Final Report of the Trial AMLSG 11-08

Title	Open-label, multicenter phase Ib/IIa study for the evaluation of dasatinib (Sprycel™) following induction and consolidation therapy as well as in maintenance therapy in patients with newly diagnosed core binding factor (CBF) acute myeloid leukemia (AML)
Project Code:	AMLSG 11-08
Active Substance/Finished Product:	Sprycel™
Protocol Number:	Dasatinib_01_09_2010_V_3.1
Positive Vote of the Ethics Committee:	17.06.2009
Termination of the Trial	30.11.2015
Sponsor	University Hospital of Ulm, represented by the Chairman of the Board

1. Name of Sponsor/Company

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Ulm University Hospital, represented by the Chairman of the Board

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2. Name of Finished Product

Sprycel™

3. Name of Active Substance

Dasatinib

4. Individual Study Table

Not applicable

5. Title of Study

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Initial approved version of study protocol:
Dasatinib_01_11_2008_V_1.1 (Dated: 05.06.2009)

Amendments of the protocol:
Dasatinib_04_02_2010_V_2.0 (Dated: 04.02.2010)
Dasatinib_01_09_2010_V_3.1 (Dated: 01.09.2010)).

This report refers to the current version of study protocol
(Dasatinib_01_09_2010_V_3.1)

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8. Publication reference

Publication in preparation.

9. Studied period

First patient in: 03.09.2009

Last patient last visit: 30.11.2015 (completion date)

After the enrollment of initially planned 25 patients on 22.06.2010, recruitment was interrupted until approval of the amended protocol Version 3.1 (01.09.2010). Recruitment was restarted on 01.12.2010.

10. Phase of Development

Phase Ib/IIa

11. Objectives

Primary Objective

- To assess the feasibility of dasatinib 100 mg QD given after intensive induction (daunorubicin and cytarabine) and consolidation chemotherapy (high-dose cytarabine) and as single agent in maintenance therapy in adult patients with newly diagnosed core-binding factor (CBF) acute myeloid leukemia (AML)

Secondary Objectives

- To assess survival endpoints including cumulative incidence of relapse (CIR), cumulative incidence of death (CID), and overall survival (OS)

12. Methodology

Study Design

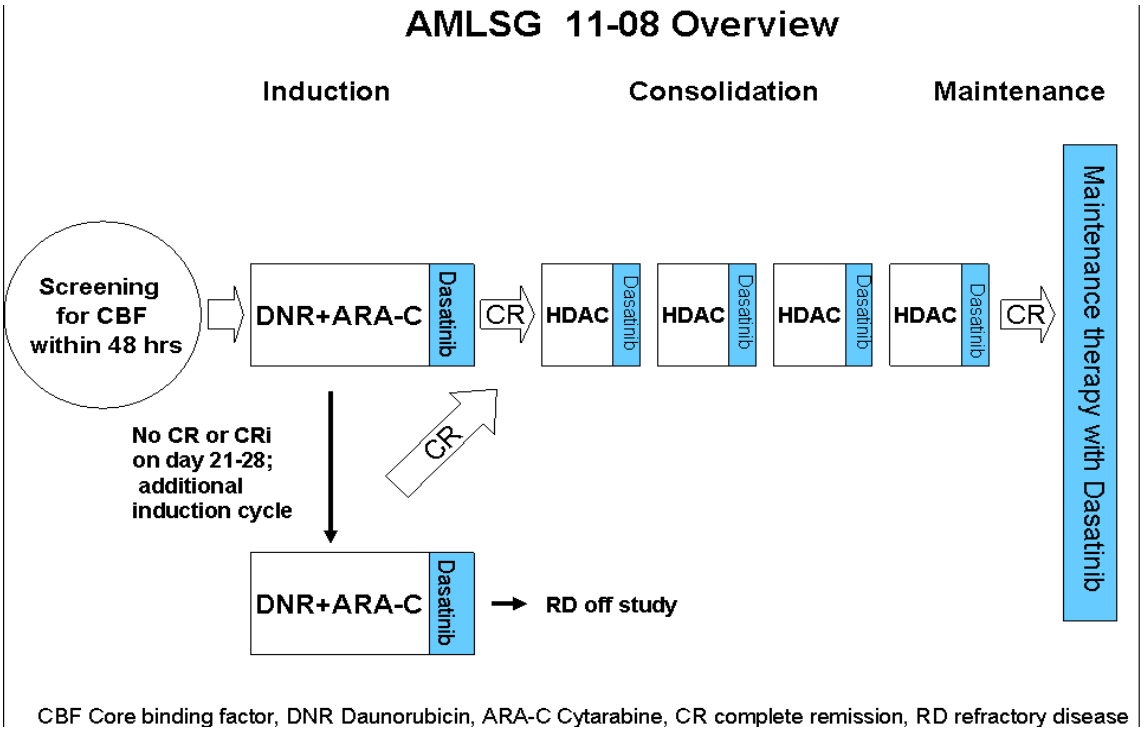
This was a phase Ib/IIa open-labeled multi-center trial evaluating the feasibility of dasatinib given after standard induction therapy with daunorubicin (DNR) and cytarabine (ARA-C), after consolidation therapy with high-dose cytarabine (HDAC), and as single agent in a one-year maintenance therapy in patients with newly diagnosed CBF AML.

