recurrence. Eight died. Median CR duration was 821 days and median patient survival was 894 days. In the study the results were significantly longer by 2.9 and 2.3 fold respectively when compared to those of 18 historical patient treatments with same regimen of combination chemotherapy without imatinib. [16]

Wassmann et al. enrolled 92 patients with newly diagnosed Ph+ ALL in a prospective multi-center study to investigate sequentially 2 treatment schedules with imatinib administrated concurrent to or alternating with a uniform induction and consolidation regimen. Coadministration of imatinib and induction cycle2 (INDII) resulted in a CR rate of 95 % and polymerase chain reaction (PCR) negativity for BCR/ABL in 52 % of the patients compared with 19% in patients in the alternating treatment cohort. Remarkably, patients with and without a CR after induction cycle 1 (INDI) had similar hematologic and molecular responses after concurrent imatinib and INDII. 7 % of the patients underwent allogeneic stem cell transplantation (SCT), in first CR (CR1) both schedules of imatinib had acceptable toxicity and facilitated SCT in CR1 in the majority of patients but concurrent administration of imatinib and chemotherapy had greater antileukemic efficacy for this group. [17]

Labarthe et al. in 2007 published the results of 45 patients with Ph+ ALL treated in the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAAPH) 2003 study, where imatinib was started with HAM (mitoxantrone with intermediate-dose cytarabine) as consolidation therapy in good early responders (corticosenstive and chemosensitive ALL) or earlier during the induction course in combination with dexamethasone and vincristine in poor early responders (corticoresistant and/or chemoresistant ALL). Imatinib was then continuously administered until stem cell transplantation (SCT). Overall, complete remission (CR) and *BCR-ABL* real-time quantitative polymerase chain reaction (RQ-PCR) negativity rates were 96% and 29%, respectively. All of the 22 CR patients (100%) with a donor received allogeneic SCT in first CR. At 18 months, the estimated cumulative incidence of relapse, disease-free survival, and overall survival were 30%, 51%, and 65%,

respectively. The authors described these 3 end points were favorable compared with results obtained in the pre-imatinib LALA-94 trial. [18]

Ottmann et al. recognized the potential benefit of administering imatinib simultaneously with chemotherapy rather than in an alternating manner which was investigated in two successive cohort of patients who were treated according to GMALL protocol and received imatinib either alternating with chemotherapy (first cohort) or simultaneously with induction and consolidation cycles (second cohort). The reported rate of complete molecular remission (CMR) was 19% and 52 % respectively, but this greater antileukemia efficacy did not translate into significant improvements in DFS or overall survival. [19] So far, the analyzed data showed the superiority of adding Imatinib to conventional chemotherapy and it was strongly suggested by historical comparison between the outcome of the patients using similar chemotherapeutic with or without imatinib. The magnitude of improvement was as high as 30% in the studies from MD Anderson and the GRAALL. These results were also confirmed by a pediatric study of Schultz et al. in which imatinib was given at 340 mg/m² for an increasing number of days in combination with intensive chemotherapy. Early (1 year) EFS improved with increasing imatinib exposure from 70% to 95%. [20]

5. Imatinib-based therapy in elderly patients

5.1. Approach in older patients

While the strategy of combining imatinib with standard intensive chemotherapy protocol was explored primarily in younger patients, therapeutic approaches in elderly patients were focused more on reducing the intensity of chemotherapy. Vignetti et al. by GIMEMA (LAL0201) initiated a study with 30 patients who received a prephase with prednisone at increasing doses from 10 to 40 mg/m²/day followed by 45 day induction treatment with imatinib at the fixed dose of 800mg/day in combination with oral prednisone (40mg/m²/day) followed by maintenance with imatinib in all responding patients until occurrence of disease relapse or excessive toxicity. Complete remission was achieved in all patients (n=29). median survival from diagnosis was 20 month. In this study, the authors showed that elderly Ph(+) patients with ALL, often considered eligible only for palliative treatment strategies, may benefit from an imatinib-steroids protocol, which does not require chemotherapy or a long hospitalization; it is feasible, highly active, and associated with a good quality of life. [21]

