# Imatinib mesylate as treatment for blastic transformation of Philadelphia chromosome positive chronic myelogenous leukemia

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*Background and Objectives*. Imatinib mesylate (STI571) is a selective inhibitor of the bcr/abl tyrosine kinase with therapeutic potential in the blast crisis (BC) of chronic myelogenous leukemia (CML).

*Design and Methods*. We report the characteristics and clinical outcome of 30 patients [16 males and 14 females, median age 50 (range, 18 to 72) years] with CML in BC included in a phase II international multicenter extended trial of treatment with imatinib. The initially administered dose of imatinib was 600 mg orally once daily.

*Results*. Eighteen patients (60%) achieved a sustained hematologic remission (SHR) at a median time of 4 weeks (range, 2 –14) after starting therapy. The median duration of SHR was 5 months (range, 4 - 13). Four patients (13%) achieved a cytogenetic remission at a median time of 8 weeks (range, 6 – 10) after beginning imatinib therapy. The rates of event-free survival (EFS) and overall survival (OS) at 1 year were 29%±8% and 36%±13%, respectively. In univariate analysis, the achievement of a SHR was more frequent in patients without a complex karyotype and in those receiving imatinib without having had previous chemotherapy. A long interval between the diagnosis of BC and imatinib therapy (≥ 9.5 weeks) ($p$=0.0011), the presence of additional cytogenetic abnormalities ($p$=0.015), and extramedullary involvement ($p$=0.02) were associated with significantly shorter EFS. In contrast, longer OS was observed in patients treated with imatinib shortly after the diagnosis of BC ($p$=0.0003) and in those without additional cytogenetic abnormalities ($p$=0.0043). Multivariate analyses indicated that the time interval between the diagnosis of BC and the beginning of imatinib therapy was the only significant prognostic factor for both EFS and OS.

*Interpretation and Conclusions*. STI571 therapy produces a high percentage of SHR in patients with CML in BC; a minority of the patients also obtain some degree of cytogenetic response. Nevertheless, these responses are transient and additional therapy should be offered.

Key words: chronic myeloid leukemia, STI571, blast crisis.

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Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder characterized by a typical translocation between chromosomes 9 and 22. This translocation is named the Philadelphia chromosome (Ph) and leads to the production of the bcr/abl fusion protein p210. CML has different and subsequent clinical-biological pictures – an indolent or chronic phase, an accelerated phase and a blast crisis (BC).[1-3]

The development of a BC in CML carries an extremely poor prognosis.[4] There is no single standard therapy for patients with CML at this advanced stage of their disease. Treatment usually comprises combination chemotherapy regimens developed for acute leukemias, with the most common therapy being an anthracycline plus cytarabine. Allogeneic stem cell transplantation induces durable remissions in less than 10% of the patients and is usually associated with a high peri-transplant mortality from regimen-related toxicity.[5]

Imatinib (imatinib mesylate; formerly STI571; Gleevec©, Novartis Pharmaceuticals, Basel, Switzerland) is a potent and selective competitive inhibitor of the bcr/abl protein tyrosine kinase.[6,7] In an ascending-dose clinical phase I study, imatinib induced substantial and durable responses, with minimal toxicity, when used at daily doses of 300 mg or higher in nearly all patients with chronic-phase CML.[8] At daily doses of 300 mg to 1000 mg imatinib also induced hematologic responses in 21 of 38 patients with CML in BC.[9] No dose-limiting toxicity was observed in these studies showing that selective inhibition of bcr/abl tyrosine kinase could arrest the progression of CML, even in patients with BC. More recently, two large phase II clinical trials, one including 75 patients,[10] the other 260 patients,[11] of CML in BC confirmed that imatinib induced hematologic responses in 52% of the patients with 16% of them achieving a major cytogenetic remission. When compared with a historical control group treated with standard cytarabine combinations,[10] the group treated with imatinib at the MD Anderson Cancer Center was found to have fewer toxic restrictions, a higher response rate and a longer median survival. Imatinib was not demonstrated to prolong survival in a study by the Hammersmith group which analyzed factors having an impact on response to treatment and survival in 78 consecutive patients with CML in BC.[12] Taking into account the results from both studies, imatinib has recently received Federal and Drug Administration approval for the treatment of CML in BC. In this study we evaluated the efficacy and safety of imatinib, and the prognostic factors

affecting outcome in a group of 30 patients with CML in BC. These patients were treated in 4 Spanish institutions in the setting of a multicenter extended phase II trial (protocol code CSTI571 0115, Novartis Pharmaceuticals, Basel, Switzerland). These results have never been published before and will not be published by Novartis Pharmaceuticals.

