ORIGINAL ARTICLE

Current results on the use of imatinib mesylate in patients with relapsed philadelphia chromosome positive leukemia after allogeneic or syngeneic hematopoietic stem cell transplantation

Andrew J. Ullmann, Georg Hess, Karin Kolbe, A. Friedrich-Freksa[1], Ralf G. Meyer, Harald Gschaidmeier[2] Christoph Huber and Thomas Fischer

3rd Medical Department, Johannes Gutenberg-University, [1]Institute for Clinical Genetics, Mainz
[2]Novartis Pharma, Nürnberg, Germany

(Received for publication on March 10, 2003)

Abstract. Here, we describe a patient diagnosed with chronic myelogenous leukemia who relapsed after matched unrelated donor SCT. The patient was treated with imatinib mesylate and donor lymphocyte infusions, and achieved a complete molecular remission. Additionally, safety and efficacy of imatinib mesylate in a total of 134 patients from 8 centers who underwent allogeneic or syngeneic stem cell transplantation (SCT) and had a relapse of Philadelphia chromosome positive leukemia was reviewed. Data was compiled from abstracts accepted as oral or poster presentations at the ASH (American Society of Hematology) 2001 and EBMT (European Group for Blood and Marrow Transplantation) 2001 & 2002 meetings and additionally literature published on this patient group. Efficacy of imatinib therapy was assessed by morphology, cytogenetic analysis, and determination of donor chimerism. In the evaluable population, hematologic and cytogenetic responses were observed in 66% and 60% of the patients, respectively. Fifty-one of 114 (45%) patients achieved a complete cytogenetic response. No response or progress of disease was noted in 22 out of evaluable 91 patients. The observation period was limited to a maximum of 28 months. A significant improvement in donor chimerism was frequently observed. Only five cases of significant GVHD were reported. Preliminary results show that imatinib mesylate has the potential to positively influence the ratio of donor and recipient cells without inducing a high incidence of severe GVHD. The data suggest that earlier start of imatinib mesylate prior to hematologic relapse in minimum residual disease (MRD) positive patients is a promising treatment concept. (Keio J Med 52 (3): 182–188, September 2003)

Key words: STI-571, imatinib mesylate, allogeneic, syngeneic, transplantation

Introduction

Allogeneic stem cell transplantation is the therapy of choice for a selected patient population with chronic myelogenous leukemia (CML).[1] Overall, long term disease free survival after transplantation is accomplished in up to 70% of eligible patients.[2]

In patients transplanted in chronic phase of CML, relapse after allogeneic stem cell transplantation (SCT) is noted in 5 to 30% of the cases. The incidence rate of relapse in patients transplanted in more advanced stages of disease is significantly higher. Currently, interferon-α, donor lymphocyte infusions (DLIs) or a second allogeneic SCT are alternatives to treat relapse after allogeneic transplantation. DLIs from the original SC donor result in complete molecular remissions in a high proportion of relapsed CML patients and are currently considered standard of care. However, patients

Presented at the 1256th Meeting of the Keio Medical Society in Tokyo, May 31, 2002.
Reprint requests to: Dr. Andrew J. Ullmann, Klinikum der Johannes Gutenberg-Universität, III. Medizinische Klinik & Poliklinik, Langenbeckstr. 1, 55101 Mainz, Germany, facimile +49 6131 17 476564, e-mail: A.Ullmann@3-med.klinik.uni-mainz.de

in accelerated phase or blast crisis respond poorly to DLIs with response rates between 0 and 30%.[3–5] In the event of donor unavailability, other curable therapeutic approaches do not exist.

