# Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: current situation and future challenges

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**Online Supplementary Table S1. Search terms used for the literature databases.**

| Topic | PubMed search and Cochrane Library search | | EMBASE search | | Conference abstracts | |
|---|---|---|---|---|---|---|
| CML | #1 | "Leukemia, Myelogenous, Chronic, BCR-ABL Positive"[Mesh] | #1 | 'chronic myeloid leukemia'/exp | #1 | Chronic Myeloid Leukemia |
| | #2 | chronic myeloid leukemia | #2 | chronic myeloid leukemia | #2 | Chronic Myelogenous Leukemia |
| | #3 | chronic myelogenous leukemia | #3 | chronic myelogenous leukemia | #3 | CML |
| | #4 | CML | #4 | CML | #4 | #1 OR #2 OR #3 |
| | #5 | #1 OR #2 OR #3 OR #4 | #5 | #1 OR #2 OR #3 OR #4 | | |
| Adherence/ compliance | #6 | "Medication Adherence"[Mesh] | #6 | 'patient compliance'/exp | #5 | Adherence |
| | #7 | "Patient Compliance"[Mesh] | #7 | 'treatment refusal'/exp | #6 | Compliance |
| | #8 | "Treatment refusal"[Mesh] | #8 | adherence | #7 | "Treatment refusal" |
| | #9 | adherence | #9 | compliance | #8 | "medication possession ratio" |

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| | #10 | compliance | #10 | “treatment refusal” | #9 | concordance |
| | #11 | “treatment refusal” | #11 | “medication possession ratio” | #10 | “intentional discontinuation” |
| | #12 | “medication possession ratio” | #12 | concordance | #11 | #5 OR #6 OR #7 OR #8 OR #9 OR #10 |
| | #13 | concordance | #13 | “intentional discontinuation” | | |
| | #14 | “intentional discontinuation” | #14 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 | | |
| | #15 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 | | | | |
| BCR-ABL inhibitors | #16 | imatinib | #15 | imatinib | #12 | imatinib |
| | #17 | dasatinib | #16 | dasatinib | #13 | dasatinib |
| | #18 | nilotinib | #17 | nilotinib | #14 | nilotinib |
| | #19 | Protein Kinase | #18 | ‘protein tyrosine | #15 | “protein kinase |

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| | 9 | Inhibitors[Mesh] | 8 | kinase inhibitor'/exp | 5 | inhibitor" |
| | #20 | "tyrosine kinase inhibitor" | #19 | 'protein kinase inhibitor'/exp | #16 | "tyrosine kinase inhibitor" |
| | #21 | "bcr-abl inhibitor" | #20 | "tyrosine kinase inhibitor" | #17 | "bcr-abl inhibitor" |
| | #22 | "protein-tyrosine kinase inhibitor" | #21 | "bcr-abl inhibitor" | #18 | "protein-tyrosine kinase inhibitor" |
| | #23 | #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | #22 | "protein-tyrosine kinase inhibitor" | #19 | #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 |
| | | | #23 | #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | | |
| Combined search | #24 | #5 AND #15 AND #23 | #24 | #5 AND #14 AND #23 | #20 | (#1 OR #2 OR #3) AND (#5 OR #6 OR #7 OR #8 OR #9 OR #10) AND (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) |

*CML: chronic myeloid leukemia; exp: explosion search.*

**Online Supplementary Table S2. Data parameters extracted.**

| Study details | Baseline patient characteristics | Adherence/compliance | Endpoints reported | Conclusions |
|---|---|---|---|---|
| First author<br>Journal, year of publication<br>Country<br>Study design<br>Study population (including outpatient *versus* inpatient)<br>Number of patients included in study<br>Source of data used in the study<br>Date/time period of the | Inclusion criteria<br>Exclusion criteria<br>Demographics: age, sex, race/ethnicity<br>Clinical characteristics:<br>• Disease (expected to be CML only)<br>• BCR-ABL positive or negative<br>• Resistant or intolerant to imatinib<br>• CML risk score if available | Definitions of adherence and non-adherence and compliance<br>Tools used to measure adherence<br>Predictors of (non)adherence<br>Adherence outcome measured in the study<br>Measures or interventions that can be taken to improve adherence (if reported) | Effect of (non)adherence on:<br>- Clinical outcomes:<br>• Overall survival<br>• Progression-free survival/event-free survival<br>• Hematologic response<br>• Cytogenetic response<br>• Molecular response<br>- Safety outcomes<br>- Quality of life: | Conclusions of the study |