## Design and Methods

### *Patients*

Patients were eligible for inclusion in this study if aged at least 18 years and suffering from Ph chromosome positive CML in myeloid or lymphoid BC. CML in BC was defined as there being ≥ 30% blasts in peripheral blood and/or bone marrow (BM); and/or extramedullary disease (other than liver or spleen enlargement). Diagnosis of the myeloid phenotype required myeloperoxidase positivity and was confirmed by flow cytometry showing myeloid markers and not more than one lymphoid marker. BC was considered of lymphoid origin if myeloperoxidase staining was negative and terminal deoxynucleotide transferase staining was positive in 40% or more blasts. BC was of undifferentiated origin if all stains were negative and immunophenotyping demonstrated the presence of myeloid markers (CD13 or CD33) in ≥ 20% cells or c-kit in ≥ 5% cells.

Patients were required to be free of significant liver or kidney disease. This means that levels of serum transaminases had not to be higher than 3 times the upper-normal limit in the absence of liver involvement by leukemia or 5 times if the latter was suspected. Absence of significant kidney disease was considered as a serum creatinine not higher than twice the upper normal limit. Women with childbearing potential were required to have a negative pregnancy test before starting therapy and both male and female patients were required to use barrier contraceptive measures throughout therapy with imatinib. Patients were excluded from the trial if they had an ECOG score ≥ 3, grade 3 or 4 cardiac disease, or any serious concomitant medical condition. The patients had to discontinue prior therapy before initiation of treatment with imatinib, with a minimal interval of six weeks for busulfan or hematopoietic stem cell transplantation, 48 hours for interferon-α, 24 hours for hydroxyurea, 7 days for low-dose cytarabine, 14 days for intermediate-dose cytarabine, 28 days for high-dose cytarabine, and 21 days for anthracycline or etoposide-containing therapies. No prior therapy with imatinib was allowed.

All patients gave written informed consent to their participation in the study and the study was approved by the Ethics Review Committee of each participating center.

### *Study design and treatment*

The study was an open-level, non-randomized, multicenter, phase II trial to evaluate the clinical efficacy of imatinib and the safety of the therapy. Enrolled patients received treatment with imatinib at daily oral doses of 600 mg for 48 weeks, with subsequent indefinite prolongation when the investigator judged that further therapy was of clinical benefit. Patients received continuous therapy unless adverse effects or disease progression occurred. Treatment was interrupted or reduced due to non-hematologic, hepatic, or hematologic toxicity, graded according to the WHO common toxicity criteria. In those patients requiring dose reduction, daily doses were reduced from 600 mg to 400 mg, or from 400 to 300 mg. If grade 2 non-hematologic toxicity occurred, therapy was interrupted until recovery to grade 1 or lower and then resumed at the original dose. If grade 2 toxicity recurred following treatment resumption, treatment was again interrupted until recovery and then resumed at a reduced dose. If grade 3 or 4 non-hematologic toxicity occurred, therapy was interrupted until recovery to grade 1 or lower and then resumed at a lower dose.

Treatment was not modified because of hematologic toxicity during the first 28 days. After this time, dose reductions were considered only for patients with grade 4 neutropenia (neutrophil counts< $0.5\times10^9$/L) or thrombocytopenia (platelets < $10\times10^9$/L) lasting at least 2 weeks. Decisions were based on marrow hypocellularity and disease status as determined by bone marrow biopsies done after a minimum of 28 days of therapy. In those patients with persistent marrow cellularity below 10% and blasts below 10%, the daily dose was reduced at 2-week intervals or the therapy interrupted until recovery of neutropenia to grade 2 or higher (neutrophil count > $1.0\times10^9$/L). On recovery, treatment was resumed at the full initial dose. Treatment was not interrupted or reduced for patients with marrow cellularity or blast values above 10%.

### *Evaluation of patients*

Patients were evaluated for hematologic and cytogenetic responses, and for relapse at specified intervals. Peripheral blood counts were obtained every week for the first three months and every two weeks thereafter. BM aspiration was performed at diagnosis and every three months. Extramedullary leukemic involvement was assessed by physical examination at baseline, every 4 weeks during therapy, and on the last day of treatment.