The disadvantage of DLIs is the potential development of graft-versus-host-disease (GVHD) which is a major contributing factor of morbidity and mortality in this patient population. Up to 60% of the patients receiving DLIs experience GVHD.[5,6] If donor hematopoiesis is missing, DLIs induce bone marrow aplasia which can be long lasting and is also associated with an increased morbidity and mortality rate. Application of DLIs is contraindicated in patients with preexisting GVHD. DLIs administered in an escalated dose scheme reduce the incidence of GVHD without reducing its efficacy.[7,8]

Imatinib presents an interesting alternative in the treatment of relapsed CML after allogeneic SCT. Imatinib mesylate is a selective inhibitor of the abl protein-tyrosine kinase.[9–11] Philadelphia (Ph) chromosome-positive leukemia presents an ideal target for therapy with imatinib mesylate because the bcr-abl kinase plays a dominant role in deregulated cell proliferation. It has recently been approved by the FDA (Food and Drug Administration) and EMEA (The European Agency for the Evaluation of Medical Products) for patients in chronic phase of CML intolerant or refractory to interferon-α, and for patients in accelerated phase or blast crisis. In clinical trials imatinib mesylate induced a high rate of hematologic and cytogenetic responses in bcr-abl positive CML with a low toxicity profile.[12–14]

Materials and Methods

Patients

Here we report on a patient who received imatinib mesylate for relapsed CML following matched unrelated donor stem cell transplantation. Additionally, we compiled data from abstracts accepted as oral or poster presentations at the ASH (American Society for Hematology) 2001 and EBMT 2001 & 2002 meetings. This far, only two papers were published on patients with relapsed Philadelphia chromosome positive leukemia after allogeneic transplantation.[15,16] Abstracts were only selected if more than 5 patients were reported to have relapsed after allogeneic or syngeneic transplantation and received imatinib.[15–26] If numerous submissions from the same group were available, only the latest submission was considered. Abstracts were not considered if their content did not differentiate between autologous and allogeneic transplantation.

A total of 134 patients from 8 centers underwent allogeneic or syngeneic stem cell transplantation and had a relapse of the Philadelphia chromosome positive leukemia (Table 1).

One-hundred patients were in blast crisis, relapse of Philadelphia chromosome positive ALL, in an accelerated phase (including additional chromosomal abnormalities), or had extramedullar manifestation (high-risk group). The remaining 34 patients were in the chronic phase/cytogenetic relapse group. The time interval since transplantation ranged between 1–234 months.

In abstracts where data was available, twenty-three patients received HLA-identical donor transplantation, 10 patients received matched unrelated donor transplantation, 3 patients received mismatched donor transplantation and additional 4 patients were transplanted with a syngeneic donor transplant. The only available information on the remaining patients was that an allogeneic transplantation had been performed. Treatment with imatinib mesylate was initiated at a single daily oral dose of 400 mg for the chronic phase/cytogenetic relapse group or 600–1000 mg for high-risk group.

Treatment duration ranged between 1–28 months. Efficacy was assessed by peripheral blood and bone marrow evaluations, cytogenetic analysis, and determination of donor chimerism.

Molecular analysis

PCR-positivity for bcr-abl and breakpoint characteristics of the CML patient in our case report were evaluated by utilizing a nested PCR procedure as published previously.[27] For follow-up evaluation, a commercially available quantitative PCR (qPCR) assay was applied using hybridization probes and detection on the LightCycler device (Roche, Mannheim, Germany). This assay can quantify levels above $1:10^4$ translocation bearing cells. In brief, mononuclear cells (MNC) of blood or bone marrow samples were prepared and RNA was extracted using a commercially available kit (HighPure RNA extraction kit, Roche, Mannheim, Germany) or a standard protocol using tripure reagent (Roche, Mannheim, Germany). cDNA synthesis was performed according to the manufacturers' instruction and real-time PCR was performed using a defined amount of the transcription product. Using a second PCR-reaction as internal standard resulted in expression of bcr-abl levels relative to GAPDH-levels. To avoid interassay variation, samples of each patient were analyzed in a single run whenever possible. If qPCR did not result in a quantifiable result, nested PCR was performed to evaluate for remaining minimal residual disease with a maximum sensitivity of $1:10^5$–10^6.

Chimerism analyses were performed in bone marrow and peripheral mononuclear cells by analysis of short tandem repeat systems.

