

Prognostic factors for patients with chronic myeloid leukaemia in chronic phase treated with imatinib mesylate after failure of interferon alfa

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We assessed clinical results in 145 patients with chronic myeloid leukaemia in chronic phase who satisfied criteria for interferon- α failure and were thus eligible for treatment with imatinib at the Hammersmith Hospital. We used univariate and multivariate analyses to develop a risk score based on features defined after treatment for 3 months. We identified a low neutrophil count and poor cytogenetic response (<35% Ph-negative marrow metaphases) at 3 months as principal independent predictive factors and incorporated them into a three-tier prognostic scoring system for individual patients. For patients in the low-, intermediate- and high-risk groups, the probabilities of survival at 24 months were 100, 82 and 40% ($P < 0.0001$) and progression-free survival 100, 66 and 15% ($P < 0.0001$), respectively. This Hammersmith prognostic scoring system was validated with an independent cohort of patients treated at another UK centre.

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Introduction

Chronic myeloid leukaemia (CML) is a clonal haematological malignancy that results from transformation of a multipotent haematopoietic stem cell.¹ This transformation is believed to be due to the constitutive activation of the kinase component of the BCR-ABL oncoprotein present in the leukaemia cells from >95% of patients with CML. Typically, CML is diagnosed while still in a readily defined *chronic phase* (CP) that can usually be controlled with ease for some years. Invariably, the disease progresses eventually to a more advanced phase which is usually subclassified as either *accelerated phase* or *blastic transformation*; the latter phase is especially resistant to therapy and leads to death within 6–8 months.² Allogeneic stem cell transplant is the only therapy that can cure CML, but age and lack of a suitable donor limit this procedure to a minority of patients.³ Interferon- α (IFN α) has until recently been the gold standard for treating patients who are not candidates for transplant. With IFN α therapy the best survival is seen in patients who achieve complete cytogenetic response (CCR)⁴ and thus achievement of CCR has been one of the main targets of treatment in CML and can be considered as a surrogate marker for survival.⁴

Imatinib mesylate, a synthetic ATP analogue, occupies the ATP-binding site of the ABL tyrosine kinase component of the BCR-ABL oncoprotein and maintains it in an inactive conformation.^{5,6} It is given orally, is well tolerated, and has a manageable side-effect profile. Preliminary results from phase II and III trials suggest that CCR can be obtained in a proportion of patients in all phases of the disease.^{7,8} In the ongoing phase III study

involving previously untreated patients in chronic phase, progression-free survival (PFS) is significantly better for patients treated initially with imatinib compared with the combination of IFN α and cytarabine.⁹ We have treated with imatinib a series of patients with CML in chronic phase who were resistant to or intolerant of IFN α . We have tried to identify those patients most likely to benefit from continuing imatinib therapy by constructing a scoring system based on criteria defined after 3 months of treatment. The system has been validated with an independent cohort of patients.

Patients and methods

Patients

Between January 2000 and January 2003, 145 patients with CML in chronic phase who had failed IFN α (defined as refractory to or intolerant of IFN α ¹⁰) were treated with imatinib (previously STI571, Glivec[®]) at the Hammersmith Hospital as part of various multicentre phase II clinical studies. Written informed consent was obtained from all patients before enrolment. Blood samples were taken for analysis weekly for the first 6 weeks and then at monthly intervals. Bone marrow samples for morphology and cytogenetics were taken at baseline and thereafter at 3-month intervals.

The characteristics of the patients were typical of those with IFN α -treated 'late' chronic phase (Table 1). The median interval from diagnosis to starting imatinib was 4.2 years. The median follow-up after starting imatinib was 734 days; 98% of the patients were followed for at least 365 days. Imatinib was administered as described by others.^{7,10} Briefly, a single oral dose of 200–800 mg daily was given according to tolerance and response. Doses were reduced in the presence of grades III–IV thrombocytopenia or neutropenia or if there was grades II–IV nonhaematological toxicity; wherever possible doses were maintained above 300 mg/day. If a patient failed to achieve or lost a complete haematological response or a CCR, the dose of imatinib was increased in 200 mg steps to a maximum of 800 mg daily.

