

ORIGINAL ARTICLES

Successful Use of National Cancer Registry Data to Monitor the Effective Use of Imatinib for Treating Chronic Myeloid Leukaemia

P Shepherd¹, C Dhanapala², C Maguire³, J White³, M Drummond⁴, T Holyoake⁴, PRE Johnson¹

¹Department of Haematology, Western General Hospital, Edinburgh

²Glasgow Area Medicines Evaluation Unit, Royal Infirmary, Glasgow

³Scotland Leukaemia Registry, Public Health Sciences, University of Edinburgh, Edinburgh

⁴University of Glasgow Academic Transfusion Medicine Unit and Cancer Division, Royal Infirmary, Glasgow

Correspondence to

Dr Pat Shepherd, Department of Haematology, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU

Email: pat.shepherd@luht.scot.nhs.uk

Abstract

Imatinib is a tyrosine kinase inhibitor, which selectively antagonises the *BCR-ABL* molecular pathway which causes chronic myeloid leukaemia (CML). Imatinib was first approved by the Scottish Medicines Consortium (SMC) in January 2002 with the recommendation that its use be audited. The cost of the drug has major financial implications for health resources.

Methods

All imatinib usage since its first prescription in Scotland in September 2000 to July 2003 was audited through pharmacy records and through the Scotland Leukaemia Registry (SLR), an existing national registry of patients with CML.

Results

One hundred and four patients in Chronic Phase (CP), 36 in Accelerated Phase (AP) and five in Blast Phase (BP) received imatinib. The median duration of therapy was not reached for CP, 17 months for AP, and two months for BP patients. Major (complete) cytogenetic response rates were 74% (63%) and 38% (24%) respectively for CP and AP. Overall survival for all CP patients from the start of imatinib therapy was 94% at one year, 91% at two years and 83% at three years. An audit of the effectiveness of the SLR as an auditing agency, showed complete registration in 95% of cases.

Conclusions

We believe such data collection should be an important ongoing resource for assessing outcomes in a rare form of leukaemia but one which already has major implications for health economics and will continue to do so given the future development of dual tyrosine kinase inhibitors for imatinib resistant cases.

Introduction

Imatinib is a signal transduction inhibitor, which selectively antagonises the tyrosine kinase activity of the *BCR-ABL* gene product of the Philadelphia chromosome (Ph+).^{1,2}

The Philadelphia chromosome or the *BCR-ABL* gene product is present in all patients with chronic myeloid leukaemia (CML).³ The incidence of CML in Scotland is 0.7-1 per 100,000 per annum.⁴ The prevalence of CML in the imatinib era would be 10 per 100,000 if there was a median survival of 10 years. This may not be unreasonable given the reported responses to imatinib so far. This has major financial implications for NHS drug budgets given the high cost of the drug. In addition, new second line tyrosine kinase inhibitors are becoming available for those who develop resistance to imatinib. These are likely to be tested head to head versus imatinib for newly diagnosed cases. Auditing the outcome of these patients is mandated as part of the Scottish Medicines Consortium (SMC) recommendation for its use.⁵

CML is a bi or triphasic disorder with a chronic phase (CP) and then disease progression either through an accelerated phase (AP) or directly to blast phase (BP) with increasing resistance to therapy. Prior to the introduction of imatinib, median survival was of the order of five to six years years on interferon based therapy. The initial Phase II studies of imatinib were in CML patients in CP who had failed, or who were intolerant of interferon and in patients who had progressed to AP or to BP. The remarkable results in terms of efficacy from these trials provided the licensing data for imatinib in the USA in May 2001 and by the European Medicines Agency (EMA) in November 2001.^{6,7,8} In March 2002 SMC approved the use of imatinib in Scotland for the treatment of CML in AP, BP and in CP patients who failed interferon therapy based on the Phase II trial data. In January 2003 SMC extended its recommendation to include treatment of newly diagnosed patients with CML in CP, ie first line therapy on the basis of the significantly improved response to imatinib compared to interferon in a Phase III randomised trial, the International Randomised Study of Interferon and STI571 (IRIS) Trial.⁹ The SMC also recommended the maintenance of a patient register recording patient outcome data for all patients treated with imatinib. This is important, as imatinib is a very expensive drug costing approximately £22,000 per annum at standard doses of 400mg daily. It is current practice for patients to remain on imatinib continuously unless evidence of resistance or disease progression occurs. Thus it can be anticipated that patients could stay on this drug for many years with increasing cumulative cost. The availability of the Scottish Leukaemia Registry (SLR) enabled us to undertake an audit of imatinib use for CML in Scotland.