Dalannoy et al., in another study from the GRALL (AFRO9 study), are currently testing a low intensity schedule (vincristine and dexamethasone), in combination with high dose imatinib (800mg/d) in elderly patients above 55 years (DIV regimen). Thirty patients were included in this study and were compared with 21 historical controls. Out of 29 assessable patients, 21 (72%) were in CR after induction chemotherapy vs 6/21 (29%) in control. Five additional CRs were obtained after salvage with imatinib and four after salvage with additional chemotherapy in the control group. Overall survival (OS) was 66% at 1 year vs 43% in the control group. The

Subtype	Chemotherapy regimen	Imatinib dosing				Results(%)			
		Induction (mg/d)	Consolidation (mg/d)	Maintenance (mg/d)	No	CR	Relapse	DFS (at y)	Survival (at y)
Adults									
Vinetti et al	GIMEMA	+Pred (800)	Only (800)	Only (800)	30	100	48	48 (1)	74 (1)
Delannoy	GRAALL AFR09	None	C(600)	A (600)	30	72	60	58 (1)	66 (1)
Réa et al	GRAALL AFR07 pilot	C(800)	C(600)	C(600)	31	90	NR	48 (1)	60 (1)

Table 2. Studies combining imatinib with chemotherapy for de novo Philadelphia chromosome positive (Ph+) ALL in Elderly Patients [10]

1 year- relapse-free survival is 58 vs 11%. The author showed that the use of imatinib in elderly patients with Ph+ ALL is very likely to improve outcome, including OS. [22]

A pilot study of these combinations had shown promising results in relapsing and refractory Ph+ ALL with a CR rate of 90% in patients older than 55 years. This group, considers the hypothesis that Imatinib, combined with high-dose chemotherapy, is now becoming the gold standard for treatment of Philadelphia chromosome-positive acute leukemias. However, in all studies, imatinib dosage was tapered to 400–600 mg per day.) The group decided to initiate a clinical trial to evaluate an opposite strategy based on high-dose imatinib (800 mg per day) combined with a less intensive chemotherapeutic regimen (vincristine and dexamethasone), which we called the DIV induction regimen. Thirty-one patients (18 relapsing or refractory Ph + acute lymphoblastic leukemias and 13 lymphoid blast crisis chronic myelogenous leukemias) were enrolled. Complete remission (CR) was obtained in 28 out of 30 assessable patients. The median bcr-abl/abl ratio after the induction course was 0.1%. Median time to neutrophil recovery was 21 days. Nine out of 19 patients under 55 years old received allogeneic stem cell transplantation after a median time of 78 days post-CR. Patients older than 55 experienced a 90% CR rate without additional toxicities, suggesting the DIV regimen may also be proposed as a front line therapy in older patients.[23]

6. Dasatinib in combination with chemotherapy

The combination of dasatinib with a variety of cytotoxic chemotherapy regimen both in younger and elderly patients with de novo or minimally pretreatment Ph+ ALL was explored in different groups of treatment. Ravandi et al. in one study phase II trial, showed patients with newly diagnosed Ph+ ALL who received dasatinib 50 mg PO BID (or 100 mg daily) for the first 14 days of each of 8 cycles of alternating hyperCVAD and high dose cytarabine plus methotrexate. Patients in CR continue to receive maintenance dasatinib 50 mg po BID (or 100 mg daily) and vincristine and prednisone monthly for 2 years followed by dasatinib indefinitely. With a median follow up of 10 months, 21 pts were alive and 18 were in CR; 2 died at induction, 3 pts died in CR; 1 from an unrelated cardiac event and 2 from infections. 5 pts relapsed (response durations were 54, 48, 47, 32, and 22 weeks) and 2 of them died. In 2 pts morphological relapse was preceded by flow and molecular relapse. Four relapsed pts

developed new ABL mutations (3 T315I and 1 F359V). One patient underwent an allogeneic stem cell transplant. The author concluded that Dasatinib with HyperCVAD is effective in achieved molecular remission in patients with Ph+ ALL. They also found high incidence of T 315I ABL mutation among the relapsed patients. [24]

Reference	N (evaluated)	Age (range)	Dasatinib mg/d	ChThx regimen	Schedule of T14 and ChThx	CR%	PCR negative %	Induction death, n(&)	Relapse %	Outcome
Ravandi F 2008	28*	52(21-79)	100 QD	HyperCVAD	D1-14 of e/ cycle	93	50	2(7)	5(18)	CR (10m):18 (64%) OS (10): 21 (75%)
Rousselot P 2008	22	71 (61-83)	140 QD 100 QD	EWALLelderly	IND: parallel, then	95	28	1 (4.5)	1 (4.5)	na
Foa R 2008	48 (34)	54 (24-76)	70 BID	Steroid prephase then 12w	Post-Induction therapy not	100	na	0	9 (27)	OS (10): 81%

*22 patients with de novo Ph+All, 6pts, with one prior treatment cycle
 OSindicates 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 of the Europena LeukemiaNet

*22 patients with de novo Ph+All, 6pts, 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 of the Europena LeukemiaNet

Table 3. Studies with dasatinib for de novo Philadelphia chromosome + (Ph+) ALL.