Because only patients with CBF AML were eligible for this interventional study, the diagnosis of CBF AML had to be confirmed prior to inclusion of a patient into the trial by the detection of CBF fusion genes in one of two central AMLSG laboratories within 48 hours after diagnosis of AML as part of the initial diagnostic work-up.

Feasibility and/or tolerability in individual patients was defined as lack of pleural or cardiac effusion exceeding 2°, lack of liver toxicity of more than 2°, and achievement of a complete remission (CR) after induction therapy.

At the participating AMLSG study centers a total of 25 patients were enrolled before Amendment No. 3, and after the Amendment No. 3 additional 57 patients.

Treatment:



- Dasatinib = study drug; Dasatinib + DNR+ARA-C induction and Dasatinib + HDAC consolidation = study regimen

Induction cycle:

Patients received one cycle of induction therapy with daunorubicin 60 mg/m^2/day administered on days 1 through 3 and cytarabine 200 mg/m^2/day administered by continuous IV infusion daily for 7 days (days 1 through 7). Patients received dasatinib 100 mg QD on days 8-21. Bone marrow evaluation for assessment of response was done between day 21 and 28.

In patients not achieving CR or a CR without complete hematologic recovery (CRi) at the end of cycle 1, a second induction cycle (identical to the first cycle) was administered (after Amendment No.3, Protocol Dasatinib_01_09_2010_V_3.1).

Consolidation Cycles 1, 2, 3, 4:

Patients achieving CR or CRi at the end of cycle 1 (or 2) received 4 cycles of consolidation therapy. Consolidation therapy consisted of high-dose cytarabine 3 g/m^2 (reduced dose in patients >60 years: 1 g/m^2) q12h, d 1, 3, 5, administered intravenously over three hours. Patients received dasatinib 100 mg QD on days 6-28.

Maintenance therapy:

Patients completing consolidation therapy continued to receive single-agent dasatinib 100 mg QD for one year (or until relapse).

13. Number of patients (planned and analysed)

Number of patients planned: 82

Number of patients recruited: 91

Number of patients analysed: 89

14. Diagnosis and main criteria for inclusion

Diagnosis: Acute myeloid leukemia

Main Inclusion Criteria:

1. Core-binding factor (CBF) AML with molecular diagnosis of *RUNX1-RUNX1T1* fusion transcript resulting from t(8;21)(q22;q22) (or a variant form) or of *CBFB-MYH11* fusion transcript resulting from inv(16)(p13.1q22)/t(16;16)(p13.1;q22) as assessed in one of the central AMLSG reference laboratories.
2. Age ≥18 years; there was no upper age limit.
3. No prior chemotherapy for leukemia except hydroxyurea for up to 5 days during the diagnostic screening phase.
4. Non-pregnant and non-nursing. Due to the unknown teratogenic potential of dasatinib in humans, pregnant or nursing patients were not allowed to be enrolled. Women of childbearing potential (WOCBP) had to have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration. Women of child-bearing potential either had to commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control - one highly effective method (e.g., IUD, hormonal, tubal ligation, or partner's vasectomy), and one additional effective method (e.g., latex condom, diaphragm, or cervical cap) - AT THE SAME TIME, at least four weeks before she began dasatinib therapy. "Women of childbearing potential" was defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months.
5. Men had to agree not to father a child and had to use a latex condom during any sexual contact with women of childbearing potential while taking dasatinib and for 4 weeks after therapy was stopped, even if they had undergone a successful vasectomy.
6. Signed written informed consent.