The primary efficacy end point of this study was sustained hematologic response (SHR) lasting at least 4 weeks, including both complete and partial hematologic responses. Complete hematologic response (CHR) was defined according to conven-

tional criteria as a blast cell count below 5% in BM with no circulating peripheral blast cells, a neutrophil count of at least $1.5\times10^9$/L, a platelet count of at least $100\times10^9$/L and no evidence of extramedullary involvement. Partial hematologic response (PHR) was defined as a blast cell count below 5% in the BM with no circulating peripheral blast cells but a neutrophil count of at least $1.0\times10^9$/L and/or a platelet count of $20\times10^9$/L with no need of platelet transfusions.

Secondary end points were the induction of a cytogenetic response, the duration of the hematologic response, overall survival (OS) and event-free survival (EFS). The cytogenetic response was based on the number of Ph-positive metaphases among 20 marrow metaphases analyzed. Response was defined as complete (0% Ph-positive metaphases), partial (1-35%), minor (36-65%), minimal (66-95%) or none (> 95%). Major cytogenetic response (MGR) included complete, partial and minor cytogenetic responses.

The duration of response was calculated from the date of response to the date of relapse or death. Duration of response was censored at the last examination date for patients with ongoing response or those who discontinued therapy for reasons other than adverse events, progression or death. OS was calculated from the initiation of imatinib therapy to the date of death. EFS was calculated from the date of achievement of a second chronic phase to death in second blastic phase.

### *Statistical analysis*

Comparisons between categorical variables were performed by means of the $\chi^2$ test. The following characteristics were analyzed for SHR and cytogenetic responses, EFS and OS: age (<50 years vs ≥ 50 years), duration of the CP (< 12 months vs ≥ 12 months), preceding accelerated phase (yes vs no), performance status (ECOG) (< 2 vs ≥ 2), blast immunophenotype (lymphoid vs myeloid), leukocyte (< $50\times10^9$/L vs ≥ $50\times10^9$/L) and platelet counts (< $100\times10^9$/L vs ≥ $100\times10^9$/L) at diagnosis, presence of circulating blast cells (< 50% vs ≥ 50%), blast infiltration in the BM (< 50% vs ≥ 50%), presence of additional chromosomal abnormalities, BM fibrosis, extramedullary involvement at presentation, time interval between the diagnosis of the BC and the beginning of imatinib therapy (< 9.5 weeks vs ≥ 9.5 weeks), prior therapy before imatinib (yes vs no) and imatinib dosage modification during treatment (yes vs no). As indicated above, all continuous variables were analyzed as categorical variables.

A multivariate analysis was also performed including the same clinical and biological baseline characteristics. All analyses were performed using the SPSS 7.5 package software. A *p* value lower than 0.05 was considered statistically significant.

**Table 1. Characteristics of the 30 patients at diagnosis of blast crisis.**

| *Characteristics* | *Median (range) n (%)* |
|---|---|
| Sex | |
| Male | 16 (53%) |
| Female | 14 (47%) |
| Age (years) | 50 (18-72) |
| Duration of CP (months) | 44 (0-168) |
| Previous AP | 9 (30%) |
| Duration of AP (months) | 4 (1-10) |
| ECOG at diagnosis of the BC | |
| 0-1 | 23 (77%) |
| 2-3 | 7 (23%) |
| Extramedullary involvement | 6 (20%) |
| Immunophenotype | |
| Myeloid | 24 (80%) |
| Lymphoid | 6 (20%) |
| Additional chromosomal abnormalities | 12 (40%) |
| Bone marrow fibrosis | 5 (17%) |
| Prior therapy (chemotherapy protocols) | 19 (63%) |

*CP: chronic phase; AP: accelerated phase; BC: blast crisis.*

## Results

### *Patients and treatment*

From October 2000 to January 2002, 30 patients [16 males and 14 females with a median age of 50 (range, 18 to 72) years] diagnosed as having CML in BC were treated with imatinib in 4 Spanish institutions [Hospital de la Santa Creu i Sant Pau, Barcelona (n=11); Hospital Clínico Universitario San Carlos, Madrid (n=10); Hospital La Fe, Valencia (n=8); Hospital Marqués de Valdecilla, Santander (n = 1)]. The main clinical characteristics of these patients are shown in Table 1.

All the patients had received treatment for CML before blast transformation. Nine patients had been treated with cytoreductive therapy using hydroxyurea or busulphan alone; the remaining 21 patients had received several lines of therapy including α-interferon in 17 of them (57%). Nine patients (30%) had had a previous accelerated phase with a median duration of 4 months (range, 1 to 10).