Table 1 Summary of Abstracts Approved for Oral or Poster Presentation at EBMT and ASH Meetings 2001 and 2002. The Results of the Two Publications are Also Included

Author	Kantarjian *et al.*[15,19]	Chambon-Pautas *et al.*[18]	Wassmann/Pfeifer *et al.*[21,25]	Soiffer *et al.*[22]	Rodrieguez *et al.*[16]	Ottmann/Wassmann *et al.*[20,26]	Ullmann *et al.*[23,24]	Au *et al.*[17]
Patients	28	15	21	16	8	20	18	8
Median time SCT-STI	1–137 months	9–132 months	6.5 months (2–50)	12 months (2–24)	N/A	N/A	17 months (2–234)	N/A
Treatment duration (median)	11 months[19]	2–15 months	4.6 months	N/A	4 months	N/A	6 months	N/A
Hematologic response	18/24[19]	10/10	13/21	9/11	7/8	11/20	12/18	N/A
Cytogenetic response	17/28	8/10	6/17	4/5	N/A	N/A	N/A	6/8
Complete cytogenetic response	11/28	5/10	7/13	4/9	4/8	11/20	3/18	6/8
Molecular remission	1/28	1/10	4/6	N/A	Unknown	1	2	1
GVHD >2° or chronic extensive GVHD	3	0	[3/21 GVHD no grading]	N/A	0 (3 active GVHD at start)	1 gut	0	1
Other toxicity	6/14 >II° NCI granulocytopenia 4/15 >II° NCI thrombocytopenia	4 cytopenia	3 subdural hygroma/ hematoma 1 neutropenic colitis 12/21 >II° cytopenia	4 LFT increase (3× GVHD, 1× leukemia), 2 BM hypoplasia	2 rash & cytopenia	1 aspergillosis & MOF	6/18 >II° NCI cytopenia, muscle cramps	2/8 cytopenia, muscle cramps

N/A: not available; NCI: NCI/NIH Common Toxicity Criteria.

Case report

A previously healthy 32-year-old woman was diagnosed in November 1994 with Philadelphia chromosome positive CML. Treatment with hydroxyurea and interferon-α was started and no siblings were available as donors for a transplant. HLA-matched unrelated donor stem cell transplantation was performed in July of 1998. The post transplantation phase was complicated by a grade III GVHD of the skin. She received cyclosporine A (CSP) and prednisolone for immunosuppressive therapy. Steroids were tapered within 2 months and then discontinued. Post transplantation, a molecular remission documented by nested PCR was noted. CSP was being tapered when consecutive blood samples turned positive for bcr-abl (first noted 268 days after transplantation). Despite slow tapering of CSP due to ongoing limited chronic GVHD, 402 days after transplantation negativity for bcr-abl was not accomplished. Chronic limited GVHD was constantly eminent during tapering and after discontinuation of the immunosuppressive therapy. DLI was not feasible due to donor unavailability at that time.

After 570 days post transplantation, the patient developed accelerated phase (AP) of CML. Imatinib mesylate treatment was initiated with 400 mg once daily. Therapy was well tolerated by the patient except for mild muscle cramps. Prior to imatinib mesylate treatment, cytogenetic analysis revealed 100% Philadelphia chromosome positive (Ph+) recipient metaphases. After three months, cytogenetic analysis demonstrated three divergent types of metaphases: Philadelphia chromosome negative recipient (XX), Philadelphia chromosome positive recipient (XX,t),[9,22] and donor cells (XY). After a total of 180 days of imatinib treatment, no Philadelphia chromosome positive metaphases were detectable (Fig. 1). The percentage of donor metaphases increased to 80% after additional 180 days, the proportion of Ph-negative recipient metaphases was at 20%. Again, no Philadelphia chromosome positive cells were detectable during the patient's further clinical course.