15. Test product, dose and mode of administration, batch number

Dasatinib (Sprycel™) in 50 mg tablets was supplied for oral use in a daily manner.

Batch numbers: 2A73927
2D70589
2E71787
1H59833
0F62959
0C65175
8M32129

16. Duration of treatment

Intended duration of treatment for an individual patient was

- 18 months for patients with one induction cycle, four consolidation cycles and maintenance therapy.
- 19 months for patients with two induction cycles, four consolidation cycles and maintenance therapy.

17. Reference therapy, dose and mode of administration, batch number

There was no reference therapy.

18. Criteria for evaluation: Efficacy, Safety

The frequency and timing of efficacy and safety measurements were defined in the study protocol.

Efficacy Measurements

Efficacy assessments were done after every treatment cycle and thereafter during maintenance therapy and during follow-up period every 3 months. They were based on analysis of full blood count, bone marrow aspirate and, for patients with extramedullary disease, on clinical examination and/or tumor imaging.

The response to treatment was evaluated using standard criteria defined by the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (see Appendix A).

The response at every assessment time point was recorded for all patients.

Primary Efficacy Variables

The primary efficacy variable for this trial was feasibility as a combined end point defined by:

- Rate of early/hypoplastic death (Rate(ED/HD))
- Rate of pleural or pericardial effusion grade 3/4 (Rate(effuse))

- Rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver))
- Rate of refractory disease (Rate(RD))

Secondary Efficacy Variables

Secondary efficacy variables for this trial were:

- Overall survival (OS)
- Cumulative incidence of relapse (CIR) and death (CID) in CR.

Safety Measurements

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, chest X-ray, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF.

Adverse events were coded and graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 of the US National Cancer Institute (http://ctep.info.nih.gov/reporting/ctc.html).

19. Statistical methods

Endpoints and Statistical Analysis

The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion grade 3/4 (Rate(effuse)), rate of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (Rate(liver)), and rate of refractory disease (Rate(RD)). Feasibility/tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed grade 2, as well as a liver toxicity equal to or less than grade 2 and the achievement of a complete remission after induction therapy.

The maximally tolerated rates (MTR) of the different endpoints before Amendment No.3 in August 2010 were defined as:

- MTR of early/hypoplastic death (MTR(ED/HD)) = 10%
- MTR of pleural or pericardial effusion grade 3/4 (MTR(effuse)) =10%
- MTR of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (MTR(liver)) =10%
- MTR of refractory disease (MTR(RD)=10%)

The maximally tolerated rates (MTR) of the different endpoints after Amendment No.3 in August 2010 were defined as:

- MTR of early/hypoplastic death (MTR(ED/HD)) = 10%
- MTR of pleural or pericardial effusion grade 3/4 (MTR(effuse)) =10%
- MTR of liver toxicity grade 3 or 4 that does not improve to grade 2 or less within 14 days after discontinuing responsible medication (MTR(liver)) =10%
- MTR of refractory disease (MTR(RD)=5%)

The studied regimen was considered tolerable, if at the end of the trial the probabilities that the true (unobserved) rates of the single primary events exceed the maximum tolerated rates are not greater than 90%, i.e., if:

Before Amendment No.3 in August 2010:

(1) Pr(r(ED/HD)>0.10) ≤ 90%,
(2) Pr(r(effuse)>0.10) ≤ 90%,
(3) Pr(r(liver)>0.10) ≤ 90%,
(4) Pr(r(RD)>0.10) ≤ 90%.

After Amendment No.3 in August 2010:

(5) Pr(r(ED/HD)>0.10) ≤ 90%,
(6) Pr(r(effuse)>0.10) ≤ 90%,
(7) Pr(r(liver)>0.10) ≤ 90%,
(8) Pr(r(RD)>0.05) ≤ 90%.

These probabilities are posterior probabilities based on the Bayesian approach suggested by Thall and Simon (1994), using a binomial-beta model with a non-informative Uniform[0,1] prior. Estimates for all primary endpoints was computed in both cohorts separately. In addition, for endpoints (1)-(3) (r(ED/HD), r(effuse), r(liver)) the rates was also estimated based on the combined cohort.

Secondary survival efficacy variables were analyzed by the use of the product limiting method according to Kaplan and Meier and the cumulative incidence function introduced by Kalbfleisch and Prentice.