Methods

The SLR registered all cases of acute myeloid leukaemia, acute lymphoblastic leukaemia, and CML from November 1998 to March 2004. Since the introduction of imatinib, follow up forms for CML cases were adapted specifically to capture outcome data for patients treated with imatinib. In addition, a letter was sent to all haematologists in Scotland, asking for permission to approach pharmacy departments to obtain a list of patients with CML who had received treatment with imatinib. This list was compared with SLR registrations. Basic core data on every patient were collected at presentation and at six monthly intervals during follow up. Cases on the SLR database registered as receiving imatinib, but not on the pharmacy records were investigated. Disease phase was classified according to standard criteria.¹⁰ Disease phase for analysis was defined as that phase at the start of treatment with imatinib. Response to treatment with imatinib was assessed by evaluation of haematological response and cytogenetic response. A complete haematological response (CHR) was defined as white blood cells $< 10 \times 10^9/l$, platelets $< 450 \times 10^9/l$, no circulating immature cells, and no palpable splenomegaly. Anything not fulfilling all of these criteria was categorised as less than CHR. Cytogenetic responses were defined as follows: complete cytogenetic response (CCR) 0% Ph+ cells, partial cytogenetic response 1-35% Ph+ cells, minor cytogenetic response 36-94% Ph+ cells, and no cytogenetic response as $\geq 95\%$ Ph+ cells. Major cytogenetic response (MCR) is $< 35\%$ Ph +ve cells and is the sum of complete and partial cytogenetic responders. Cytogenetic response is the best achieved with imatinib therapy over the length of follow-up.

Kaplan Meier survival was used to determine projected survival, confidence intervals and comparisons of groups by log rank test in Table II, Figures 1 and 2.

Imatinib was first used in Scotland in the treatment of CML in September 2000. The current analysis is based on patient data entered up to July 2003. Follow-up is to October 2004.

Results

The total number of patients in the SLR with CML is 238, of whom we have identified 145 from 21 hospitals as having received imatinib. Thirty nine are alive and have not received imatinib. These patients have had other treatment, eg interferon or stem cell transplantation. The remaining 54 patients had died without receiving imatinib.

Patient Demographics

A summary of the characteristics of the patients who received imatinib is presented in Table I. The major indications for imatinib were patients in CP refractory to, or intolerant of, interferon or who had progressed to AP or BP as per the licensing indications. Later, newly diagnosed patients were entered when the licence was extended to first line use. Other indications included the use of imatinib for relapse post allografting, and those who either were not candidates for interferon or were switched from interferon or hydroxycarbamide when first line therapy was approved.

Imatinib dose and duration of therapy

Ninety per cent of patients in CP received the standard dose of 400mg daily. Ninety two per cent of patients in AP or BT received the appropriate dose of 600mg daily. An increase in dose was indicated if a satisfactory response to imatinib was

Table I: Demographic Characteristics of Patients Treated with Imatinib

	Chronic Phase	Accelerated Phase	Blast Phase	All Phases
Number of patients	104	36	5	145
Age				
Median – yrs	60	62	59	60
Range – yrs	18-81	28-84	39-64	18-84
>60 yr – no. of patients (%)	47 (45%)	19 (53%)	2 (40%)	68 (47%)
Sex				
Male – no. (%)	62 (60%)	21 (58%)	1 (20%)	84 (58%)
Female – no. (%)	42 (40%)	15 (42%)	4 (80%)	61 (42%)
Euro risk score (diagnosis)#				
Low	12 (27%)	1 (10%)	0 (0%)	13(24%)
Intermediate	22 (50%)	5 (50%)	1 (100%)	28(51%)
High	10 (23%)	4 (40%)	0 (0%)	14(25%)
Unevaluable*	60	26	4	90
Year imatinib commenced				
2000	22	9	3	34
2001	35	18	2	55
2002	23	8	0	31
2003	24	1	0	25
Indication for imatinib				
Chronic phase patients:				
- Newly diagnosed	9	N/A	N/A	9
- IFN refractory	35	N/A	N/A	35
- IFN intolerant	50	N/A	N/A	50
Accelerated phase	N/A	35	N/A	35
Blast phase	N/A	N/A	5	5
Other	10	1	0	11
Interval from diagnosis to start of treatment with imatinib				
Median (months)	16.7	31.0	8.9	17.7
Range	0.5-125.0	0.3-125.8	2.7-29.1	0.3-125.8

* insufficient data from diagnosis. Spleen size not collected until 2001 and missing in 79, missing WBC differential 11.

