Kaohsiung Journal of Medical Sciences (2011) **27**, 49–54

available at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Additional chromosome abnormalities in chronic myeloid leukemia
額外染色體變化於慢性骨髓性白血病之表現

Hui-Hua Hsiao [a,b,c], **Yi-Chang Liu** [a,b,c], **Hui-Jen Tsai** [a,c], **Jui-Feng Hsu** [a], **Wen-Chi Yang** [a,c], **Chao-Sung Chang** [a,b], **Sheng-Fung Lin** [a,b,*]
蕭惠樺 [a,b,c], 劉益昌 [a,b,c], 蔡慧珍 [a,c], 許瑞峰 [a], 楊文祺 [a,c], 張肇松 [a,b], 林勝豐 [a,b,*]

[a] *Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[b] *Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 29 June 2010; accepted 21 September 2010
Available online 10 February 2011

KEYWORDS
Additional chromosome abnormality;
BCR-ABL;
Chronic myeloid leukemia;
Variant Philadelphia chromosome

關鍵詞
慢性骨髓性白血病;
額外染色體變化;
變異的費城染色體;
BCR-ABL

Abstract The Philadelphia (Ph) chromosome and/or Breakpoint cluster region-Abelson leukemia virus oncogene transcript are unique markers for chronic myeloid leukemia (CML). However, CML demonstrates heterogeneous presentations and outcomes. We analyzed the cytogenetic and molecular results of CML patients to evaluate their correlation with clinical presentations and outcome. A total of 84 newly diagnosed CML patients were enrolled in the study. Patients were treated according to disease status. Bone marrow samples were obtained to perform cytogenetic and molecular studies. Clinical presentations, treatment courses, and survival were reviewed retrospectively. Among 84 patients, 72 had chronic phase and 12 had accelerated phase CML. Cytogenetic study showed 69 (82.1%) with the classic Ph chromosome, 6 (7.2%) with a variant Ph chromosome, and 9 (10.7%) with additional chromosome abnormalities. Fifty-four (64.3%) cases harbored b3a2 transcripts, 29 (34.5%) had b2a2 transcript, and 1 had e19a2 transcript. There was no difference in clinical presentations between different cytogenetic and molecular groups; however, additional chromosome abnormalities were significantly associated with the accelerated phase. Imatinib therapy was an effective treatment, as measured by cytogenetic response, when administered as first- and second-line therapy in chronic phase patients. Survival analysis showed that old age, additional chromosome abnormalities, high Sokal score, and no cytogenetic response in second-line therapy had a significant poor impact ($p < 0.05$). In conclusion, we presented the cytogenetic and molecular pattern of CML patients and demonstrated that the additional chromosome abnormality was associated with poor outcome.

* Corresponding author. Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan.
E-mail address: shlin@cc.kmu.edu.tw (S.-F. Lin).

doi:10.1016/j.kjms.2010.09.001

摘要 慢性骨髓性白血病通常帶有獨特的標記，包括費城染色體和BCR-ABL的基因，然而此病之臨床表現及預後卻往往有很大的差異。因此我們分析慢性骨髓性白血病病患之染色體及基因檢查之結果，來看是否這些資料和臨床表現及預後有相關。共有84位新診斷的慢性骨髓性白血病病人進行分析，而這些病人的治療是依據病患的狀況予以治療。染色體及基因檢查是由病患的骨髓檢體所做之檢查，而病患的臨床表現、治療狀況及預後是由病歷資料回顧所得。於84位病人中有72位是屬於慢性期，有12位是屬於加速期。染色體檢查中有69位 (82.1%)是屬於標準的費城染色體，有6位 (7.2%)是屬於變異的費城染色體，有9位 (10.7%) 是屬於額外染色體變化。基因檢查中有54位(64.3%)是屬於b3a2，有29位(34.5%)是屬於b2a2，有1位是屬於e19a2。病患的臨床表現和不同組的染色體及基因並無差別，但是額外染色體變化卻和病患的加速期有相關。而Imatinib對慢性期病患於一線及二線的治療均有不錯之反應。生存分析中發現年紀愈大、有額外染色體變化、有較高的Sokal分數、對二線的治療反應不佳者有有意義的負面影響($p<0.05$)。我們於此報告中顯示了慢性骨髓性白血病病患之染色體及基因變化，且顯示出額外染色體變化對慢性骨髓性白血病有不良之影響。