Adverse events were coded according to the CTCAE dictionary (Version 3.0). Summaries (absolute number of patients / percentage) were provided for adverse events, adverse events determined by the investigator to be treatment related (defined as possibly, probably, and definitely related), treatment-related adverse events by severity, serious adverse events, and adverse events causing withdrawal from study or death during study treatment.

20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Efficacy Results

Single rates of the combined primary endpoint were below the predefined maximal tolerated rates. At every sequential testing time point during the study and for all single primary endpoints, the cumulative number of events was below the critical value. Therefore, no overall dose reduction of dasatinib was performed and the study had not to be discontinued prematurely.

After 48 months the estimated OS was 74.7%, the CIR and CID rates were 35.2% and 4.2% respectively.

20.2 Safety Results

Overall, AEs occurred most frequently in the categories of gastrointestinal disorders (93%), infections (93%) and constitutional symptoms (92%). With regard to the

treatment cycles, categories of gastrointestinal disorders, infections, blood/bone marrow and constitutional symptoms were most frequently affected.

The most frequent AE overall was nausea (83%). Other frequent AEs were decrease in hemoglobin (81%) or platelet counts (81%), and diarrhea (70%). Decrease in platelet counts and hemoglobin were the most frequent AEs during all treatment cycles. Other frequently occurring AEs were nausea, diarrhea, fever, and decrease in leukocytes. During maintenance therapy, the most frequent AEs reported were decrease in platelets, diarrhea, fatigue, and upper airways infections.

The frequently occurring severe adverse reactions with CTCAE of at least 3° included: decrease of platelet count, leukocytopenia, decreased hemoglobin, decreased neutrophil count, and febrile neutropenia.

There were 5 deaths during treatment with dasatinib and the 28-day follow-up period. Two of the deaths on study were due to sepsis, the remaining 3 deaths were due to toxic colitis, airway obstruction and sudden death. Four deaths were early deaths or hypoplastic deaths and one patient died in CR. Three deaths were reported as related to the study drug dasatinib (airway obstruction, n=1; sepsis with multi-organ failure, n=1; toxic colitis, n=1).

A total of 152 SAEs were reported in 56 (63%) patients, of which 80 SAEs in 32 (36%) patients were treatment related. A total of 123 SAEs (81%) were reported during the induction and consolidation cycles, and 63 (51%) of them were related to dasatinib. Twenty-nine SAEs (19%) were observed during the maintenance treatment, of which 17 SAEs (59%) were treatment related. Sepsis, febrile neutropenia, lung infection, colitis and pleural effusion were the most frequently reported in the induction and consolidation cycles, compared to colitis, diarrhea and fever in the maintenance therapy.

Study treatment with dasatinib was discontinued due to AEs in 33 patients. Overall, 23 events were reported to be related and 10 events not related to the treatment with dasatinib. The most frequent reasons for withdrawal were diarrhea, sepsis and pleural/pericardial effusion. Among 53 patients who started maintenance treatment with dasatinib, 15 patients (28%) discontinued treatment due to AEs. The most frequent reasons for withdrawal were hematologic toxicities (leukocytopenia, thrombocytopenia and neutropenia), diarrhea and fever.

20.3 Conclusion

Discussion

This is an open-label, non-randomized, multicenter phase Ia/IIb study in adult patients with newly diagnosed CBF AML evaluating the feasibility and safety of the KIT inhibitor dasatinib in combination with intensive chemotherapy and subsequently as single-agent for one year maintenance therapy. The study was conducted at 49 active AMLSG sites in Germany (n=44) and Austria (n=5). Between September 2009 and June 2012 a total of 91 patients with a median age of 49.5 years (range: 19 to 73 years) were consented for the study. Two patients were excluded from the safety and outcome analyses due to violation of inclusion or exclusion criteria and did not start treatment within the study. Thus, for the safety and efficacy analyses 89 patients (females, n=42; males, n=47) were included. Among the 89 patients, 23.6% were above the age of 60 years, the ECOG status in 89% did not exceed 1; 37 patients

had AML with t(8;21) and 52 had AML with inv(16). A *KIT* mutation involving exon 8 or exon 17 was detected at diagnosis in 23% of the patients.