Hasford J, Pffirman M, Hehlmann R et al. A new prognostic score for survival of patients with chronic myeloid leukaemia treated with interferon alfa. *J Natl Cancer Inst* 1998; 90: 850-8

not achieved. This was seen in 13% of CP and 6% of AP patients. The major indication for dose reduction was toxicity, predominantly for cytopenias. This was seen in 17% and 47% of CP and AP patients respectively. The median duration of therapy for CP patients has not yet been reached. For those remaining on therapy, median duration is 32 months at the time of this report. The median duration of therapy was 17 months and two months for AP and BT patients respectively. The estimated percentage of patients remaining on imatinib over time is shown in Table II.

Table II: Estimated Percentage of Patients Continuing Treatment

	Chronic Phase	Accelerated Phase	Blast Phase
Total number of patients treated	104	36	5
Percentage of patients remaining on imatinib treatment			
[CI 95%]			
12 months	87% [81;94]	64% [48;80]	20% [0;51]
24 months	80% [73;88]	47% [31;64]	
36 months	79% [70;87]	40% [23;57]	

Haematological and cytogenetic response to imatinib

The rates of haematological and cytogenetic responses are shown in Table III. The great majority of patients achieved CHR within six months of therapy. Major Cytogenetic Response (MCR) was 74% for patients in CP and 38% in AP.

Complete Cytogenetic Remission (CCR) was seen in 63% and 24% respectively. Again the majority of patients (44/55 CCR) in CP achieved this within six months. Achieving a MCR was associated with improved outcome for patients in CP. (Figure 2.)

Table III: Response to Imatinib. Haematological Response is Best Response Achieved over 12 months; Cytogenetic Response is the Best Ever Response Achieved.

	Chronic Phase	Accelerated Phase	Blast Phase
Total number of patients	104	36	5
Haematological Response			
Evaluable	88 (85%)	26 (72%)	2 (40%)
CHR - n (%)	81 (92%)	17 (65%)	0
Cytogenetic Response			
Evaluable	88 (85%)	29 (81%)	4 (80%)
Complete CR (0% Ph+)	55 (63%)	7 (24%)	0
Partial CR (1-35%)	10 (11%)	4 (14%)	0
Minor CR (36-94%)	10 (11%)	6 (21%)	0
No response (95%+)	13 (15%)	12 (41%)	4 (100%)

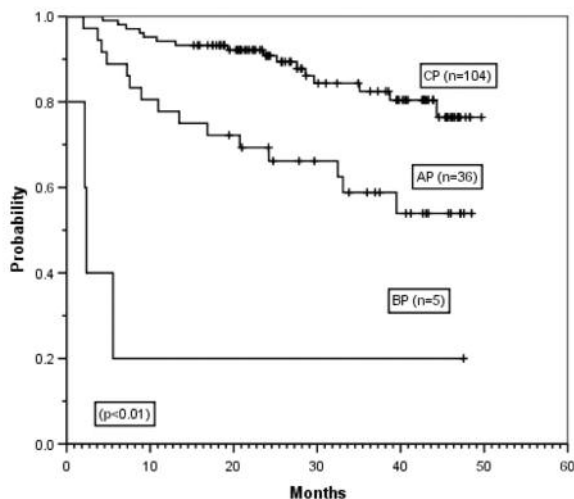
Reasons for discontinuing treatment

Treatment discontinuation was defined as discontinuation of therapy for >1 month. A total of 49(34%) patients have discontinued treatment, 22(21%) in CP, 22(61%) in AP and all BP patients. The majority of patients in AP or BP discontinued therapy because of progressive disease. Adverse events were the major cause of discontinuation in CP. The adverse events described were predominantly cytopenias, including one patient with severe aplasia for six months, skin rashes and gastrointestinal toxicity. Other reasons were failure to achieve a cytogenetic response, death due to unrelated disease, referral for allograft and the achievement of molecular remission following donor lymphocytes, in conjunction with imatinib for those who had relapsed after an allograft.