Introduction

Chronic myeloid leukemia (CML) is characterized by the presence of Philadelphia (Ph) chromosome, a result of a balanced translocation between chromosomes 9 and 22, that is, t(9;22)(q34;q11) [1,2]. The translocation results in the formation of the chimeric oncogene, Breakpoint cluster region-Abelson leukemia virus oncogene (*BCR-ABL*), encoding the protein $p210^{BCR-ABL}$ [3—5]. Despite the presence of unique cytogenetic and molecular hallmarks, CML demonstrates heterogeneous clinical presentations and outcomes [6]. Patients show variable survival from several years to decades and also respond differently to the medications. In addition, the heterogeneous characteristics of CML are also apparent at cytogenetic and molecular levels [6,7]. Most CML patients harbor the classic Ph; however, 5%—10% of patients have variant translocations in which at least a third chromosome is involved in the rearrangement [8—10]. Additionally, depending on the different breakpoints of the BCR gene, most CML cases harbor a fusion oncogene comprising either the b3a2 or b2a2 transcripts [4,11].

Although some studies demonstrated that the diversities in cytogenetic and molecular levels might explain the heterogeneities of CML patients in some respects, the results are still equivocal [6,12—15]. In this study, newly diagnosed CML patients in our hospital were analyzed to see whether diversity at the cytogenetic and molecular levels was correlated with clinical features and outcome.

Materials and methods

Patients

From January 2001 to January 2010, a total of 84 newly diagnosed CML patients were treated in our hospital and enrolled in the study. The diagnosis of CML was established on the basis of bone marrow examination, supported by cytogenetic, molecular studies, and low peripheral blood leukocyte alkaline phosphatase activity. The disease status was classified into chronic phase (CP) and accelerated phase (AP), defined as the presence of at least 15% blasts, 30% blasts plus promyelocytes in the blood or marrow, at least 20% peripheral basophils, or thrombocytopenia unrelated to treatment [16]. Patients were treated according to the status of the disease with cytotoxic agents, including hydroxyurea, interferon-alpha, cytarabine, imatinib mesylate, and/or allogeneic stem cell transplant (SCT). Cytogenetic response (CgR) was defined as 0%—35% of cells with Ph chromosome in the follow-up examination. Clinical presentations, treatment courses, and survival duration were reviewed from the medical records retrospectively.

Cytogenetic study

Cytogenetic studies were obtained from bone marrow samples of the patients at the time of diagnosis. The study was performed from unstimulated specimens by Giemsa-banding method. The results were identified according to the Human System for Cytogenetic Nomenclature.

Molecular study

BCR-ABL transcript was detected by standard reverse transcriptase polymerase chain reaction (RT-PCR) [17]. Briefly, RNA was extracted from Ficoll-separated mononuclear cells from the bone marrow specimens. RT-PCR was performed with standard technique. The resulting fragments were separated and identified by 3% gel electrophoresis and visualized by ethidium bromide stain. Different types of the transcript were identified from the electrophoresis as reported.

Statistical analysis

The results were analyzed by SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) for Windows. Chi-squared test was used to test the categorical variables. Continuing variables were compared by the *t*-test. The Kaplan-Meier method was used for survival analysis and the differences between each group were compared by the Long-rank test. All living patients were censored in January 2010 or at the date of last visit. A p value of less than 0.05 was considered as statistically significant.