After one year, chimerism analysis revealed a change from undetectable donor chimerism at initiation of imatinib to 68% in the bone marrow and to 73% in the peripheral blood. This increase in donor chimerism

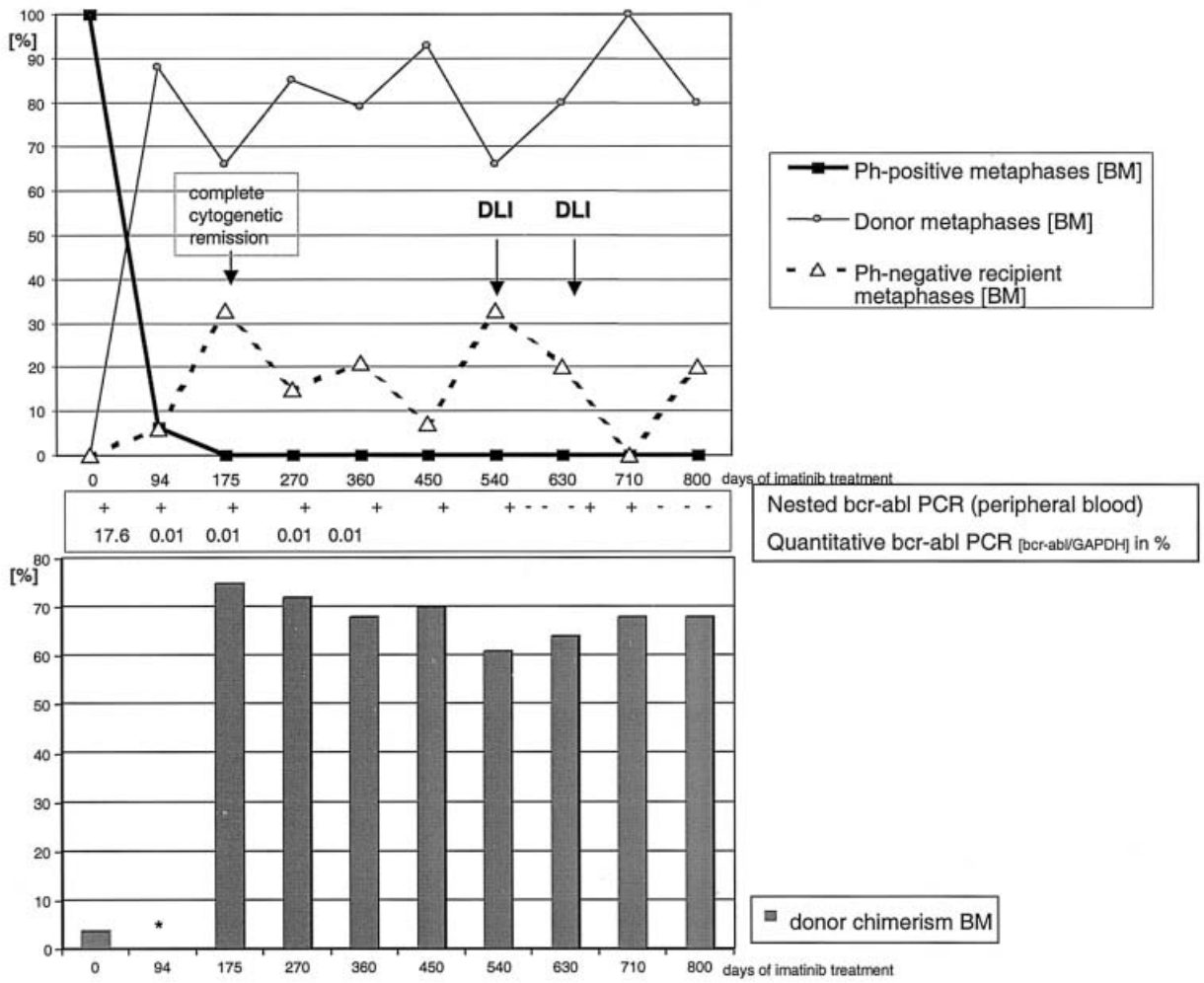

Fig. 1 Cytogenetic analysis, PCR and chimerism assessment during treatment with imatinib in a 34 year-old woman with CML, who relapsed after MUD transplantation. Chimerism was analyzed in bone marrow (BM) mononuclear cells. The level of detection for donor chimerism is at 5% donor cells. At initiation of imatinib therapy there was no detectable donor chimerism. [*: not done]. Not all metaphases were considered in the counts, since various structural and numeral chromosome aberrations were additionally observed and were considered neither pathogenic nor a cell line.