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| data collection<br>Study duration<br>Definition of the outcomes measured in the study<br>Strengths and limitations of the study<br>Risk of bias | • CML state (i.e. chronic phase, accelerated, blast crisis)<br>• Date of CML diagnosis<br>• Comorbidities (if any)<br>• Concomitant medications (if any)<br>CML treatment:<br>• Duration of CML treatment<br>• Treatment/ type of BCR-ABL inhibitor(s) used (including line of treatment)<br>• Treatment related adverse events | • Quality of life<br>• Other patient reported outcomes<br>- Resource utilization and costs:<br>• Costs<br>• Resource utilization (e.g. inpatient admissions and hospital days) |

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| | • Past CML treatments (if information is available)<br>• Doses of BCR-ABL inhibitor(s) |

*CML: chronic myeloid leukemia.*

**Online Supplementary Table S3. Studies and main characteristics.**

| # | First author, publication year | Title | Publication type | Country | *n* | Study design | Treatment | Method of adherence measurement or metrics used |
|---|---|---|---|---|---|---|---|---|
| 1 | Baccarani M, 2004.[18] | Imatinib and pegylated human recombinant interferon-alpha2b in early chronic-phase chronic myeloid leukemia | Article | Italy | 76 | Prospective clinical | Imatinib in combination with pegylated interferon | Blood sampling/ Scheduled *versus* administered dose |
| 2 | Breccia M, 2011.[19] | Imatinib treatment in chronic myelogenous leukemia: what have we learned so far? | Article | Italy | NA | Literature review | Imatinib | NA |
| 3 | Darkow T, 2007.[20] | Treatment interruptions and non- | Article | USA | 267 | Retrospective claims | Imatinib | Claims data/ MPR |

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| | | adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia | | | | | | |
| 4 | Eliasson L, 2011.[21] | Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed | Article | UK | 21 | Cross-sectional (patient survey) | Imatinib | Mixed method/ MEMS® and questionnaire |
| 5 | Ganesan P, 2011.[22] | Nonadherence to imatinib adversely affects event free | Article | India | 516 | Retrospective observational | Imatinib | Pharmacy refill data/ Patient visits for drug refills |

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| | | survival in chronic phase chronic myeloid leukemia | | | | | | |
| 6 | Halpern R, 2009.[23] | Costs and utilization associated with imatinib adherence in patients with chronic myeloid leukemia or gastrointestinal stromal tumors | Article | USA | 374 CML and 91 GIST | Retrospective claims | Imatinib | Claims data/ MPR |
| 7 | Ibrahim AR, 2011.[24] | Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy | Article | UK | 87 | Prospective clinical | Imatinib | MEMS® |

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| 8 | Jönsson S, 2012.[25] | Good adherence to imatinib therapy among patients with chronic myeloid leukemia a single center observational study | Article | Sweden | 38 | Cross-sectional | Imatinib | Questionnaire /MMAS-Morisky score |
| 9 | Kiguchi T, 2009.[26] | Compliance with taking imatinib mesylate in patients with chronic myeloid leukemia in the chronic phase | Article | Japan | 52 | Retrospective observational | Imatinib | Pharmacy refill data/ Dose prescribed *versus* dose obtained |
| 10 | Kong DC, 2006.[27] | Factors influencing adherence to molecular therapies in haematology-oncology outpatients | Article | Australia | 13 CML and 11 multiple myeloma | Cross-sectional (patient survey) | Imatinib | Questionnaire/ Morisky score |