The immunophenotype was myeloid in 24 patients (80%) and lymphoid in the remaining six (20%). At diagnosis of BC, ECOG performance status was 0-1 in 23 patients and > 2 in 7 patients (23%). Ten patients (33%) presented with unex-

plained fever, 6 (20%) had bone pain and 8 patients (27%) experienced weight loss. Six patients (20%) had extramedullary involvement. The median size of the liver enlargement at diagnosis of BC was 2 cm below the right costal margin (range, 1 to 15) and that of the spleen was 4 cm (range, 1 to 25). The median peripheral blood leukocyte count was $15\times10^9$/L (range, 2-290) with a median percentage of blast cells of 15% (range, 0 to 75) in the peripheral blood and 41 % (range, 4 to 94) in the BM aspirate. BM biopsy demonstrated fibrosis in 5 patients (17%).

### *Efficacy*

The 30 patients are evaluable for hematologic response. All patients started therapy with imatinib at a daily dose of 600 mg. Eighteen patients achieved a SHR: ten patients (30%) a CHR, with a median response duration of 5 months (range 4-13) and eight patients achieved a PHR. Responses usually occurred soon after the start of treatment, after a median time of 4 weeks (range 2-14). Univariate analysis showed that age ≥ 50 years, presence of chromosome abnormalities in addition to the Ph chromosome, and use of chemotherapy to treat the BC prior to imatinib therapy were significant adverse prognostic factors for achieving a SHR (Table 2).

Four patients (13% of the series) achieved a cytogenetic remission (1 partial cytogenetic remission, 3 minor cytogenetic remissions). There were no complete cytogenetic remissions in the 30 patients. The median time to cytogenetic response was 8 weeks (range, 6 to 10) and the median duration of the cytogenetic response was 2 months (range, 0 to 2). All patients achieving a cytogenetic response were receiving a daily dose of 600 mg of imatinib at the time of the response.

The rates of event-free survival and OS for the whole series were, respectively, 29±8% and 36±13% at 1 year (Figures 1a and b). A long time interval between the diagnosis of BC and imatinib therapy (≥ 9.5 weeks), the presence of additional cytogenetic abnormalities and extramedullary involvement were significantly associated with a shorter EFS. Longer OS was observed in patients starting imatinib therapy shortly after the diagnosis of the BC (< 9.5 weeks) and in those without additional cytogenetic abnormalities (Table 2). The most important favorable prognostic factor for both EFS and OS was the achievement of a SHR (Figures 2A and 2B). Multivariate analyses indicated that a time interval ≥ 9.5 weeks between the diagnosis of BC and the beginning of imatinib therapy was the only significant prognostic factor for both EFS [relative risk (RR) 6.3, 95% confidence interval (CI) 0.85–46.94, $p = 0.05$] and OS [RR 16.24, 95% CI (2.02–130.55), $p = 0.009$] and that both additional cytogenetic abnormalities [RR 18.66, 95% CI (2.55–136.40), $p = 0.004$] and a long time interval between the diagnosis of the BC and the beginning of imatinib therapy [RR 28.57, 95% CI (1.21–166.66), $p = 0.035$] were bad prognostic factors for a SHR.

**Table 2. Univariate analysis of significant prognostic factors for sustained hematologic response, EFS and OS.**

| *Variable* | *Sustained hematologic response n (%)* | *p* |
|---|---|---|
| Age at diagnosis of BC | | |
| < 50 years (n = 15) | 6 (33) | 0.01 |
| ≥ 50 years (n = 15) | 12 (67) | |
| Cytogenetics | | |
| Ph+ (n=18) | 15 (83) | 0.001 |
| Complex karyotype (n=12) | 3 (25) | |
| Interval BC - imatinib therapy | | |
| < 9.5 weeks (n=15) | 13 (87) | 0.003 |
| ≥ 9.5 weeks (n=15) | 5 (33) | |