Results

A total of 84 CML patients were enrolled in the study, including 51 males and 33 females (Table 1). Twelve cases (14.3%) were

Table 1 Clinical features of the patients ($n = 84$)[a]

Male/female	51/33 (60.7%/39.3%)	
Age, yr	41.8 (13–81)	
White cell count ($\times 10^9$/L)	138,789 (11,400–968,000)	
Hemoglobin (g/dL)	10.1 (6.5–14.2)	
Platelet count ($\times 10^9$/L)	409,158 (87,000–2,509,000)	
Phase		
Accelerating phase	12 (14.3%)	
Chronic phase	72 (85.7%)	
Cytogenetics		
Classical	69 (82.1%) (7 AP)	
Variant	6 (7.2%) (1 AP)	
Additional	9 (10.7%) (4 AP)	
Molecular		
b3a2	54 (64.3%)	
b2a2	29 (34.5%)	
e19a2	1 (1.2%)	
Treatment		
Chronic phase ($n = 72$)		
First-line therapy		
Cytotoxic agents	42	No CgR (3 expired)
Imatinib	30	29 CgR (1 expired because of car accident)
Second-line therapy		
Imatinib	22	16 CgR (4 expired)
SCT	18	16 CgR (1 expired)
Accelerating phase ($n = 12$)		
First-line therapy		
Imatinib + cytotoxic agents	9	3 CgR (2 expired)
Cytotoxic only	3	No CgR (2 expired)

[a] Data presented as mean (range) or *n* (%).
AP = accelerated phase; CgR = cytogenetic response; CP = chronic phase; SCT = stem cell transplant.

in the AP in the diagnosis and other 72 (85.7%) were in CP. Forty-two CP patients received cytotoxic agents as the first-line treatment resulting in no CgR and 3 mortalities; whereas 29 of other 30 CP patients with imatinib therapy achieved CgR. Forty patients, 39 from cytotoxic group and 1 from the imatinib group, received second-line therapy with imatinib (22 patients) and SCT (18 patients). Sixteen of the 22 patients who had imatinib as second-line therapy achieved CgR, whereas 16 of the 18 SCT patients had CgR. Among 12 AP patients, 3 had cytotoxic agents without a CgR. Other nine patients with imatinib plus cytotoxic agents as first-line therapy showed three CgR in the follow-up.

Cytogenetic and molecular results

All patients were positive for *BCR-ABL* transcripts, 54 cases (64.3%) harbored b3a2 transcripts, whereas 29 cases (34.5%) had b2a2 transcript and 1 case had e19a2 transcript (Table 1). The different molecular type had no significant difference in gender, age, white cell count, hemoglobin level and platelet count, cytogenetic subtype and disease status.

In these patients, 69 (82.1%) cases showed classical Ph chromosomes, whereas 6 patients (7.1%) had variant Ph chromosome and other 9 (10.7%) patients harbored additional chromosome abnormalities at the time of diagnosis (Tables 1 and 2). Four out of nine patients in additional group were in AP at the diagnosis. Compared with classical Ph group, patients with additional chromosome abnormalities were associated with AP significantly (7/69 in classical Ph group *vs.* 4/9 in additional group; $p = 0.023$) and have a trend of transformation from CP to AP ($p = 0.096$). Among six cases with variant Ph, only one case showed AP in the diagnosis. There was no difference in gender, age, white cell count, hemoglobin level, platelet count, disease status and survival between variant, additional and classical groups.

Outcomes

With a mean follow-up of 40.8 months, 13 mortalities were noted, including 1 car accident (Table 1). Patients in AP were significantly associated with poor survival ($p = 0.0137$), whereas therapy with imatinib showed a borderline benefit ($p = 0.0541$) in these patients. In CP patients, old age, additional chromosome abnormality, high Sokal score, and no CgR in second-line therapy had poor impact on survival significantly by univariable analysis