The primary endpoint was a combined endpoint integrating the rates of early/hypoplastic death (Rate(ED/HD)), rate of pleural or pericardial effusion 3° or 4° (Rate(effuse)), rate of liver toxicity 3° or 4° not improving to 2° or less within 14 days after discontinuing responsible medication (Rate(liver)), and the rate of refractory disease (Rate(RD)). Feasibility and tolerability for an individual patient was defined as a pleural or cardiac effusion level that does not exceed 2°, as well as a liver toxicity equal to or less than 2° and the achievement of a complete remission (CR) after induction therapy. Single rates of the combined primary endpoint were below the maximum tolerated rates. At every sequential testing time point during the study and for all single primary endpoints, the cumulative number of events was below the critical predefined value. Therefore, in terms of the primary endpoint no overall dose reduction of dasatinib was performed and the study had not to be discontinued prematurely.

Generally, dasatinib administration was associated with acceptable tolerability with no unexpected excess of toxicity. No new safety findings have been revealed in the study. Adverse events with ≥3° that were reported as being related to dasatinib (adverse reaction; ADRs) occurred mainly during the induction and consolidation cycles. ADRs during the maintenance treatment were most mild or moderate. In fact, the assessment of causality in some cases might be difficult in patients with hematologic malignancies in the setting of combination with standard intensive chemotherapy and given the clinical presentation of the disease.

Eighty-one percent of severe adverse events (SAEs) occurred during the induction and consolidation cycles, and half of them were related to dasatinib. Only 17 SAEs were observed during maintenance treatment and were linked to dasatinib. Gastrointestinal symptoms (colitis, diarrhea)), infections and fever were most frequently reported as SAEs related to dasatinib.

Overall, 5 deaths were reported in the study; only 3 deaths were considered to be related to dasatinib (airway obstruction, n=1; sepsis with multi-organ failure, n=1; toxic colitis, n=1).

Thirty-three patients discontinued treatment with dasatinib due to SAEs/AEs. The most frequent reasons for withdrawal were hematologic toxicities (leukocytopenia, thrombocytopenia and neutropenia), diarrhea and fever.

The overall CR rate in the study cohort was 94% (84/89); 79% (73/89) of the patients achieved CR after one induction cycle. After 48 months, the estimated overall survival (OS) was 74.7%, and the cumulative incidences of relapse (CIR) and death (CID) were 35.2% and 4.2% respectively. Since this study did not have a comparator arm, we compared the outcomes of the study cohort with an historical control group of CBF AML patients (n=325) that were intensively treated on our previous AMLSG trials. Although the median age in the AMLSG 11-08 cohort was higher than in the historical control group (49.5 vs 45 years; P=0.01), the CR rate was similar (94% vs 91%; P=0.67). With the current follow-up, there was an improved cumulative incidence of relapse (CIR) in the AMLSG 11-08 cohort compared to historical controls (at 4-years: 31% *vs* 43%; P=0.07); so far no significant improvement in OS is noticed.

Overall conclusions

The results of this phase Ia/IIb study in adults with newly diagnosed CBF AML evaluating dasatinib in induction, consolidation and maintenance therapy did not show any unexpected excess in toxicity. Thus, the primary endpoint of the trial was met, that is, the demonstration of the feasibility and tolerability of combining dasatinib with intensive chemotherapy in this patient population. The beneficial safety profile in the AMLSG 11-08 trial and the signals for a potential positive effect on outcome obtained from the comparison of the AMLSG 11-08 cohort with historical controls, provided a basis for a confirmatory randomized phase III trial with dasatinib in adults with newly diagnosed CBF AML (clinicaltrials.gov: NCT02013648).

21. Date of Report

Date 23. 11. 2016

Prof. Dr. Hartmut Döhner
Leiter der klinischen Prüfung

APPENDIX A

Response Definition

Response to treatment will be evaluated according to the following criteria (modified from the National Cancer Institute/Cancer and Leukemia Group B criteria, Ref: Cheson et al. 2003):

- Complete remission (CR)

Peripheral blood: neutrophils ≥1,000/µl and platelets >100,000/µl and no leukemic blasts in the peripheral blood smear or by FACS analysis. Maturation of all cell lines and <5% blasts by morphologic criteria and no Auer rods. Extramedullary involvement: no detectable involvement at any site.

- Complete remission with incomplete neutrophil or platelet recovery (CRi)

All of the above criteria for CR must be met, except that neutrophils <1,000/µl or thrombocytes <100,000/µl in the peripheral blood.

- Partial remission (PR)

All of the above criteria for CR must be met, except that the bone marrow contains ≥ 5% but <25% blasts in cases of pretreatment BM-basts above 50% or a ≥50% reduction of pretreatment blast count in cases with pretreatment BM-basts 20-50%), or ≤5% blasts in the presence of Auer rods or abnormal morphology.