In another study, Rousselot et al. evaluated that after a pre-phase with dexamethasone 10 mg/m² d-7 to d-3, dasatinib was administered at 140 mg QD (100 mg in patients over 70y) during the induction period in combination with IV injections of vincristine 1 mg and dexamethasone 40 mg 2 days (20 mg over 70y) repeated weekly for 4 weeks. Consolidation cycles consisted of dasatinib 100 mg/d administered sequentially with methotrexate 1000 mg/m² IV d1 (500 mg/m² over 70y) and L-asparaginase 10,000 UI/m² IM d2 (5,000 UI/m² over 70y) for cycles 1, 3 and 5 and cytarabine 1,000 mg/m²/12h IV d1, d3, d5 (500 mg/m² over 70y) for cycles 2, 4 and 6. Maintenance phase consisted of dasatinib alternating with 6-MP and methotrexate orally every other month and dexamethasone/vincristine once every 2 months for up to 24 months. Median RFS and OS were 22.1 and 27.1 months, respectively. The group also showed dasatinib with low-intensity chemotherapy was highly effective in elderly patients with Ph+ ALL with a 90% CR and 22.1 months RFS. In concordance with Ravandi et al. the mutation T315I was associated with relapses. [25]

In these studies the CR rates were from 93 % until 100% independent of the regimen used, with molecular remission rates from 28% to 72%.

7. Dasatinib monotherapy

Dasatinib was used without chemotherapy. In this modality Foa et al by GIMEMA LAL1205 protocol, the patients with newly diagnosed Ph+ ALL older than 18 (with no upper age limit) received dasatinib 70 mg BID IN induction therapy for 84 days combined with steroids for the first 32 days and intrathecal chemotherapy. Post-remission therapy was free. Fifty-three

patients were evaluable. All patients achieved a complete hematologic remission (CHR), 49 (92.5%) at day 22. At this time point, 10 patients achieved a BCR-ABL reduction to $< 10^{-3}$. At 20 months, the overall survival was 69.2% and disease-free survival was 51.1%. A significant difference in DFS was observed between patients who showed a decrease in BCR-ABL levels to $< 10^{-3}$ at day 22 compared with patients who never reached these levels during induction. No deaths or relapses occurred during induction. Twenty-three patients relapsed after completing induction. A T315I mutation was detected in 12 of 17 relapsed cases. Treatment was well tolerated; only 4 patients discontinued therapy during the last phase of the induction when already in CHR. In adult Ph⁺ ALL, induction treatment with dasatinib plus steroids is associated with a CHR in virtually all patients, irrespective of age, good compliance, no deaths, and a very rapid de bulking of the neoplastic clone.[26]

8. Maintenance therapy

To date there is no consensus as to what constitutes the most effective maintenance therapy in patients in whom allogeneic SCT is not possible. The recommendations of the European Working Group for Adult ALL provide no recommendations for maintenance therapy in patients not eligible for allogeneic stem cell transplantation. Usually Imatinib is given either alone or in combination with classical ALL maintenance such as low dose methotrexate and 6-mercaptopurine. However, data on the efficacy of these strategies is scarce. [22]

Potenza et al. in a study, with seven patients with Ph⁺ ALL who were in first complete remission and received maintenance therapy with imatinib alone, at 2 year progression free survival was 75%. The qPCR monitoring of BCR/ABL, persisting molecular complete response was associated with long lasting CR. The molecular relapse did not invariably mean hematological relapse and only the wide and rapid increment of BCR/ABL values was predictive of leukemia relapse. [27]

However, larger studies show less favorable results with Imatinib based maintenance.