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| 11 | Marin D, 2010.[15] | Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib | Article | UK | 87 | Prospective clinical | Imatinib | MEMS®/ dose taken *versus* dose prescribed |
| 12 | Moon JH, 2012.[28] | Patient counseling program to improve the compliance to imatinib in chronic myeloid leukemia patients | Article | Korea | 114 | Cross-sectional | Imatinib | Prescription control/ Dose taken *versus* dose should have been taken |
| 13 | Muramatsu H, 2011.[29] | Excellent outcomes of children with CML treated with imatinib mesylate compared to | Article | Japan | 28 | Retrospective observational | Imatinib or HSCT. One patient in the imatinib | Not specified |

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| | | that in pre-imatinib era | | | | | group also received HSCT after 4 months treatment with imatinib | |
| 14 | Noens L, 2009.[14] | Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study | Article | Belgium | 169 | Prospective observational | Imatinib | Mixed/ BAAS (patient and family member), VAS (patient, family member and physician), appointments kept, pill count |
| 15 | Prejzner W, 2010.[30] | Compliance during therapy of patients with chronic myeloid leukemia | Article | Poland | NA | Literature review | Not specified | NA |

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| 16 | Wu EQ, 2010.[31] | Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukemia | Article | USA | 521 | Retrospective claims | Dasatinib or nilotinib as second line treatment | Claims data/ PDC |
| 17 | Wu EQ, 2010.[32] | Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients | Article | USA | 592 | Retrospective claims | Imatinib | Pharmacy refill data/ MPR |
| 18 | Yood MU, 2012.[33] | Adherence to treatment with second-line therapies, dasatinib and nilotinib, | Article | USA | 250 | Retrospective claims | Dasatinib and nilotinib | Claims data/ MPR |

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| | | in patients with chronic myeloid leukemia (CML) | | | | | | |
| 19 | Yoshida C, 2011.[35] | Adherence to the standard dose of imatinib, rather than dose adjustment based on its plasma concentration, is critical to achieve a deep molecular response in patients with chronic myeloid leukemia | Article | Japan | 38 | Retrospective observational (and cross-sectional) | Imatinib | Blood sampling/ Dose of imatinib taken |
| 20 | Almeida MH, 2010.[36] | High adherence to tyrosine kinase inhibitors seems to be related to best | Abstract | Brazil | 122 | Prospective observational | Imatinib, nilotinib, dasatinib and | MPR |

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| | | cytogenetic response in the Hasford lower risk group in chronic myeloid leukemia | | | | | bosutinib | |
| 21 | Almeida MH, 2010.[38] | Adherence to tyrosine kinase inhibitors (TKI) in chronic myeloid leukemia (CML) seems to be related to duration of treatment and type of TKI | Abstract | Brazil | 131 | Retrospective observational | Imatinib, dasatinib and nilotinib | MPR |
| 22 | Almeida MH, 2011.[37] | Higher adherence related to complete molecular response (CMR) in chronic myeloid leukemia patients using imatinib mesilate | Abstract | Brazil | 86 | Prospective observational | Imatinib | MPR |

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| 23 | Daouphars M, 2011.[39] | Adherence assessment in chronic myeloid leukemia patients treated by tyrosine kinase inhibitors | Abstract | France | 64 | Cross-sectional | Imatinib, dasatinib and nilotinib | SRA, MPR |
| 24 | Doti CA, 2008.[40] | Adherence to imatinib mesylate treatment: 2 years follow-up | Abstract | Argentina | 24 | Prospective clinical (case-control) | Imatinib | Patient log, pill count, dose prescribed *versus* dose taken |
| 25 | Fogliatto L, 2010.[41] | Impact of comorbidity in event-free survival, toxicity and adherence to treatment In chronic myeloid leukemia patients treated with imatinib | Abstract | Brazil | 185 | Retrospective observational | Imatinib | More than 20 days treatment suspension |
| 26 | Funke VAM, 2011.[42] | Impact of non-adherence to imatinib | Abstract | Brazil | 386 | Retrospective observational | Imatinib | MPR |