- No change (NC)

Patient surviving ≥7 days after completion of initial treatment course with persistent leukemia in the last peripheral blood smear or bone marrow (>25% blasts), or with persistent extramedullary disease, but without further clinical deterioration due to leukemia or increase of blast population in the bone marrow or peripheral blood in comparison to pretreatment blast counts.

- Progressive disease (PD)

Patient surviving ≥7 days after completion of initial treatment course with increase of blast population in the bone marrow or peripheral blood or aggravation or new development of extramedullary disease or further deterioration or death due to leukemia. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be classified as having ‘symptomatic deterioration’. Every effort should be made to document the objective PD even after discontinuation of treatment.

APPENDIX B

Background information and study rationale

The core-binding factor (CBF) acute myeloid leukemias (AML) are characterized by the presence of distinct genetic abnormalities. Cytogenetically, one of these abnormalities is t(8;21)(q22;q22), the other are pericentric inversion of chromosome 16 [inv(16)(p13.1q22)] or less frequently the balanced translocation t(16;16)(p13.1;q22) [hereafter collectively referred to as inv(16)] (Arber, 2016). Upon detection of these clonal genetic abnormalities, the diagnosis of AML can be made regardless of the proportion of bone marrow blasts (Arber, 2016). Both AML with t(8;21) and AML with inv(16) are recognized by the World Health Organization (WHO) classification as unique entities within the category “AML with recurrent genetic abnormalities” (Arber, 2016). Among adults with *de novo* AML, t(8;21) and inv(16) are found in 7% and in 5% to 8% of the patients, respectively (Byrd , 2002, Grimwade , 2010). The frequency of t(8;21) and inv(16) decreases in older patients, and only 7% of AML patients above the age of 60 years harbor one of both chromosome aberrations (Fröhling, 2006). Both t(8;21) and inv(16) aberrations result in formation of novel chimeric fusions involving genes of the CBF complex providing the common designation “CBF AML” to these AML cases; the t(8;21) aberration results in the fusion of *RUNX1* on chromosome 21q22 with *RUNX1T1* (*ETO*; *MTG8*) on chromosome 8q22 and the inv(16) mutation results in the *CBFB* gene on chromosome 16q22 being fused to *MYH11* on chromosome 16p13.1 (Erickson, 1992; Liu, 1993; Shurtleff, 1995). Compared with other cytogenetic AML groups, patients with CBF AML are considered as a favorable AML risk group based on the high complete remission rate and high survival probabilities. However, because approximately one-half of patients with CBF AML are still not cured, there is a need for novel therapeutic approaches.

Although the *RUNX1-RUNX1T1* and *CBFB-MYH11* fusions are believed to interfere with normal hematopoietic differentiation and as predisposition to leukemia, they alone are not sufficient to induce leukemic transformation. The acquisition of additional genetic hits is necessary for the development of a leukemic phenotype (Okuda, 1998; Castilla, 1999). Some secondary alterations cooperating with CBF fusion proteins in the process of leukemogenesis are mutations in genes encoding protein effectors controlling cell proliferation and/or conferring survival advantage to the malignant cells. Indeed, almost 90% of AML with t(8;21) and more than 90% of AML with inv(16) harbor additional secondary chromosome aberrations and/or mutations affecting *KIT*, *FLT3*, *NRAS*, and *KRAS* (Paschka and Döhner K, 2013).

Mutations in *KIT* have been identified in approximately one third of patients with CBF AML (Paschka and Döhner K, 2013). The *KIT* gene, located at chromosome band 4q11-12, encodes a 145-kD transmembrane glycoprotein, which is a member of the type III receptor tyrosine kinase family. Following ligand binding, the receptor dimerizes, becomes phosphorylated, and activates downstream signaling pathways involved in proliferation, differentiation, and survival. Ligand-independent activation of KIT can be caused by gain-of-function mutations that have been reported in CBF AML and in other human malignancies (e.g., gastrointestinal stromal tumors, systemic mastocytosis, and germ cell tumors). In CBF AML, *KIT* mutations cluster most frequently within exon 17, which encodes the KIT activation loop (A-loop) in the kinase domain, and in exon 8, which encodes an evolutionary highly conserved region in the extracellular portion of the KIT receptor. In a number of studies, *KIT* mutations, in

particular exon 17 mutations, have been associated with inferior outcome (Paschka and Döhner K, 2013).