Survival

Overall survival from the start of imatinib therapy according to disease phase at the start of therapy is given in Figure 1.

Figure 1: Overall survival from start of imatinib treatment according to disease phase at start of therapy. CP chronic phase, AP accelerated phase, BP blast phase.



For all patients projected survival at three years was 83% for CP, 59% for AP and 20% for BP. Median survival for BP was 2.4 months. An analysis of the best cytogenetic response achieved shows a trend for improved survival for those in CP, with a major response compared to a minor or no response. (Figure 2a) Unfortunately cytogenetic analysis was not performed in all patients. Adding in those patients who were non evaluable for cytogenetics increased the difference between the best cytogenetic responders and the rest. (Figure 2b) Landmark analysis at six months did not have the power to detect a significant advantage for major cytogenetic responders (data not shown). Progression free survival is not available as data on dates of AP and BP were not routinely collected.

Figure 2a: Survival in Chronic Phase by best cytogenetic response at any time. A) Major cytogenetic response (CCR+PCR) vs minor/no cytogenetic response (MiCR/NR), B) Major cytogenetic response (CCR + PCR) vs the rest (Mi-CR, NR, N/E)
 CCR: complete cytogenetic response, PCR: partial cytogenetic response. MiCR: minor cytogenetic response, NR: no cytogenetic response, N/E: non evaluable.

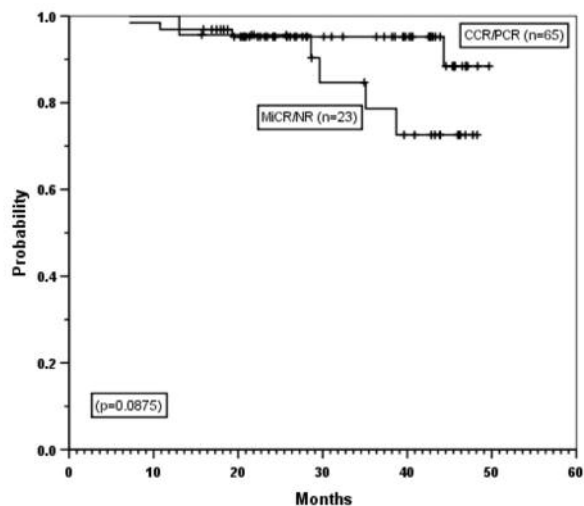
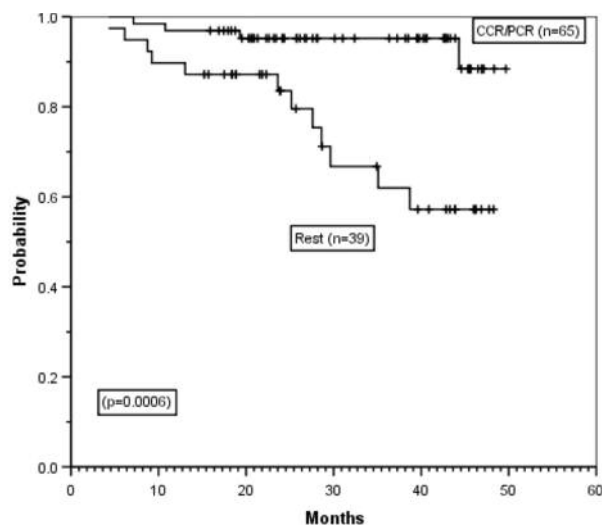


Figure 2b



Audit of SLR Registration

Overall 101/129 (78%) patients identified by pharmacy records as diagnosed with CML and had imatinib prescribed were registered with the SLR. When we looked at the patients identified by pharmacy but not registered with SLR, 22 were diagnosed prior to 1998 and so were not prospectively registered on the SLR database. These patients were subsequently added to the database and their outcome monitored on imatinib. This leaves 6/129 (5%) identified by pharmacies but not registered with SLR after a reasonable period of time. We also looked at patients with CML identified by the registry as having had imatinib who were not picked up by pharmacy records. There were 13 of these cases. The reason why the data on these patients were not captured by pharmacies is not known. Thus, neither of these methods is failsafe regarding identification of all patients. In addition two patients were identified who were not registered with SLR or picked up by pharmacy records.