Table 2 Characters of nonclassic Philadelphia chromosomes

No	Chromosome result	Disease status	First-line therapy	Second-line therapy	Survival (mo)
Variant Philadelphia chromosome					
1	46,XY,t(3;22)(p24;q11)[8]	CP	Cy	SCT	99
2	46,XY,t(9;9;22)(p13;q34;q11)[20]	CP	Cy	SCT	46
3	46,XY,t(9;22;12)(q34;q11;q13)[20]	CP	Cy	SCT	44
4	46,XX,t(9;22;15)(q34;q11;q24)[20]	CP	Cy	SCT	45
5	46,XY,t(9;22;14)(q34;q11;q23)[20]	CP	Cy	Imatinib	18
6	46,XY,t(4;9;22)(q21;q34;q11)[19]	AP	Imatinib	-	20
Additional chromosome abnormalities					
7	46,XY,t(9;22)(q34;q11),ins(19)(q13.3:q13.4)[14]	CP	Cy	Imatinib	44[a]
8	47,XY,t(9;22)(q34;q11),+Ph[17]/48,XY, idem,+8[3]	CP	Cy	Imatinib	40[a]
9	46,XX,t(9;22)(q34;q11)[5]/46,XX,idem,der(1)(q?)[10]	AP	Cy	-	10[a]
10	47,XY,t(9;22)(q34;q11),+Ph[5]/45-47, XY,idem,-17[15]	AP	Cy	-	16[a]
11	46,XY,t(9;22)(q34;q11),t(2;3)(p25;p21)[10]	CP	Cy	Imatinib	63
12	46,XY,t(9;22)(q34;q11)[15]/47,XY,idem,+Ph[5]	CP	Cy	SCT	58
13	46,XY,t(2;12)(p11;p11),t(3;5)(q12;p15),t(9;22)(q34;q11)[5]	CP	Cy		36[a]
14	46,XY,t(9;22)(q34;q11)[17]/46,XY,idem,t(2;21)[3]	AP	Imatinib + Cy	-	23[a]
15	46,XY,t(9;22)(q34;q11)[11]/46,XY,idem,+Ph,-7[9]	AP	Imatinib	-	26

[a] Patient died.
AP = accelerated phase; CP = chronic phase; Cy = cytotoxic agents; SCT = stem cell transplant.

(Table 3). However, none of them reached a statistically significant difference on survival by the multivariable analysis. Compared with cytotoxic therapy, imatinib therapy showed a significant higher CgR ($p = 0.028$) as the first-line therapy in CP patients and the response of imatinib was higher in the first-line than second-line therapy (93.1% *vs.* 72.7%; $p = 0.048$).

Discussion

Although most CML patients harbor unique hallmarks, such as the Ph chromosome and/or the *BCR-ABL* fusion transcript [1—6], they demonstrate heterogeneous characteristics in clinical presentations and outcomes [6,7]. Some studies showed that the heterogeneity might contribute with the diversity at the molecular and cytogenetic levels, but other reports did not concur with it [6,12—15]. In our study, we report the clinical presentations of CML and showed that the additional chromosome abnormalities at diagnosis are associated with poor outcomes and a high frequency in AP.

Table 3 Statistic result of patients in chronic phase ($n = 72$)

Characters	*p*
Age (>60 yr)	0.0483[a]
Gender	0.8335
WBC (>100,000 × 10^9/L)	0.6587
Platelet count (>500,000 × 10^9/L)	0.4309
Anemia (Hg<12 g/dL)	0.5930
Additional chromosome	0.0070[a]
Molecular type (b3a2 *vs.* b2a2)	0.0713
First-line therapy (imatinib *vs.* cytotoxic agents)	0.5688
CgR in first-line therapy	0.1658
Second-line therapy (imatinib *vs.* SCT)	0.2009
CgR in second-line therapy	0.0010[a]
High Sokal risk	0.0291[a]

[a] Significant difference with $p < 0.05$.
CgR = cytogenetic response; SCT = stem cell transplant.

The prognostic impact of clonal evolution in CML patients during follow-up is well established, which is highly associated with disease progression [9,18—20]. In contrast, the role of additional chromosome abnormality at diagnosis is still uncertain [21,22]. However, the fact that many patients (four of nine) with additional abnormality were at AP at diagnosis and three of the other five patients suffered from transformation to AP in the follow-up suggested that the additional chromosome was associated with the advanced status of CML [19,23]. Furthermore, our study also demonstrated that additional chromosome abnormalities had a significant impact on survival in CP patients. It concurred with previous reports and implied that additional chromosome abnormalities at diagnosis should be taken into consideration in the outcome of CML [22,24—28].