Definitions of disease phase and cytogenetic response

Chronic phase was defined as fulfilling all the following criteria: (a) peripheral and marrow blasts both less than 15%, (b) peripheral or marrow blasts plus promyelocytes less than 30%, (c) peripheral or marrow basophils less than 20%, and (d) platelets greater than $100 \times 10^9/l$.^{7,10} Disease progression was defined as progression to advanced phase (accelerated phase or blastic transformation as defined by Kantarjian *et al.*^{8,10,11} Clonal evolution alone (ie the presence of any new cytogenetic abnormality) in the absence of features of advanced phase was not considered evidence of disease progression.^{7,10} Cytogenetic

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Table 1 Pre-imatinib therapy characteristics of the patients (*n*=145)

Variable	
Age (year)	
Median, (range)	53 (17–76)
>65 year, no. (%)	25 (17.2)
Gender M/F (%)	47/53
Time from diagnosis (year)	
Median (range)	4.2 (0.35–17.9)
Autologous SCT, no. (%)	20 (13.8)
Sokal score ^a	
Low risk, no. (%)	40 (31.0)
Intermediate risk, no. (%)	44 (34.1)
High risk, no. (%)	45 (34.9)
Hasford score ^b	
Low risk, no. (%)	36 (37.1)
Intermediate risk, no. (%)	39 (40.2)
High risk, no. (%)	22 (22.7)
Spleen >5 cm, no. (%)	12 (8.3)
Additional cytogenetic abnormalities, no. (%) ^c	31 (21.8)
Ph-positive metaphases, no. (%) ^c	
1–35	2 (1.4)
36–65	4 (2.8)
66–95	7 (4.8)
96–99	7 (4.8)
100	122 (84.1)
IFN α therapy (year)	
Median (range)	1.6 (0.12–12.6)
Response to IFN α	
Haematological resistance, no. (%)	39 (26.9)
Cytogenetic resistance, no. (%)	77 (53.1)
Intolerant, no. (%)	29 (20)
Peripheral blood (median, range)	
Leucocyte count ($\times 10^9/l$)	8.7 (2.5–110)
Haemoglobin (g/dl)	12.1 (7.1–18)
Haemoglobin <10.0 g/dl, no. (%)	28 (19.3)
Platelets ($\times 10^9/l$)	253 (110–1970)
Basophils (%)	0 (0–12)
Blasts (%)	0 (0–12)
Bone marrow (median, range)	
Blasts (%)	4 (0–14)
Blasts >5%, no. (%)	46 (31.7)
Blasts + promyelocytes (%)	12 (1–29)
Basophils (%)	1 (0–15)

^aData to calculate the Sokal *et al*¹² score were available for 129 patients.

^bData to calculate the Hasford¹³ score were available for 97 patients.

^cData were missing for three patients.

responses were classified in accordance with standard UK Medical Research Council practice: *complete response* was defined by the absence of detectable Philadelphia metaphases; *major, partial* and *minor responses* were defined as decreases in the proportion of Philadelphia-positive metaphases to between 1 and 34%, between 35 and 65% and between 66 and 95%, respectively.

Statistical methods

Probabilities of survival and PFS were calculated using the Kaplan–Meier method. The probability of achieving a CCR was calculated using the cumulative incidence procedure, where CCR was the event of interest, and death or disease progression

were the competitors. Potential prognostic factors for all outcome variables were examined using the log-rank test (Table 1). Pretreatment variables found to be significant at the $P < 0.20$ level (Table 2) were entered into a proportional hazards regression analysis, and a forward stepping procedure was employed to find the best model. For survival and PFS after 3 months of treatment with imatinib, potential prognostic factors were examined as above (Table 3). Variables found to be significant at the $P < 0.20$ level were entered together with significant pretreatment factors into a second multivariate analysis. P -values of 0.05 or lower were considered significant. The proportional-hazards assumption was confirmed using log cumulative hazard plots. P -values are two-sided and confidence intervals (CI) refer to 95% boundaries.