Discussion

This study highlights some major issues. It focuses on the availability of good quality population based data on which to perform ongoing audit of an expensive drug, imatinib, for a rare disease, CML. When imatinib was approved by the SMC, it was recommended that a register of patients treated with the drug be maintained. The SLR was a good candidate to fulfil this role. It was set up initially with local and charitable trust funding in 1998, subsequently augmented with a grant from the Scottish Executive. It involved the effective collaboration of all Scottish haematologists undertaking the care of patients with both acute leukaemia and CML. The introduction of imatinib into clinical practice in the treatment of CML encouraged further development of the national data set for CML. It has also become clear over the time the registry was in place, that specific items of clinical importance should be collected, eg for categorisation of risk scores at diagnosis and collation of cytogenetic and molecular response at defined intervals.

Secondly, the data reported here show that the results of the published trials of imatinib are applicable in a 'real world' setting to patients being treated for CML. The median age mirrors the epidemiology of the disease.^{4,11,12} The doses used were correct in the great majority of cases. Haematologic response rates are similar to those reported in the Phase II studies of imatinib in CP and AP.^{6,7} Of more interest in CML is cytogenetic response, which indicates a greater depth of anti-leukaemic activity and is the first goal of therapy. In the phase II studies an MCR was reported in 64%, 24% and 16% of patients in CP, AP and BP respectively.^{6,7,8} Corresponding figures in this study are 74% and 38% for evaluable patients in CP and AP. However, 15-20% of patients did not have regular cytogenetic or molecular follow-up, which reduces the quality of the data. One can clinically speculate that the reason that follow-up cytogenetics were not performed was due to disease progression. These patients had worse survival, as shown in Figure 2b, when these patients are combined against those with an MCR. Efforts are now being made to try to agree a standard procedure of cytogenetic and molecular testing to facilitate future analyses. In Scotland we have developed a website for clinicians treating patients with CML, summarising relevant published data and current guidelines for treatment. These have been developed through the three Cancer Networks in Scotland.¹³ The overall survival for CP patients in this study appears similar to that reported in the Phase II trial in CP.⁶ Unfortunately we do not have the figures for progression free

survival as reported by the Phase II trial. It does however also compare favourably to the data from the recently published IRIS study in which newly diagnosed CP patients receiving imatinib had an overall survival of 97% at 18 months.⁹ These data highlight the likely prolonged duration of therapy in CP patients. Whether imatinib can be discontinued in patients with major or complete molecular remission is the subject of ongoing review. Two small case reports describe four of five patients in complete molecular remission, ie undetectable BCR-ABL transcripts with a sensitive nested RT-PCR assay, who developed rapid molecular and cytogenetic relapse within three to seven months of stopping treatment.^{14,15} General consensus at the moment is that imatinib should be continued in all patients until loss of response is documented. Stopping therapy unless for toxicity while still in CCR should only be performed in the context of a clinical trial.

Finally, responsibility for the development of cancer registration and outcome data has now been transferred to the regional cancer networks. Support for the SLR ended in 2004 due to financial constraints and to date no effective substitute for data collection in CML has yet been implemented in Scotland. Ideally such a system would collect similar agreed data sets across the country or indeed nationally within the UK and would allow data for a rare disease, CML, to be integrated through all the cancer networks, ideally through a web based approach. Such registration and data collection for all haematological malignancies not just CML would address not only waiting time targets but monitor meaningful clinical outcomes for this diverse range of malignancies. One of the strengths of the SLR was a dedicated staff working towards full and timely registration, follow-up and checking the accuracy of data etc. It is hoped that the new network based approach will allow the same quality of data collection. Ongoing assessment of the use of imatinib and outcomes will be required.

Acknowledgements

The Scotland Leukaemia Registry was funded for three years by a grant from the Lloyds-TSB Research Foundation and for one year by a grant from the Scottish Executive. Staff from Glasgow Area Medicines Evaluation Unit and the Scotland Leukaemia Registry performed this audit. Thanks are also given to consultant haematologists throughout Scotland who registered their patients with the Scotland Leukaemia Registry, and pharmacy staff throughout Scotland who assisted with the audit.