was detectable within 6 months of imatinib therapy and did not change significantly thereafter. Simultaneously, levels of bcr-abl mRNA transcripts, as evaluated by quantitative PCR, decreased rapidly (Fig. 1) without reaching complete molecular remission by nested PCR. Thus, in this patient who had relapsed in AP of CML at start of imatinib mesylate therapy, minimum residual disease (MRD) was achieved.

Consequently, in June 2001, the patient received a first dose of DLI (1×10^6 CD3 positive cells/kg) and in October 2001 a second dose (5×10^6 CD3 positive cells/kg). Of note, imatinib mesylate therapy was continued and no significant side-effects were noted. After the second DLI, leukocytes dropped briefly to 2000/μl and the dosage of imatinib mesylate was decreased intermittently to 300 mg qd. Thereafter, a sustained complete molecular remission, evaluated by nested PCR, was accomplished without developing severe GVHD. Only limited chronic GVHD of the skin was clinically observed. The above noted mixed chimerism (donor cells and Ph-negative recipient cells) remained unchanged. The patient continues on imatinib mesylate.

Results of the Literature Review

Table 1 depicts essential data on efficacy and toxicity of imatinib mesylate therapy derived from abstracts reviewed. Overall, 80 of 112 evaluable patients (71%) (Table 1) showed some hematologic response and 66 of 99 evaluable patients achieved a complete hemato-

logic response. No response or progress of disease was reported in 22 out of 91 evaluable patients. Most of these patients were in the high risk group (beyond chronic phase).

Overall cytogenetic responses were observed in 41 of 68 evaluable patients (60%) (Table 1). In 51 patients out of 114 evaluable patients (45%) a complete cytogenetic response was noted (Table 1). Where discrimination between low and high risk patients was possible, it was reported that 6 of evaluable 13 patients (46%) in the low risk group (chronic phase at the initiation of imatinib mesylate) and 25 of evaluable 48 patients (52%) in the high-risk group developed a complete cytogenetic response.

Mixed chimerism was noted in numerous patients at therapy initiation. Limited available data demonstrated that donor chimerism increased after the start of imatinib in responding patients. Most abstracts and literature were not equipped with detailed data concerning donor chimerism.

Generally, imatinib mesylate was well tolerated. Relevant treatment related side effects were reported to be limited with mild to moderate gastrointestinal discomfort, elevated liver function tests (of which GVHD could be a cause) and muscle cramps. In 34 of 134 (25%) evaluable patients, greater than grade II (NCI/NIH common toxicity criteria) myelosuppression (anemia, thrombocytopenia and/or neutropenia) was observed. This was reported to be mostly reversible and responded to dose reduction.

Symptoms of chronic extensive or >II° acute GVHD were reported in five patients. In another three patients who experienced a grade III acute GVHD at start of imatinib mesylate no exacerbation was observed.

Twenty patients died due to refractory or progressive disease. Most of these patients were members of the high risk group.

Discussion

Imatinib is a selective tyrosine kinase inhibitor targeting bcr-abl, c-kit and PDGF-R kinases. Phase I and II clinical trials using this drug demonstrated a high rate of hematologic and cytogenetic remissions in bcr-abl positive leukemia without previous transplantation.[29]

The case report presented here and the preliminary analysis of single center experiences derived from abstracts presented at ASH 2001, EBMT 2001 & 2002, and papers published to date show encouraging results for patients with relapse of bcr-abl positive leukemia after allogeneic or syngeneic transplantation.[15–26]

Imatinib was well tolerated in most patients. Non-hematological adverse events grade $\leq$ II (as defined by NCI Common Toxicity Criteria) were frequently reported. Twenty-seven percent of the patients suffered >II myelosuppression, necessitating a dose reduction and/or interruption of imatinib. Severe hematological adverse events occurred more frequently in the high risk group suggesting that myelosuppression is primarily related to inadequate recovery of bcr-abl negative hematopoiesis. Induction of GVHD is expected in patients, in which donor chimerism was increasing. However, in most of the patients reported here, GVHD was not observed. Clinically significant GVHD (more than grade II of acute GVHD or chronic extensive GVHD) was described in only five patients. At the start of imatinib mesylate, three patients had grade III GVHD, but no exacerbation was reported.