Prognostic score

A prognostic score was constructed by combining (as described below and in Table 4) the independent predictors for PFS. The prognostic score was based on PFS because our objective was the early detection of patients who would not obtain benefit from imatinib, which would allow prompt intervention with alternative therapy. Data from 69 consecutive patients with CML in chronic phase resistant to or intolerant of IFN α treated with imatinib in the same Novartis protocols at the Royal Victoria Infirmary in Newcastle, UK were analysed subsequently in order to validate the score.

Results

Survival

During follow-up, 27 (18.6%) of the 145 patients treated at the Hammersmith Hospital died. The probabilities of survival at 12 and 24 months were 87.3% (CI 92.3–79.7%) and 63.4% (CI 78.0–55.8%), respectively. Table 2 shows the results of the univariate analysis based on pretreatment prognostic factors. In the subsequent multivariate analysis, haemoglobin <10.0 g/dl (RR = 3.6, CI 1.6–8.1), bone marrow blast cells >5% (RR = 4.2, CI 2.5–13.7) and clonal evolution (RR = 4.8, CI 2.1–11.1) proved to be independent poor prognostic factors. At 3 months, 140 patients remained in the study (four patients had died and one was lost to follow-up). Table 3 shows the results of the univariate landmark analysis performed at 3 months. A second multivariate analysis was performed that considered both pretreatment variables and variables identified after 3 months of imatinib therapy. Three factors remained as independent predictors, namely the lowest absolute neutrophil count achieved between days 45 and 90 of therapy ($<1.0 \times 10^9/l$, RR = 3.9, CI 1.7–8.9), failure to achieve at least partial cytogenetic response (RR = 12.1, CI = 3.4–22.7), and the presence pre-imatinib of clonal evolution (RR = 3.8, CI 1.4–10.3).

Progression-free survival

During follow-up, 44 (30.3%) patients progressed to accelerated phase or blastic transformation. The probabilities of PFS at 12 and 24 months were 75.3% (CI 68–83%) and 52.1% (CI 47–60%), respectively. As in the analysis for survival, haemoglobin <10 g/dl (RR = 3.8, CI 2.0–8.0), blasts in bone marrow >5% (RR = 5.7, CI 2.6–10.0) and presence of pretreatment clonal evolution (RR = 1.9, CI 1.1–5.1) were independently associated

Table 2 Probabilities of survival, PFS and achieving CCR at 24 months for pretherapy factors found to be significant in univariate analyses

Variable	No.	Survival (%)	PFS (%)	CCR (%)
<i>Sokal risk group</i>		<i>P=0.001</i>	<i>P=0.004</i>	<i>P=0.01</i>
Low risk	40	92	82	59
Intermediate risk	44	88	65	31
High risk	45	52	50	18
<i>IFNα response</i>		<i>P=0.0002</i>	<i>P=0.0003</i>	<i>P=0.0004</i>
Haematological resistance	39	48	20	3
Cytogenetic resistance	69	94	73	45
Intolerant	37	81	53	28
<i>Palpable spleen</i>		<i>P=0.001</i>	<i>P=0.0001</i>	<i>P=0.01</i>
Yes	27	51	33	4
No	118	78	68	38
<i>Percentage of Ph-pos marrow metaphases</i>		<i>P=0.06</i>	<i>P=0.02</i>	<i>P<0.0001</i>
1–99%	20	100	95	80
100%	122	68	49	21
<i>Clonal evolution</i>		<i>P<0.0001</i>	<i>P<0.0001</i>	<i>P=0.41</i>
Yes	31	32	28	24
No	111	81	71	33
<i>Percentage of bone marrow blasts</i>		<i>P<0.0001</i>	<i>P=0.0001</i>	<i>P=0.1</i>
$\leq 5\%$	99	84	64	39
$>5\%$	46	28	25	22
<i>Percentage of peripheral blood blasts</i>		<i>P=0.003</i>	<i>P=0.0008</i>	<i>P=0.01</i>
0%	116	86	66	37
$>0\%$	29	54	20	5
<i>Haemoglobin</i>		<i>P<0.0001</i>	<i>P=0.0001</i>	<i>P=0.05</i>
<10.0 g/dl	117	81	61	37
≥ 10.0 g/dl	28	39	27	12
<i>Platelet count</i>		<i>P=0.01</i>	<i>P=0.0008</i>	<i>P=0.03</i>
$\leq 400 \times 10^9/l$	97	79	73	37
$>400 \times 10^9/l$	48	60	30	14