M D Anderson employed more intensive maintenance therapy. They used imatinib 800 mg for 24 months with monthly vincristine and prednisone interrupted by 2 intensifications with Hyper-CVAD and imatinib, then imatinib indefinitely. [10]

The GMALL A and GRAAL presented an interesting approach in which imatinib is given concurrently with standard dose of Interferon or peg -Interferon. Wassmann et al. had a hypothesis that the experimental data suggested that interferon- α (IFN- α) enhances the antileukemic activity of imatinib. Therefore, the group combined imatinib and low-dose IFN- α in six patients with Ph⁺ ALL who were ineligible for stem cell transplantation. All patients had received imatinib for 0.5–4.8 months prior to IFN- α , for relapse or refractory Ph⁺ ALL or as an alternative to chemotherapy following severe treatment related toxicity. The results were encouraging, but longer follow up is needed to determine whether this strategy will translate into better relapse free survival. [28-29]

Longer follow up is needed to determine if this strategy will translate into better relapse-free survival. The European recommendation concluded that the standard approach to de novo Ph + ALL is the combination of intensive chemotherapy with imatinib (400 mg/d to 800/d) in young patients and reduced dose of chemotherapy with high dose imatinib (600 mg/d to 800 mg/d) for elderly patients. Allogeneic SCT is recommended to all eligible patients with a suitable donor and to continue imatinib with or without additional therapy in patients not undergoing SCT.[30]

9. Central nervous system (CNS) prophylaxis

Central nervous system leukemia is infrequent (5%) at initial presentation, but there is significant risk of developing meningeal leukemia during the course of treatment and the CNS directed prophylactic therapy should be considered mandatory in this patients.

Imatinib does not cross the blood brain barrier to an appreciable extent, levels in the cerebrospinal fluid have shown to reach approximately 1 - 2 % of serum level. This low degree of penetration into the CNS is most likely due to p-glycoprotein export pumps, and it is not increased in the setting of active meningeal leukemia. Therefore, active CNS directed prophylactic therapy is mandatory in all patients with Ph+ ALL. Both repeat intrathecal injection of chemotherapy e.g. methotrexate, alone or in combination with cytarabine and corticosteroid, and prophylactic cranial irradiation have been used successfully. There is currently no conclusive data whether for how long and at what interval intratecal chemotherapy should be continued in patients with sustained hematological even molecular remission and whether it may be prudent to administer some form of CNS prophylactic after SCT.[31,32]

Dasatinib showed in the clinical trials CA180006 better penetration of the CSF and achieved clinically active concentrations in small series of patients in whom stabilization and regression of CNS disease were achieved. The doses of Dasatinib 140 mg once a day or 70 mg twice a day. It remains to be determined whether the current approach to CNS directed prophylaxis can be modified in the context of dasatinib based treatment.[33]

10. Mechanism of resistance to therapy and progression

The mechanism of resistance to therapy is related to acquired genetic abnormalities in Ph+ ALL blast cells, which provide insights into pathogenesis and strongly influence prognosis. Cytogenetic abnormalities in addition to the Ph+ chromosome are present in approximately one third of cases of adult leukemia. Other Overexpression of bcr/abl fusion gene e.g. due to double Ph+ chromosome, activates a number of downstream signaling pathways involving the Ras/Raf/mitogen activated protein kinase and JAK-STAT (Janus Kinase signal transducer and transcription activator of transcription) development of growth factor independent malignant clones contributes to progression of the disease. [34]

11. Relapse associated with a BCR-ABL kinase domain point mutation

The development of clinical resistance to imatinib has now surfaced in several sites. Acquisitions of point mutations in the ABL tyrosine kinase domain (KD) that interfere with the binding of imatinib appear to be the most influential. ABL KD mutations generally are comprised of two categories. The first includes mutations that directly impede contact between imatinib and Bcr-Abl, such as the gatekeeper mutations T315I or F317L. [35] The second involves mutations that alter the spatial conformation of the Bcr-Abl protein by affecting one of the two flexible loops: (1) the P-loop containing the ATP binding pocket, or (2) the activating loop. [36.37.38] To date, more than 50 ABL KD mutations have been identified. Although the prognostic significance of many of these remains unclear, the T315I mutation has been associated with a particularly adverse outcome since it disrupts a hydrogen bond critical for binding the TKI to the ATP- binding site. It has been identified in up to 20% of patients with imatinib-resistant Ph+ ALL, and also confers resistance to the second-generation TKIs nilotinib and dasatinib.[39]