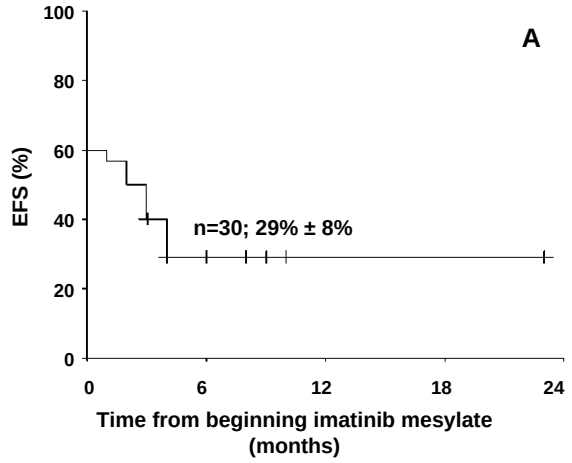
*Ph+: Philadelphia positive; BC: blast crisis.*

| *Variable* | *Event-free survival 1-year EFS (mean±SD)* | *p* |
|---|---|---|
| Cytogenetics | | |
| Ph+ (n=18) | 44±12% | 0.015 |
| Complex karyotype (n=12) | 8±8% | |
| Extramedullary involvement | | |
| Yes (n=6) | 0 | 0.02 |
| No (n=24) | 36±10% | |
| Interval BC - imatinib therapy | | |
| < 9.5 weeks (n=15) | 52±13% | 0.0011 |
| ≥ 9.5 weeks (n=15) | 0 | |

*Ph+: Philadelphia positive; BC: blast crisis; EFS: event-free survival; SD: standard deviation.*

| *Variable* | *Overall survival 1-year OS (mean±SD)* | *p* |
|---|---|---|
| Cytogenetics | | |
| Ph+ (n=18) | 57±18% | 0.0043 |
| Complex karyotype (n=12) | 0 | |
| Interval BC - imatinib therapy | | |
| < 9.5 weeks (n=15) | 93±7% | 0.0003 |
| ≥ 9.5 weeks (n=15) | 13±9% | |

*Ph+: Philadelphia positive; BC: blast crisis; OS: overall survival; SD: standard deviation.*



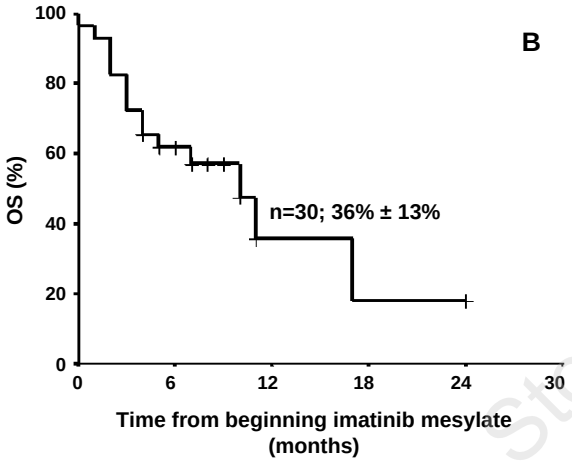
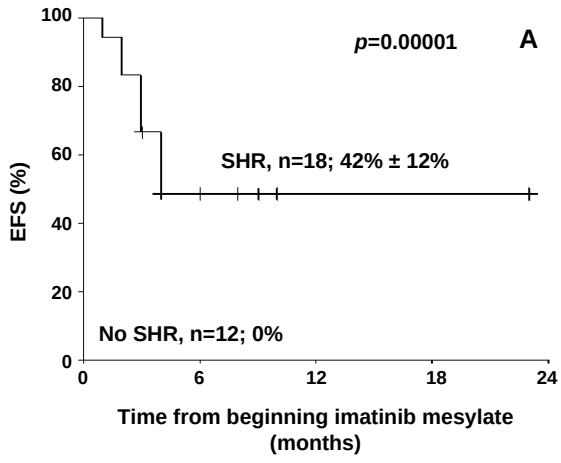




**Figure 1. Survival curves of the whole series. A. One-year event-free survival. B. Overall survival at 1 year.**



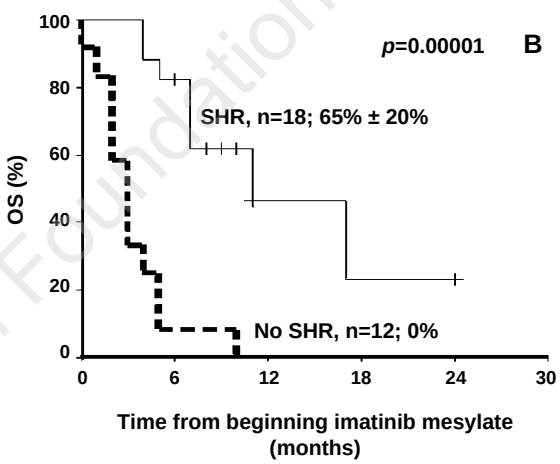




**Figure 2. Survival curves as a function of the hematologic response achieved with imatinib treatment. A. One-year event-free survival. B. Overall survival at 1 year.**



*Toxicity*

The most frequent grade 3-4 side effects were neutropenia (20%) and thrombocytopenia (20%) although these were difficult to separate from the pre-treatment degree of myelosuppression. One patient developed grade 3-4 nausea, 1 patient muscle cramps, 2 patients cutaneous toxicity [one patient developed a Steven-Johnson syndrome as previously described[13] and the other a pruriginous rash, both of them requiring discontinuation of imatinib therapy] and 2 patients liver toxicity (Table 3).