The following factors were also entered into the univariate analysis but failed to achieve statistical significance: age (≥ 65 vs <65), gender, interval from diagnosis of CML to starting imatinib (<1 year vs 1–3 years vs >3 years), duration of IFN α therapy (<2 vs ≥ 2 years), prior autologous stem cell transplant, percentage of bone marrow promyelocytes (≤ 8 vs >8), percentage of bone marrow basophils (≤ 1 vs >1), peripheral blood leucocyte count (≤ 10 vs $>10 \times 10^9/l$), percentage peripheral blood promyelocytes (≤ 1 vs >1), percentage of peripheral blood basophils (≤ 1 vs >1), serum lactic dehydrogenase (normal vs elevated).

with poor outcome (Table 2). At 3 months, 132 (91%) patients remained in chronic phase. Table 3 shows the result of the univariate landmark analysis performed at 3 months. In the second multivariate analysis with pretreatment and 3 months post-treatment factors, only the absolute neutrophil count $<1.0 \times 10^9/l$ (RR 4.2, CI 2.4–8.8), and failure to achieve at least partial cytogenetic response (RR = 15.9, CI 4.2–31.3) remained as independent predictors. The prognostic value of imatinib dose intensity was investigated extensively, but we failed to find any significant relation between imatinib dose intensity and either survival or PFS.

Cytogenetic response

Of the 145 patients, 42 (29%) achieved a CCR and 27 (19%) a major cytogenetic response (MCR). Eight patients lost their CCR (19%) and six lost their MCR (22%) during follow-up. Of the 42 patients who achieved CCR, 29 (70%) achieved this by 6 months and 36 (86%) by 12 months. A similar pattern was seen with MCR. Table 3 shows the pretherapy variables found to

be predictive for CCR in the univariate analysis. Two variables remained independent in the multivariate analysis: previous response to IFN α (cytogenetically resistant, RR = 1; intolerant RR = 0.66, CI 0.19–0.90; haematologically resistant, RR = 0.07, CI 0.008–0.48) and the presence of Ph-negative metaphases prior to imatinib therapy (RR = 5.3; CI 2.6–8.7). Interestingly, the persistence of any degree of residual Ph-negative haematopoiesis at the time of starting imatinib strongly predicted that CCR would be achieved.

Within our study population, the degree of cytogenetic response to IFN α was documented in the 96 patients who were neither intolerant to IFN α nor primarily haematologically resistant (irrespective of their eventual loss of response or development of haematological resistance). Of these, 39 (41%) on IFN α achieved at least a minor cytogenetic response and 57 (59%) remained $>95\%$ Ph-positive. Patients with at least a minor cytogenetic response on IFN α were more likely to achieve CCR on imatinib than those who had not had any cytogenetic response to IFN α , with estimated probabilities at 24 months of 88.2% (CI 61.6–97.2%) and 27.1% (CI 13.7–46.4%), respectively ($P<0.0001$).

Table 3 The 3-month landmark analysis for survival and PFS at 24 months – results of univariate analysis

Variable	N=140	Survival (%)	N=132	PFS (%)
<i>Percentage of bone marrow blasts</i>				
≤5%	107	84	107	68
>5%	21	58	14	59
<i>Trephine cellularity</i>				
≤60%	93	87	92	67
>60%	38	56	34	26
<i>Absolute neutrophil count</i>				
<1.0 × 10 ⁹ /l	52	43	48	P<0.0001
≥1.0 × 10 ⁹ /l	88	92	84	25 72
<i>Platelet count</i>				
≤400 × 10 ⁹ /l	125	83	119	P=0.07
>400 × 10 ⁹ /l	15	48	13	58 45
<i>Ph-positive marrow metaphases</i>				
0–65%	52	96	52	P<0.0001
66–100%	88	52	71	83 32