Evaluable high risk patients experienced a hematologic response in approximately 61% of the cases and a cytogenetic response was noted in 52%. In the low risk population, hematologic and cytogenetic responses were noted in 100% and 46% of the evaluable patients, respectively. Complete cytogenetic responses were observed in 41% of all evaluable patients. The observation period was limited to a maximum of 28 months. In comparison, Druker and colleagues reported in their study a rate of 31% complete cytogenetic response in patients with CML in chronic phase.[29]

Complete cytogenetic response is an important predictor for survival in interferon therapy.[30] Its value for imatinib mesylate is so far incompletely understood. However, preliminary data, derived from phase II trials, predict a positive outcome in patients achieving a significant cytogenetic response.

However, 14 of 22 patients, despite achieving a major or complete hematologic or cytogenetic response, relapsed. All of these patients were in the high-risk group. This advocates for additional therapy using DLIs shortly after achievement of a maximal cytogenetic response to imatinib mesylate.

Real-time quantitative and qualitative (nested) PCR demonstrated a complete molecular remission in the patient depicted in Fig. 1, after introduction of DLI. Other groups also reported complete molecular responses (Table 1). However, different molecular evaluation procedures and interlaboratory variations make a comparison of results difficult. Two different systems are utilized frequently, namely Taqman and LightCycler technology.[28,31] Both systems allow quantification of minimal residual disease within a sensitivity of $1:10^4$. In addition, comparison of results from various laboratories is difficult, as sample and RNA preparation also influence the results.[32]

A significant improvement in donor chimerism was frequently observed without introducing or exacerbating GVHD (only reported in five patients). The patient depicted in Fig. 1 showed the appearance of normal bcr-abl negative recipient metaphases upon treatment with imatinib mesylate. This demonstrates survival of

recipient hematopoietic system cells despite myeloablative conditions (Fig. 1). No exacerbation of GVHD or aplasia was observed. Surprisingly, upon DLI therapy the proportion of the Ph-negative recipient cells was not significantly altered despite a documented achievement of PCR negativity for bcr-abl. Thus, the T-cell response derived from the donor apparently tolerates the Ph-negative recipient hematopoietic cells. This argues for a specific leukemia-associated antigen recognized specifically by donor immunity.

In summary, imatinib mesylate demonstrates a novel approach in treating relapsed Philadelphia positive leukemia after allogeneic SCT. Imatinib mesylate was generally well tolerated. The data presented here state that the most common side effects are mild and can easily be managed. However, frequent monitoring, especially for myelosuppression and hepatotoxicity, is required. Imatinib mesylate has the potential to positively influence the ratio of donor and recipient cells without inducing severe GVHD. The data presented suggests that earlier start of imatinib mesylate prior to hematologic relapse in a minimum residual disease situation is a promising treatment concept. Currently, a phase II clinical trial is in progress to prospectively evaluate this approach in terms of toxicity and efficacy.