In the GMALL study for elderly patients with Ph+ ALL, the incidence of ABL mutations by direct cDNA sequencing at the time of disease recurrence was 84%. In patients with ABL KD mutations, P-loop mutations predominated at a frequency of 57%, followed by the T315I mutation at 19%. The mutated clone comprised more than 50% of the ABL clones in all patients. [20] Pfeifer et al. also demonstrated that these ABL KD mutations were present in nearly 40% of the patients with de novo imatinib-naïve Ph+ ALL, with a distribution of P-loop mutations in 80% and the T315I mutation in 17%. However, the mutated ABL clone always comprised less than 2% of the sample, in contrast to the predominance of the mutated clone when associated with disease recurrence. These low-level ABL KD mutations in imatinib-naïve samples required more sensitive methods for detection (e.g., high-performance liquid chromatography). The presence of ABL KD mutations prior to imatinib did not correlate with known prognostic factors. There was no difference in the probability of achieving CR or molecular response based on the presence or absence of ABL KD mutations prior to imatinib therapy. No difference in remission duration was observed other than for those with the T315I mutation, which adversely affected outcome. In nearly all patients with an ABL KD mutation identified pretreatment, the same mutation was noted at the time of disease recurrence. Approximately 67% of the patients without an ABL KD mutation detected prior to imatinib had developed one at the time of disease recurrence. The discovery of novel acquired ABL KD mutations had also been reported in Ph+ ALL after sequential therapy with imatinib followed by the second-generation TKI dasatinib.[39]

Soverini et al. reported the development of the T315A and F317I (as opposed to the T315I or F317L) mutations that have inherent resistance to dasatinib. These ABL KD mutations could be suppressed by either imatinib or nilotinib given the lower IC50 with these compounds, although retreatment with imatinib after a prior failure would likely be ineffective due to the potential role of other coexisting mechanisms of resistance. Resistance screening with nilotinib, the other second-generation TKI, yielded only a limited spectrum of point mutations.[40] This

suggests a lower rate of ABL KD mutations after Nilotinib therapy; however, additional analyses of ongoing clinical trials are needed to support this contention. [41]

Other mechanisms of resistance to imatinib and other TKIs include increased drug efflux, amplification of the BCR-ABL gene, and signaling independence of BCR-ABL after secondary transforming events (e.g., Src kinase pathway). Theoretically, dose escalation of imatinib or the use of more potent ABL inhibitors could circumvent the first two events, whereas use of novel Src inhibitors or multitargeted inhibitors would be required to restore sensitivity in the latter case [42]

12. 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 is not consistent. MRD levels determined at different time points 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. The authors demonstrated the positive impact of imatinib on the outcome of allogeneic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) and analyzed for risk factors that affect transplantation outcome, and they focused particularly on the prognostic relevance of minimal residual disease levels at each treatment stage. Prospective assessment of the extent of minimal residual disease reduction after the first 4-week imatinib therapy may allow the authors to identify subgroups of Ph-positive ALL transplants at high risk of relapse. [45] Stratification based upon MRD levels was also the principal prognostic parameter in two studies, Dombret H. et al. with 154 patients, and Pane F et al with 45 Ph+ ALL patients, respectively. [43,44,45,46]

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. [47]

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.

13. Treatment to relapse

Point mutations are the major mechanism of resistance to Imatinib therapy in Ph+ leukemia; different drugs active on mutant BCR/ABL or on its signal transduction pathway have been developed and tested at clinical level. Several second-generation ABL TKIs possess significant activity against imatinib-resistant BCR/ABL mutants, although their specificities vary.[48]

Dasatinib has been tested most extensively in Ph+ ALL and has been approved as second-line treatment of bcr-abl-positive leukemias in first time. Dasatinib (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.[49]

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 phase II study with 14 patients, 3 of whom had CNS involvement. [50]

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 suggested 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. [50]

Small-molecule inhibitors developed to target Aurora kinases (AK), a family of serine-threonine kinases involved in the 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.. [51.52]

Another novel chemical class of compounds that bind to different structural pockets used by ABL kinase 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. [53]

14. New kinase inhibitors

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. [54]

As a 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.[55]

15. Conclusion

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) (see the next chapter) 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 and may assist in treatment decisions, e.g., in cases 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.

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