The following factors were also entered into the univariate analysis but failed to achieve significance: spleen size (not palpable vs palpable), percentage of bone marrow promyelocytes (≤8 vs >8), percentage of bone marrow basophils (≤1 vs >1), blood leucocyte count (≤10 vs >10 × 10⁹/l), haemoglobin (<10 vs ≥10 g/dl), percentage of peripheral blood blasts (≤1 vs >1), percentage of peripheral blood promyelocytes (≤1 vs >1), percentage of peripheral blood basophils (≤1 vs >1), serum lactic dehydrogenase (normal vs elevated). Imatinib dose intensity during the first 90 days and imatinib dose intensity during days 45–90 were treated as a continuous variable, and were also considered as <200 vs ≥200 mg/day, <300 vs ≥300 mg/day, <350 vs ≥350 and <400 vs ≥400 mg/day.

Prognostic score

A prognostic score was constructed by combining the two independent predictors for PFS defined at 3 months (Table 4), namely the absolute neutrophil count and the cytogenetic response. A patient scored one point if they failed to obtain at least a partial cytogenetic response; a patient also scored one point if they sustained neutropenia defined as an absolute neutrophil count <1.0 × 10⁹/l between days 45 and 90 of therapy. The points were added to give a total between 0 and 2. Thus, the low-risk (*n* = 43, 35%), the intermediate-risk (*n* = 44, 36%) and high-risk (*n* = 36, 29%) groups comprised patients with 0, 1 or 2 points, respectively. At 24 months, the probabilities according to risk groups were for survival 100, 82% (CI 70–90%) and 40% (CI 25–58%) (*P* < 0.0001), and for PFS were 100, 66% (CI 54–77%) and 15% (CI 6–33%) (*P* < 0.0001) (Figures 1 and 2).

Validation of score

The score was applied to an independent cohort of 69 patients treated in Newcastle. In all, 29 patients were allocated to the low-risk group, 26 to the intermediate and 14 to the high-risk group. Table 5 shows the features of patients treated in the validation sample. Features were typical of patients in late-chronic phase, but not identical to the Hammersmith cohort. Sokal and Hasford scores were not available for the validation sample. The results obtained for the validation subset were very similar to those for the corresponding risk groups in the original population. The low-, intermediate- and high-risk groups had probabilities of survival at 18 months of 100, 91, and 41% (*P* < 0.0001) and of PFS of 100, 80 and 33%, respectively and (*P* < 0.0001).

Table 4 A prognostic score was constructed by combining the two independent predictors for PFS defined at 3 months

	<1 × 10 ⁹ neutrophils/l	≥65% Ph-positive
Low risk	No	No
Intermediate risk	No Yes	Yes No
High risk	Yes	Yes

A patient scored one point if they failed to obtain at least a partial cytogenetic response; a patient also scored one point if they sustained neutropenia defined as an absolute neutrophil count <1.0 × 10⁹/l between days 45 and 90 of therapy. The points were added to give a total between 0 and 2 defining the three groups: low risk 0 points, intermediate risk, 1 point, and high risk 2 points, respectively.

Discussion

Many attempts have been made in the last 20 years to define clinical factors assessed at the time of diagnosis that may predict survival for individual patients with CML. For example, Sokal *et al*¹² identified factors that allow them to classify patients treated predominantly with busulphan into three prognostic groups and Hasford *et al*¹³ performed a similar analysis in patients treated predominantly with IFNα. To ascertain whether the same or similar factors predict for duration of survival in patients treated with imatinib, we used univariate and multivariate analyses to study patients who had been treated for varying periods of time with IFNα and had then switched to imatinib. We sought factors assessed before start of treatment and after 3 months of treatment with imatinib that would predict disease progression. We showed that the failure to achieve at