In addition to the frequent finding of *KIT* mutations, in CBF AML there is a significantly higher *KIT* expression compared to the other AML subgroups as shown in studies using global gene expression profiling and also by a RQ-PCR study (Bullinger et al., 2004; Valk et al., 2004; Gao, 2015). The overall high *KIT* expression in CBF AML provides a rationale to evaluate the therapeutic principle of KIT inhibition not only in the cases with mutant *KIT*, but in all CBF AML.

Dasatinib, formerly known as BMS-354825, is an ATP-competitive, dual SRC/ABL inhibitor. Dasatinib can inhibit BCR-ABL activation loop mutants that are found in some chronic myeloid leukemia patients with acquired resistance to imatinib. Some small-molecule SRC/ABL inhibitors also have been demonstrated to have potency against KIT kinase. In a study by Schittenhelm et al. (2006), dasatinib was shown to potently inhibit wildtype (wt) KIT with an IC50 of 5 to 10 nmol/l for inhibition of autophosphorylation and cellular proliferation. Dasatinib also potently inhibited KIT juxtamembrane domain mutations with an IC50 of 1 to 10 nmol/l. Notably, dasatinib is a potent inhibitor of KIT activation loop mutants, with IC50 values for inhibiton of autophosphorylation of KIT D816 mutants in the range of 10 to 100 nmol/l. The potency seems to be differentially influenced by the specific type of the activation loop mutation, ie, KIT D816Y is 10-fold more sensitive to dasatinib than KIT D816V or D816F.

Research hypothesis:

Taken together, based on the molecular profile in CBF AML including a high *KIT* expression and frequent occurrence of activating *KIT* mutations and given the activity of dasatinib against both wildtype and mutant KIT, there is a good rationale for the evaluation of dasatinib in the treatment of patients with CBF AML. In phase I-III clinical trials evaluating dasatinib in imatinib-resistant chronic myeloid leukemia (CML), the drug was safe, well tolerated and effective. In 2006, dasatinib (Sprycel®) was approved by FDA (and in 2007 by EMEA) for the treatment of CML resistant or intolerant to treatment with imatinib.

Appendix C

References

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogeneticabnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). Blood. 2002;100(13):4325-4336.

Castilla LH, Garrett L, Adya N, et al. The fusion gene Cbfb-MYH11 blocks myeloid differentiation and predisposes mice to acute myelomonocytic leukaemia. Nat Genet. 1999; 23(2):144-146.

Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, Lo-Coco F, Willemze R, Biondi A, Hiddemann W, Larson RA, Löwenberg B, Sanz MA, Head DR, Ohno R, Bloomfield CD; International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 21:4642-9, 2003

Erickson P, Gao J, Chang KS, et al. Identification of breakpoints in t(8;21) acute myelogenous leukemia and isolation of a fusion transcript, AML1/ETO, with similarity to Drosophila segmentation gene, runt. Blood. 1992;80(7):1825-1831.

Fröhling S, Schlenk RF, Kayser S, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood. 2006;108(10):3280-3288.

Gao X, Lin J, Gao L, Deng A, Lu X, Li Y, Wang L, Yu L. High expression of c-kit mRNA predicts unfavorable outcome in adult patients with t(8;21) acute myeloid leukemia. PLoS One. 2015;10(4):e0124241.

Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116(3):354-365.

Liu P, Tarle SA, Hajra A, et al. Fusion between transcription factor CBF beta/PEBP2 beta and a myosin heavy chain in acute myeloid leukemia. Science. 1993;261(5124):1041-1044.

Okuda T, Cai Z, Yang S, et al. Expression of a knocked-in AML1-ETO leukemia gene inhibits the establishment of normal definitive hematopoiesis and directly generates dysplastic hematopoietic progenitors. Blood. 1998;91(9):3134-3143.

Paschka P and Döhner K. Core-binding factor acute myeloid leukemia: can we improve on HiDAC consolidation? Hematology Am Soc Hematol Educ Program. 2013;2013:209-219.

Shurtleff SA, Meyers S, Hiebert SW, et al. Heterogeneity in CBF beta/MYH11 fusion messages encoded by the inv(16)(p13q22) and the t(16;16)(p13;q22) in acute myelogenous leukemia. Blood. 1995;85(12):3695-3703.