The dose of imatinib had to be reduced as per protocol in 13 patients (43% of the series) at a median time of 3 weeks (range, 2 to -16) after the start of the therapy. The dose reduction was necessary because of hematologic toxicity in 8 patients (27%), liver toxicity in 3 patients (10%) and cutaneous side effects in 2 patients (7%).

Imatinib mesylate was definitively discontinued in 17 patients (57%): in 10 patients (33%) because of grade 3-4 adverse events [hematologic toxicity in 5 patients (29%), liver toxicity in 2 patients (12%), cutaneous toxicity in 2 patients (12%) and gastrointestinal intolerance in one patient (6%)]. In the remaining 7 patients (24%), imatinib was stopped because of disease progression (n=4, 23%) or further therapy with allogeneic stem cell transplantation (n=3, 18%). The time elapsed between imatinib discontinuation and restarting treatment was 2 weeks (range, 0 to 8).

**Table 3. Imatinib toxicity using the WHO classification.**

| *Toxicity* | *NO n (%)* | *Grade 1-2 n (%)* | *Grade 3-4 n (%)* |
|---|---|---|---|
| Nausea | 20 (67 %) | 9 (30 %) | 1 (3 %) |
| Vomiting | 23 (77%) | 7 (23%) | No |
| Diarrhea | 23 (77 %) | 7 (23%) | No |
| Fluid retention | 18 (60%) | 12 (40%) | No |
| Musculoskeletal pain | 28 (94%) | 1 (3%) | 1 (3%) |
| Fatigue | 19 (63%) | 11 (37%) | No |
| Cutaneous lesions | 28 (94 %) | No | 2 (6 %) |
| Arthralgias | 26 (87%) | 4 (13%) | No |
| Liver toxicity | 24 (80%) | 4 (14%) | 2 (6%) |
| Hematologic | 3 (10%) | 20 (67%) | 7 (23%) |
| Leukopenia | 13 (43%) | 11 (37%) | 6 (20%) |
| Thrombocytopenia | 17 (57%) | 7 (23%) | 6 (20%) |

## Discussion

The prognosis of patients with CML in BC is considered extremely poor when these patients are treated with conventional chemotherapy. The recent introduction of imatinib mesylate has opened the possibility of improving the long-term outcome of this subgroup of patients.

In our series of 30 patients with CML in BC uniformly treated with imatinib mesylate, we observed a 60% incidence of SHR and a 13% incidence of minor cytogenetic responses with acceptable hematologic and extra-hematologic toxicities. Responses were quick but of short duration. Kantarjian *et al*.[10] and Sawyers[11] reported an incidence of SHR of about 30%, with 16% of the patients achieving a major cytogenetic remission in larger cohorts of patients. In both studies, clinical results in terms of hematologic and cytogenetic responses were better in patients who received higher doses of imatinib. All the patients from our trial received the same dose of 600 mg daily. As Kantarjian indicated in his report on 75 patients, the objective response rate with imatinib mesylate seemed to be significantly higher than that achieved in historical controls who received cytarabine-based chemotherapy.[10] In univariate analysis, two prognostic factors had a significant impact on the probability of achieving a hematologic response: the absence of additional cytogenetic abnormalities and a short time interval between the diagnosis of the BC and initiation of imatinib therapy. It seems reasonable to consider that imatinib therapy could be more effective in patients with no clonal evolution, as indicated by the absence of additional cytogenetic abnormalities. In this sense, Lahaye *et al*.[14] analyzed the prognostic impact of immunophenotype, karyotypic evolution and type of bcr-abl fusion transcript in a group of 59 patients with CML in myeloid BC. In this study, the presence of an additional Ph chromosome was also associated with a lower probability of achieving a hematologic response and with a shorter survival.