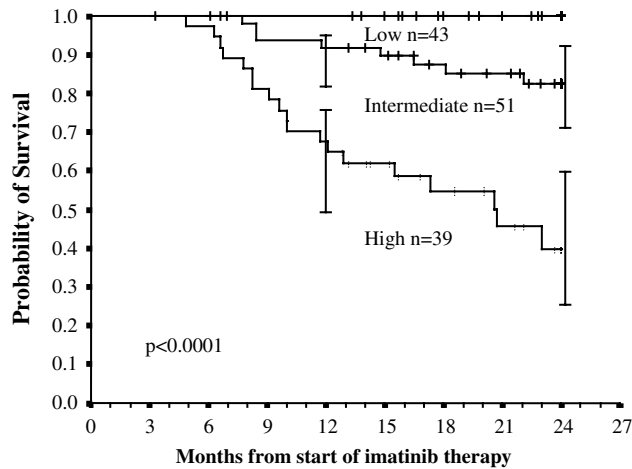


Figure 1 Survival according to prognostic group. The prognostic score was calculated (see text) for the 131 patients who were alive at 3 months and who had complete data. The probability of survival at 2 years was 100% for the low-risk group, 82% (CI 70–90%) for the intermediate-risk group and 40% (CI 25–58%) for the high-risk group ($P < 0.0001$). Patients belonging to the high-risk group had a median survival of 630 days (CI 408–852). Tick marks indicate the times at which data were censored for a given patient. Vertical lines are 95% confidence intervals.

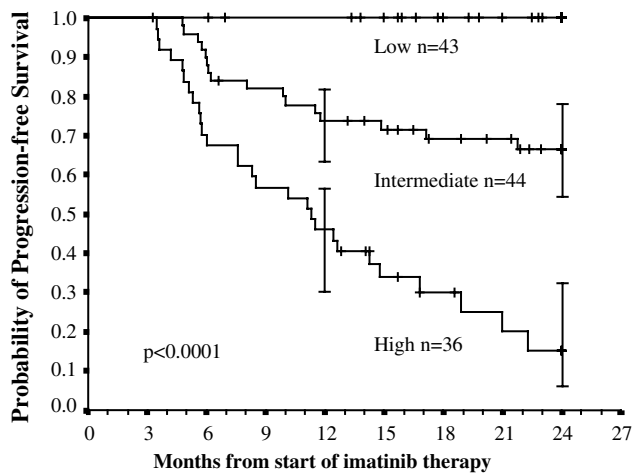


Figure 2 PFS according to prognostic group. The prognostic score was calculated (see text) for the 123 patients with complete data who remained in CP at 3 months. The probability of PFS at 2 years was 100% for the low-risk group, 66% (CI 54–77%) for the intermediate risk group and 15% (CI 6–33%) for the high-risk group $P < 0.0001$. Patients belonging to the high-risk group had a median PFS of 343 days (CI 201–485). Tick marks indicate the times at which data were censored for a given patient. Vertical lines are 95% confidence intervals.

least partial cytogenetic response and the presence of neutropenia at 3 months were the only independent predictors of PFS. We therefore constructed a risk score based on these two factors and were able to classify patients into three prognostic groups. Patients in the good risk group had an excellent prognosis with a survival and PFS of 100% at 2 years, while those in the poor prognosis group had a survival and PFS at 2 years of only 40 and 15%, respectively. We validated the risk score by applying it to an independent patient population. The fact that prognostic

Table 5 Pre-imatinib therapy characteristics of the patients of the validation sample ($n=69$)