Some reports suggested that patients with variant Ph chromosomes might have a worse outcome, especially when the 5′-ABL region was deleted [7,29—31]. However, our data did not support this result. It might come from the fact that four of these six patients underwent SCT later, which might have some positive effect on the prognosis [32,33]. Our data also could not identify any significant differences in the white cell count, hemoglobin level, platelet count, disease status, and survival between different types of BCR-ABL transcript.

Although this is a retrospective study, our data demonstrated that imatinib is an effective therapy with a high response rate in both first- and second-line therapy [16]. The late CP after initial first-line treatment might contribute to the inferior response of imatinib in second-line therapy [22]. Our results also showed that CgR in

second-line therapy had a survival benefit in CP patients. This might result from patients having an effective salvage therapy, with either imatinib or SCT, after first-line therapy. The survival benefit of imatinib compared with SCT is still unclear [32—34]. Our limited data also could not identify the survival difference.

In summary, we presented the clinical presentations, cytogenetic results, molecular data, and outcomes of 84 CML patients. The distribution of cytogenetic and molecular results was similar to that in other populations and there was no difference in clinical presentations between different cytogenetic and molecular groups. However, additional chromosome abnormality at diagnosis was associated with poor outcome because of high frequency in AP patients and a worse survival in CP patients, whereas variant Ph chromosome had no impact on the clinical presentations and outcomes. Imatinib therapy was an effective treatment with a high response rate in either first- or second-line therapy. However, further prospective studies about the role of additional chromosome in the era of imatinib are warranted to draw more obvious conclusions.

Acknowledgments

This work was supported by a grant from KMU 93 (M093011) from Kaohsiung Medical University, Taiwan. The authors are thankful for the help from Cytogentic Laboratory of Kaohsiung University Hospital for the cytogenetic results.