The 1-year EFS and OS rates of 29%±8% and 36%±13%, respectively, reported here, compare favorably with those found in previous studies.[10,11] Both the presence of a complex karyotype and a long time interval between the diagnosis of the BC and the institution of imatinib therapy significantly worsened OS and EFS in our series. Extramedullary involvement was also a significant prognostic factor for EFS. The prognostic impact of the karyotype had been indicated by two phase II prospective studies[10,11] and by the work of Lahaye *et al*.:[14] patients with additional cytogenetic abnormalities always fared worse than those with the Ph chromosome only. In contrast to other researchers,[10] we did not find that platelet counts, leukocyte counts or percentage of circulating blast cells had a prognostic significance in our series.[10] This was probably because of the low number of patients included in our analysis. Despite this, the presence of extramedullary disease at diagnosis, a surrogate marker for tumor burden, was an adverse prognostic factor for EFS.

Of note, patients with a SHR benefited most from imatinib therapy. In our series, 65% of patients achieving a SHR were still alive at 1 year, whereas none of patients not achieving a SHR was alive at 1 year. With respect to EFS at 1 year, the numbers were 48% in patients achieving a SHR vs 0% in patients without hematologic response. Comparable results have also been observed by other authors; Sawyers reported a median survival of 19 months for patients achieving a sustained response after imatinib therapy versus 6 and 3 months for

patients with unsustained response or no response during therapy, respectively.[11] Likewise, in the Houston analysis, survival was significantly better among responding patients: the median survival was 9 months in patients responding and 5 months in patients with no response.[10]

Imatinib therapy was associated with numerous although manageable side effects, but this was expected because advanced CML is associated with considerable morbidity. Most of the non-hematologic adverse events that appeared to be drug related (fluid retention, gastrointestinal toxicity) were seldom severe and rarely required discontinuation of treatment. Of note, one patient with a myeloid BC developed a rapidly progressing Stevens-Johnson syndrome needing intravenous fluid therapy, high-dose corticosteroids and discontinuation of the drug.[13] Severe cytopenias were frequent and constituted the main cause for drug discontinuation (13 patients, 43% of the series). Most cytopenias were probably due to the direct pharmacological effect of imatinib on leukemic cells and the poor normal BM reserve in patients with blast-phase disease. Despite this, cytopenias do not necessarily compel withdrawal of imatinib or dose reduction since continuation of therapy may be desirable in some patients. From all the above, it may be concluded that imatinib is relatively well tolerated by patients with CML in BC, although the incidence of deleterious effects is higher in this group of patients than in those treated in chronic or in accelerated phase.[15]

Mechanisms of resistance to imatinib which are probably responsible for the transient responses observed in this subset of patients remain to be fully elucidated. Plausible mechanisms of resistance are postulated to involve drug efflux, amplification of the bcr-abl fusion gene or increased expression of the bcr-abl protein, or decreased cellular bioavailability of imatinib.[16-19] Amplification and mutations of the bcr-abl gene have been demonstrated in samples from patients;[20,21] nevertheless, further studies are needed to fully clarify the clinical relevance of all these mechanisms.

In conclusion, imatinib mesylate is an active agent, leading to rapid hematologic control in a significant proportion of patients with CML in BC, with a relatively safe profile. Nevertheless, only a minority of patients respond durably to imatinib and major cytogenetic responses are infrequent. For this reason, the use of imatinib in this setting should be explored in the context of combinations with other investigational agents.[22,23] Imatinib also seems to be useful for achieving short-term disease control with minimal side effects in patients who are candidates for a subsequent allogeneic stem cell transplantation.