Variable	
Age (year)	57 (22–77)
Median, (range)	26 (37.7)
>65 year, no. (%)	52/48
Gender M/F (%)	
Time from diagnosis (year)	
Median (range)	3.1 (0.7–9.5)
Autologous SCT, no. (%)	4 (5.7)
Spleen >5 cm, no. (%)	4 (5.7)
Additional cytogenetic abnormalities, no. (%)	8 (11.5)
IFN α therapy (year)	
Median (range)	1.1 (0.12–9.1)
<i>Response to IFNα</i>	
Haematological resistance, no. (%)	21 (30)
Cytogenetic resistance, no. (%)	31 (45)
Intolerant, no. (%)	17 (25)
<i>Peripheral blood (median, range)</i>	
Leucocyte count ($\times 10^9/l$)	10.3 (2.7–97)
Haemoglobin (g/dl)	12.0 (8.2–19)
Haemoglobin <10.0 g/dl, no. (%)	8 (7.2)
Platelets ($\times 10^9/l$)	259 (130–1810)
Basophils (%)	0 (0–11)
Blasts (%)	0 (0–10)
<i>Bone marrow (median, range)</i>	
Blasts (%)	4 (0–13)
Blasts >5%, no. (%)	18 (26.7)
Blasts+promyelocytes (%)	13 (1–29)
Basophils (%)	0 (0–13)

factors defined at 3 months were more informative than prognostic factors assessed before start of imatinib could have been due in part to the fact that the patients had immediately previously been treated with IFN α . We speculate that identification of a ‘poor-risk’ population after treatment with imatinib for 3 months could be used as a basis for altering therapy, either by adding or substituting other drugs or by proceeding to allogeneic stem cell transplantation if a suitable donor can be identified. The extent to which the prognostic factors described here may be valid in patients whose primary treatment is imatinib remains uncertain, but preliminary evidence suggests that the Sokal scoring system applies to patients treated *ab initio* with imatinib⁹ implying a certain universality of prognostic factors. If this is so, the prognostic factors for response to imatinib in this patient cohort may also have relevance in newly diagnosed patients.

Our observation that neutropenia and failure to achieve at least a partial cytogenetic response (fewer than 66% Ph-positive metaphases) after treatment with imatinib for 3 months are associated with disease progression is consistent with current notions of the stem cell kinetics¹⁴ in CML and the capacity of imatinib to suppress selectively Ph-positive haemopoiesis. If, for example, the marrow of an ‘early’ CP patient contained coexisting populations of Ph-positive and Ph-negative (normal) stem cells, then treatment with imatinib should induce Ph-negativity. On the other hand, if the marrow of a late CP patient contained predominantly Ph-positive stem cells together with reduced numbers of residual Ph-negative normal cells and in some cases also a population of more ‘evolved’ Ph-positive cells (eg those that have an Abl kinase domain mutation¹⁵) that were relatively resistant to imatinib, the results of treatment would depend on the size and viability of the residual Ph-negative population and on the relative ‘aggressiveness’ of the more

evolved population. In the absence of residual Ph-negative cells, suppression by imatinib of the nonevolved CP clone would be likely to induce neutropenia and also would permit expansion of the more evolved clone predisposing to disease progression. A varying quantity of residual normal stem cells and a varying degree of resistance to imatinib of the evolved clone in the late CP patients could thus explain the differing prognostic groups we have observed.

Kantarjian *et al*¹⁰ have recently reported the clinical results of treating with imatinib a series of patients with CML in CP judged to have failed IFN α using the same criteria that we have used. They found a significant relation between time from diagnosis and the achievement of cytogenetic response. We however found no such relation. This disparity may be explained by the fact that the patients reported by Kantarjian *et al* had a median interval from diagnosis to start of treatment with imatinib of 2.8 years, whereas the comparable figure for the Hammersmith patients in this series was 4.2 years. In accordance with our proposed explanation, we would indeed expect the interval from diagnosis to affect the probability of cytogenetic response in 'early' chronic phase. However, in a relatively uniform group of patients in 'late' chronic phase the number of the remaining Ph-negative stem cells would be generally low but with some interpatient variability, as we have observed.

In summary we have devised a prognostic score for CML patients treated initially with interferon and subsequently with imatinib in 'late' chronic phase which may prove to be valuable in guiding further management. The fact that we have identified neutropenia and failure to achieve at least a partial cytogenetic response as the principal prognostic factors in patients receiving imatinib provides some support for the notion that the coexistence of the three haemopoietic stem cell populations referred to above may be part of the natural history of CML regardless of therapy.

Disclosure

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