References

[1] Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290—3.
[2] Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. Cell 1984;36:1—16.
[3] Bartram C, DE Klein A, Hagermeiger A. Translocation of c-abl oncogene correlates with the presence of the Philadelphia chromosome in chronic myelocytic leukaemia. Nature 1984; 306:277—80.
[4] Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. Blood 2000;96:3343—56.
[5] Laurent E, Talpaz M, Kantarjian H, Kurzrock R. The BCR gene and Philadelphia chromosome-positive leukemogenesis. Cancer Res 2001;61:2343—55.
[6] Pane F, Intrieri M, Quintarelli C, Izzo B, Muccioli GC, Salvatore F. BCR/ABL genes and leukemic phenotype: from molecular mechanisms to clinical correlations. Oncogene 2002;21:8652—67.
[7] Reid AG, Huntly BJ, Grace C, Green AR, Nacheva EP. Survival implications of molecular heterogeneity in variant Philadelphia-positive chronic myeloid leukaemia. Br J Haematol 2003;121:419—27.
[8] Mitelman F. The cytogenetic scenario of chronic myeloid leukemia. Leuk Lymphoma 1993;11:11—5.
[9] Reddy KS, Sulcova V. A FISH study of variant Philadelphia rearrangements. Cancer Genet Cytogenet 2000;118:121—31.
[10] Naumann S, Decker HJ. Genesis of variant Philadelphia chromosome translocations in chronic myelocytic leukemia. Cancer Genet Cytogenet 2003;147:18—22.
[11] Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood 1996;88:2375—84.
[12] Mills KI, Benn P, Birnie GD. Does the breakpoint within the major breakpoint cluster region (M-bcr) influence the duration of the chronic phase in chronic myeloid leukemia? Blood 1991; 78:1155—61.
[13] Emilia G, Luppi M, Marasca R, Torelli G. Relationship between BCR/ABL fusion proteins and leukemia phenotype. Blood 1997;89:3889—90.
[14] Emilia G, Luppi M, Ferrari MG, Temperani P, Marasca R, Giacobbi F, et al. Chronic myeloid leukemia with thrombocythemic onset may be associated with different BCR/ABL variant transcripts. Cancer Genet Cytogenet 1998; 101:75—7.
[15] Prejzner W. Relationship of the BCR gene breakpoint and the type of BCR/ABL transcript to clinical course, prognostic indexes and survival in patients with chronic myeloid leukemia. Med Sci Monit 2002;8:193—7.
[16] O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348: 994—1004.
[17] van der Velden VH, Hochhaus A, Cazzaniga G, Szczepanski T, Gabert J, van Dongen JJ. Detection of minimal residual disease in hematologic malignancies by real-time quantitative PCR: principles, approaches, and laboratory aspects. Leukemia 2003;17:1013—34.
[18] Johannson B, Fioretos T, Mitelman F. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta Haematol 2002;107:76—94.
[19] Deininger MWN. Cytogenetic studies in patients on imatinib. Semin Hematol 2003;40:50—5.
[20] Bacher U, Kern W, Schnittger S, Hiddemann W, Schoch C, Haferlach T. Blast count and cytogenetics correlate and are useful parameters for the evaluation of different phases in chronic myeloid leukemia. Leuk Lymphoma 2005;46:357—66.
[21] Farag SS, Ruppert AS, Mrozek K, Carroll AJ, Pettenati MJ, Le Beau MM, et al. Prognostic significance of additional cytogenetic abnormalities in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia treated with interferon-α: a Cancer and Leukemia Group B study. Int J Oncol 2004;25:143—51.
[22] Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European Leukemia Net. Blood 2006; 108:1809—20.
[23] Calabretta B, Perrotti D. The biology of CML blast crisis. Blood 2004;103:4010—22.
[24] Sokal JE, Baccarani M, Tura S, Fiacchini M, Cervantes F, Rozman C, et al. Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. Blood 1985;66:1352—7.
[25] Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alpha. J Natl Cancer Inst 1998;90:850—8.
[26] Passweg JR, Walker I, Sobocinski KA, Klein KA, Horowitz MM, Giralt SA, et al. Validation and extension of the EBMT risk score for patients with chronic myeloid leukaemia (CML) receiving allogeneic haematopoietic stem cell transplants. Br J Haematol 2004;125:613—20.
[27] Jacob RT, Gayathri K, Surath A, Rao DR. Cytogenetic profile of chronic myeloid leukemias. Indian J Cancer 2002;39: 61—5.
[28] Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27:6041—51.

[29] El-Zimaity MM, Kantarjian H, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, et al. Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. Br J Haematol 2004;126:187—96.
[30] Herens C, Tassin F, Lemaire V, Beguin Y, Collard E, Lampertz S, et al. Deletion of the 5′-ABL region: a recurrent anomaly detected by fluorescence in situ hybridization in about 10% of Philadelphia-positive chronic myeloid leukaemia patients. Br J Haematol 2000;110:214—6.
[31] Huntly BJ, Reid AG, Bench AJ, Campbell LJ, Telford N, Shepherd P, et al. Deletions of the derivative chromosome 9 occur at the time of the Philadelphia translocation and provide a powerful and independent prognostic indicator in chronic myeloid leukemia. Blood 2001;98:1732—8.
[32] Angstreich GR, Smith BD, Jones RJ. Treatment options for chronic myeloid leukemia: imatinib versus interferon versus allogeneic transplant. Curr Opin Oncol 2004;16: 95—9.
[33] Lange T, Bumm T, Mueller M, Otto S, Al-Ali HK, Grommisch L, et al. Durability of molecular remission in chronic myeloid leukemia patients treated with imatinib vs allogeneic stem cell transplantation. Leukemia 2005;19:1262—9.
[34] Sausville EA. Imatinib for chronic myelogenous leukaemia: a 9 or 24 carat gold standard? Lancet 2003;361:1400—1.