## References


1. Kantarjian HM, Deisseroth A, Kurzrock R, Estrov Z, Talpaz M. Chronic myelogenous leukemia: a concise update. Blood 1993;82:691-703.
2. Kantarjian HM, O'Brien S, Anderlini P, Talpaz M. Treatment of chronic myelogenous leukemia: current status and investigational options. Blood 1996; 87:3069-81.
3. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med 1999;131:207-19.
4. Sacchi S, Kantarjian HM, O'Brien S, Cortes J, Rios MB, Giles FJ, et al. Chronic myelogenous leukemia in nonlymphoid blastic phase. Analysis of the results of first salvage therapy with three different treatment approaches for 162 patients. Cancer 1999;86:2632-41.
5. Horowitz MM, Rowlings PA, Passweg JR. Allogeneic bone marrow transplantation for CML: a report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1996;17:S5-S6.
6. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561-6.
7. Beran M, Cao X, Estrov Z, Jeha S, Jin G, O'Brien S, et al. Selective inhibition of cell proliferation and BCR-ABL phosphorylation in acute lymphoblastic leukemia cells expressing Mr 190,000 BCR-ABL protein by a tyrosine kinase inhibitor (CGP-57184). Clin Cancer Res 1998;4:1661-72.
8. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.
9. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
10. Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood 2002; 99:3547-53.
11. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, 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;99:3530-9.
12. Wadhwa J, Szydlo RM, Apperley JF, Chase A, Bua M, Marin D, et al. Factors affecting duration of survival after onset of blastic transformation of chronic myeloid leukemia. Blood 2002;99:2304-9.
13. Vidal D, Puig L, Sureda A, Alomar A. STI571-induced Stevens-Johnson syndrome. Br J Haematol 2002;119:274-5.
14. Lahaye T, Kreil S, Schoch C. Prognostic impact of immunophenotype, karyotypic evolution, and type of BCR-ABL fusion transcripts in patients with myeloid blast crisis treated with STI571 (Glivec). Blood 2001;98:138a[abstract 580].
15. Tsao AS, Kantarjian H, Talpaz M. STI-571 in chronic myelogenous leukaemia. Br J Haematol 2002;119:15-24.
16. le Coutre P, Tassi E, Varella-Garcia M, Barni R, Mologni L, Cabrita G, et al. Induction of resístance to the Abelson inhibitor STI571 in human leukemic cells through gene amplification. Blood 2000;95:1758-66.
17. Weisber E, Griffin JD. Mechanism of resistance to the ABL tyrosine kinase inhibitor STI571 in BCR/ABL-transformed hematopoietic cells. Blood 2000;95:3498-505.
18. Mahon FX, Deininger MW, Schultheis B, Chabrol J, Reiffers J, Goldman JM, et al. Selection and characterization of BCR-ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. Blood 2000;96:1070-9.
19. Gambacorti-Passerini C, Barni R, le Coutre P, Zucchetti M, Cabrita G, Cleris L, et al. Role of a 1 acid glycoprotein in the in vivo resistance of human BCR-ABL + leukemic cells to

the abl inhibitor STI571. J Natl Cancer Inst 2000;92:1641-50.
20. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001;293:876-80.
21. Barthe C, Cony-Makhoul P, Melo JV. Roots of clinical resistance to STI-571 cancer therapy. Science 2001; 293: [abstract 2163].
22. Peters DG, Hoover RR, Gerlach MJ, Koh EY, Zhang H, Choe K, et al. Activity of the farnesyl protein transferase inhibitor SCH66336 against BCR/ABL-induced murine leukemia and primary cells from patients with chronic myeloid leukemia. Blood 2001;97:1404-12.
23. Porosnicu M, Nimmanapalli R, Nguyen D, Worthington E, Perkins C, Bhaila KN. Co-treatment with $As_3O_2$ enhances selective cytotoxic effects on STI-571 against Bcr-Abl positive acute leukemia cells. Leukemia 2001;15:772-8.

## Pre-publication Report & Outcomes of Peer Review

*Contributions*

AS was responsible for the care of patients in her institution, designed the study, contributed to the data analysis along with MC and revised the final version of the manuscript. MC was responsible for the data analysis and wrote the first version of the manuscript. MM, JAM, EC, MAS, JDM were the physicians responsible for the patients' care and development of the protocol in their institutions, contributed the patients' data and also revised the final version of the manuscript. JS is the head of the Division where the analysis and design of the manuscript were carried out and contributed to the final version of the paper. Primary responsibility for the paper: AS; primary responsibility for Tables 1-3: AS, MC; primary responsibility for Figures 1-2: AS.

*Disclosures*

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

*Manuscript processing*

This manuscript was peer-reviewed by two external referees and by Dr. Michael E. O'Dwyer, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. O'Dwyer and the Editors. Manuscript received February 26, 2003; accepted October 1, 2003.

In the following paragraphs, Dr. O'Dwyer summarizes the peer-review process and its outcomes.

*What is already known on this topic*

The disappointingly short responses of most patients with blastic transformation of CML is well documented. It is generally accepted that monotherapy with imatinib needs to be improved upon.

*What this study adds*

This study confirms previous observations and reminds us that early treatment with achievement of a sustained hematologic response is desirable but is less likely in the presence of cytogenetic clonal evolution. Unfortunately, this applies to a minority of patients.

*Caveats*

This is a relatively small group of patients with a short follow-up.