References

1. Goldman JM, Druker BJ: Chronic myeloid leukemia: current treatment options. Blood 2001; 98: 2039–2042
2. Gratwohl A, Hermans J, Goldman JM, Arcese W, Carreras E, Devergie A, Frassoni F, Gahrton G, Kolb HJ, Niederwieser D, *et al*: Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 1998; 352: 1087–1092
3. Dazzi F, Szydlo RM, Goldman JM: Donor lymphocyte infusions for relapse of chronic myeloid leukemia after allogeneic stem cell transplant: where we now stand. Exp Hematol 1999; 27: 1477–1486
4. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N, Arcese W, Ljungman P, Ferrant A, Verdonck L, Niederwieser D, *et al*: Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Blood 1995; 86: 2041–2050
5. Roman J, Alvarez MA, Torres A: Molecular basis for therapeutic decisions in chronic myeloid leukemia patients after allogeneic bone marrow transplantation. Haematologica 2000; 85: 1072–1082
6. Collins RH Jr, Shpilberg O, Drobyski WR, Porter DL, Giralt S, Champlin R, Goodman SA, Wolff SN, Hu W, Verfaillie C, *et al*: Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 1997; 15: 433–444
7. Dazzi F, Szydlo RM, Craddock C, Cross NC, Kaeda J, Chase A, Olavarria E, van Rhee F, Kanfer E, Apperley JF, *et al*: Comparison of single-dose and escalating-dose regimens of donor lymphocyte infusion for relapse after allografting for chronic myeloid leukemia. Blood 2000; 95: 67–71
8. Mackinnon S, Papadopoulos EB, Carabasi MH, Reich L, Collins NH, Boulad F, Castro-Malaspina H, Childs BH, Gillio AP, Kernan NA, *et al*: Adoptive immunotherapy evaluating escalating doses of donor leukocytes for relapse of chronic myeloid leukemia after bone marrow transplantation: separation of graft-versus-leukemia responses from graft-versus-host disease. Blood 86: 1261–1268
9. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB: Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996; 2: 561–566
10. Gambacorti-Passerini C, le Coutre P, Mologni L, Fanelli M, Bertazzoli C, Marchesi E, Di Nicola M, Biondi A, Corneo GM, Belotti D, *et al*: Inhibition of the ABL kinase activity blocks the proliferation of BCR/ABL+ leukemic cells and induces apoptosis. Blood Cells Mol Dis 1997; 23: 380–394
11. le Coutre P, Mologni L, Cleris L, Marchesi E, Buchdunger E, Giardini R, Formelli F, Gambacorti-Passerini C: *In vivo* eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. J Natl Cancer Inst 1999; 91: 163–168
12. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Niederwieser D, Resta D, Capdeville R, Zoellner U, *et al*: Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002; 346: 645–652
13. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, Schiffer CA, Talpaz M, Guilhot F, Deininger MW, *et al*: Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002; 99: 3530–3539
14. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, Schiffer CA, Fischer T, Deininger MW, Lennard AL, *et al*: Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002; 99: 1928–1937
15. Kantarjian HM, O'Brien S, Cortes JE, Giralt SA, Rios MB, Shan J, Giles FJ, Thomas DA, Faderl S, De Lima M, *et al*: Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2002; 100: 1590–1595
16. Rodriguez R, Snyder D, Nademanee A, O'Donnell M, Krishnan A, Bhatia R, Slovak M, Resta D, Forman S: Gleevec for relapsed CML after allogeneic transplant may overcome need for donor leukocyte infusions (DLI) or interferon (IFN). Blood 2001; 98: abstract 1684
17. Au WY, Lie AK, Ma SK, Wan TS, Liang R, Chan EC, Kwong YL: Tyrosine kinase inhibitor STI571 in the treatment of Philadelphia chromosome-positive leukaemia failing myeloablative stem cell transplantation. Bone Marrow Transplant 2002; 30: 453–457
18. Chambon-Pautas, Cony-Makhoul P, Giraudier S, Vigier M, Michallet M, Guilhot F, Jouet JP, Berthaud P, Kuentz M: Glivec (STI571) Treatment for chronic myelogenous leukemia (CML) in relapse after allogeneic stem cell transplantation (SCT): a report of the French experience (on behalf of the SFGM and FILMC). Blood 2001; 98: abstract 587
19. Kantarjian HM, O'Brien S, Cortes J, Giralt S, Beth Rios M, Shan J, Giles F, Thomas D, Faderl S, de Lima M, *et al*: Results of imatinib mesylate (STI571) therapy in patients (pts) with chronic myelogenous leukemia (CML) in relapse after allogeneic stem cell transplantation (allo SCT). Blood 2001; 98: Abstract 575
20. Ottmann OG, Wassmann B, Pfeifer H, Scheuring U, Thiede C, Brueck P, Binckebank A, Atta J, Martin H, Gschaidmeier H, *et al*: Activity of the ABL-tyrosine kinase inhibitor glivec (STI571) in Philadelphia chromosome positive acute lympho-