Names of haematologists registering patients with Scotland Leukaemia Registry:

Dr J Tucker, Borders General Hospital, Melrose: Dr G Erskine, Dr P Eynaud, Crosshouse Hospital, Kilmarnock: Dr A Stark, Dr F Toolis, Dumfries and Galloway Royal Infirmary, Dumfries: Dr D Ellis, Inverclyde Hospital, Greenock: Dr G Cook, Dr J Murphy, Dr A Raafat, Dr R Soutar, Dr W Watson, Monklands Hospital, Lanarkshire: Dr D Bowen, Dr P Cacchia, Prof M Pippard, Ninewells Hospital, Dundee: Dr C Lush, Raigmore Hospital, Inverness: Dr P McKay, Royal Alexandra Hospital, Paisley: Dr J Tighe, Dr D Culligan, Aberdeen Royal Infirmary, Aberdeen: Prof T Holyoake, Dr A Parker, Glasgow Royal Infirmary, Glasgow: Dr D Meiklejohn, Dr F Scott, Perth Royal Infirmary, Perth: Dr R Jones, Dr P Shepherd, St Johns Hospital, Livingston: Dr B Hogg, Dr M Leach, Stobhill Hospital, Glasgow: Dr P Vosylius, The Ayr Hospital, Ayr: Dr J McCallum, Dr S Rogers, Victoria Hospital Kirkcaldy: Dr J Davies, Dr P Johnson, Dr P Shepherd, Western General Hospital, Edinburgh: Dr N Lucie, Dr R Soutar, Western Infirmary, Glasgow: Dr L Allan, Wishaw General Hospital, Wishaw.

References

1. Druker BJ, Talpaz M, Resta DJ 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.
2. Savage GD, Antman HK. Drug therapy: imatinib mesylate – a new targeted oral therapy. *N Engl J Med* 2002; 346: 683-693
3. Deininger WN, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood* 2000; 96: 3343-3356
4. ISD Scotland. Scottish Cancer Registry. Leukaemias. Available at <http://www.isdscotland.org/isd/1538.html> (Accessed 4th June 2008)
5. Scottish Medicines Consortium. Imatinib. Advice 8th March 2002 Available at <http://www.scottishmedicines.org.uk/smc/1847.html> (Accessed 4th June 2008) Advice 10th January 2003. Available at <http://www.scottishmedicines.org.uk/smc/1824.html> (Accessed 4th June 2008)
6. Kantarjian H, Sawyers C, Hochhaus A et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002; 346: 645-652
7. Talpaz M, Silver R, Druker B et al. Imatinib induces durable cytogenetic responses to imatinib mesylate in patients with accelerated phase chronic myeloid leukemia: results of a phase II study. *Blood* 2002; 99: 1928-1937.
8. Sawyers L, Hochhaus A, Feldman E et al. Imatinib induces haematological and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002; 99: 3530-3539
9. O'Brien SG, Guilhot F, Larson R et al. Imatinib compared with Interferon and low dose Cytarabine for newly diagnosed chronic phase myeloid leukemia. *N Engl J Med* 2003; 348: 994-1004
10. Kantarjian H, Diesseroth A, Kurzrock R et al. Chronic myelogenous leukemia: a concise update. *Blood* 1993; 82: 691-703
11. Allan NC, Richards SM, Shepherd PCA. UK Medical Research Council randomised, multicentre trial of interferon alpha α 1 for chronic myeloid leukemia: improved survival irrespective of cytogenetic response. *Lancet* 1995; 345: 1392-1397
12. Kluin-Nelemans H, Buck G, le Cessie S et al, Randomized comparison of low dose versus high dose interferon alfa in chronic myeloid leukemia. Prospective collaboration of three joint trials by the MRC and HOVON groups. *Blood* 2004; 103: 4408-4415
13. Scottish Cancer Network Resource for Chronic Myeloid Leukaemia. Available at <http://www.cmlscot.info> (Accessed 4th June 2008)
14. Cortes G, O'Brien S, Kantarjian H. Discontinuation of imatinib therapy after achieving a molecular response. *Blood* 2004; 104: 2204-5
15. Mauro M, Druker B, Maziarz R. Divergent clinical outcome in two CML patients who discontinued imatinib therapy after receiving a molecular remission. *Leuk Res* 2004; 27: 71-73