blastic leukemia (PH+ALL) relapsing after allogeneic stem cell transplantation (allo-SCT). Blood 2001; 98: abstract 2470
21. Pfeifer H, Wassmann B, Scheuring U, Binckebanck A, Atta J, Brück P, Martin H, Bartmann M, Gschaidmeier H, Thiede C, *et al*: STI571 (Glivec) in the treatment of patients with chronic myeloid leukemia (CML) relapsing after allogeneic stem cell transplantation (allo SCT). Bone Marrow Transplantation 2002; 29 Supple 2: S34
22. Soiffer RJ, Galinsky I, DeAngelo D, Alyea EP, Antin JH, Restas D, Stone RM: Imatinib mesylate (Gleevec) for disease relapse following allogeneic bone marrow transplantation. Blood 2001; 98: abstract 1682
23. Ullmann AJ, Beck J, Kolbe K, Gschaidmeier H, Meinhardt PL, Huber C, Fischer T: Clinical and laboratory evaluation of patients treated with STI-571 (Gleevec^{TM}) after allogeneic and syngeneic stem cell transplantation with relapsed Philadelphia chromosome-positive leukemia. Blood 2001; 98: abstract 1685
24. Ullmann AJ, Beck J, Meinhardt P, Gschaidmeier H, Huber C, Fischer T: STI-571 in patients with relapsed Philadelphia chromosome-positive leukemia after allogeneic or syngeneic SCT. Bone Marrow Transplantation 2002; 27 Supple 1: P433
25. Wassmann B, Pfeifer H, Scheuring U, Brueck P, Binckebank A, Atta J, Martin H, Gschaidmeier H, Thiede C, Bornhauser M, *et al*: Glivec (STI571) in the treatment of patients with chronic myeloid leukemia (CML) relapsing in accelerated or blastic phase after allogeneic stem cell transplantation. Blood 2001; 98: abstract 588
26. Wassmann B, Pfeifer H, Scheuring U, Thiede C, Atta J, Klein SA, Martin H, Bartmann M, Gschaidmeier H, Brück P, *et al*: Efficacy of the ABL-tyrosine kinase inhibitor STI571 (Glivec) in Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+All) relapsing after allogeneic stem cell transplantation (Allo SCT). Bone Marrow Transplantation 2002; 29: Supple 2, S6
27. Hess G, Reifenrath C, Friedrich-Freksa A, Beyer V, Naumann S, Schuch B, Huber C, Fischer T, Decker HJ: Autologous transplantation of *in vivo* purged PBSC in CML: comparison of FISH, cytogenetics, and PCR detection of Philadelphia chromosome in leukapheresis products. Cancer Genet Cytogenet 2000; 117: 1–8
28. Preudhomme C, Revillion F, Merlat A, Hornez L, Roumier C, Duflos-Grardel N, Jouet JP, Cosson A, Peyrat JP, Fenaux P: Detection of BCR-ABL transcripts in chronic myeloid leukemia (CML) using a 'real time' quantitative RT-PCR assay. Leukemia 1999; 13: 957–964
29. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, *et al*: Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344: 1031–1037
30. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M: Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-alpha therapy. The Leukemia Service. Ann Intern Med 1995; 122: 254–261
31. Emig M, Saussele S, Wittor H, Weisser A, Reiter A, Willer A, Berger U, Hehlmann R, Cross NC, Hochhaus A: Accurate and rapid analysis of residual disease in patients with CML using specific fluorescent hybridization probes for real time quantitative RT-PCR. Leukemia 1999; 13: 1825–1832
32. Weisser A, La Rosée P, Burmeister T, *et al*: Sensitivity, quality and comparability of bcr-abl quantification by RT-PCR: results of an interlaboratory analysis. Blood 2001; 98: Abstract 1352