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| | | on progression-free survival as 1st treatment for chronic myeloid leukemia in Brazil: 2 years follow up | | | | | | |
| 27 | Gupta M, 2011.[43] | Association between treatment restrictions, patient-reported treatment burden and adherence to tyrosine-kinase inhibitor therapy among chronic myeloid leukemia patients in the United States and Europe | Abstract | USA | 303 | Cross-sectional | Imatinib, dasatinib and nilotinib | Questionnaire |

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| 28 | Guilhot F, 2010.[44] | A global retrospective and physician-based analysis of adherence to tyrosine kinase inhibitor (TKI) therapies for chronic myeloid leukemia (CML) | Abstract | Brazil, France, Italy, Spain and Russia | 1155 | Retrospective observational | Not specified | Not specified |
| 29 | Hirji I, 2011.[45] | Treatment adherence and resources use costs in chronic myeloid leukemia | Abstract | USA | 545 | Retrospective claims data | Imatinib, dasatinib and nilotinib | MPR |
| 30 | Johnson CN, 2010.[46] | Disease knowledge in chronic myeloid leukemia (CML) patients as a predictor of compliance to treatment | Abstract | USA | 39 | Cross-sectional (patient survey) | Majority on TKI | Questionnaire (patient and physician) |

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| 31 | Koren-Michowitz M, 2010.[47] | Imatinib trough plasma levels in Philadelphia positive chronic myeloid leukemia (CML) patients: results of a multicenter study | Abstract | Israel | 166 | Prospective clinical | Imatinib | Diary logs |
| 32 | Kutsev S, 2010.[48] | The role of imatinib plasma level test in evaluation of the nonadherence to therapy in chronic myelogenous leukemia patients | Abstract | Russia | 442 | Cross-sectional | Imatinib | Blood level test |
| 33 | Lee S, 2009.[49] | Imatinib mesylate plasma levels predict compliance in patients with chronic | Abstract | USA | 19 | Retrospective observational | Imatinib | Chart review and patient history |

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| | | myelogenous leukemia | | | | | | |
| 34 | Palandri F, 2009.[50] | The combination of interferon-alpha with imatinib in early chronic phase chronic myeloid leukemia patients induces a significant improvement of the molecular responses in the first 2 years of treatment: Results from 3 studies from the GIMEMA CML working party | Abstract | Italy | 495 | Prospective clinical | Imatinib or imatinib plus interferon-alpha | % of patients receiving standard dose |
| 35 | Rosti G, 2008.[51] | High and early rates of cytogenetic and | Abstract | Italy | 73 | Prospective clinical | Nilotinib | Average daily dose *versus* intended dose |

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| | | molecular response with nilotinib 800 mg daily as first line treatment of Ph-positive chronic myeloid leukemia in chronic phase: results of a phase II trial of the GIMEMA CML working party | | | | | | |
| 36 | St Charles M, 2009.[52] | Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia | Abstract | USA | 430 | Retrospective claims | Imatinib | MPR |
| 37 | Wu EQ, 2011.[53] | Impact of pleural effusion (PE) on | Abstract | USA | 186 | Retrospective claims | Any TKI | PDC |

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|---|---|---|---|---|---|---|---|---|
| | | treatment adherence, discontinuation, switching, and dose modification in patients with chronic myelogenous leukemia (CML) | | | | | | |
| 38 | Wu S, 2011.[54] | What doctors don't know about adherence: a qualitative study of adherence to imatinib amongst patients with chronic myeloid leukemia | Abstract | Australia | 16 | Cross-sectional | Imatinib | Questionnaire |
| 39 | Yood MU, 2010.[34] | Adherence to treatment in patients with chronic | Abstract | USA | 2064 | Retrospective claims | Imatinib | MPR and treatment interruptions |

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| | myelogenous leukemia during a 10-year time period: a Medical Record Review | |

*BAAS: Basel Assessment of Adherence Scale; CML: chronic myeloid leukemia; GIST: gastrointestinal stromal tumors; HSCT: hematopoietic stem cell transplantation; MEMS®: Medication Event Monitoring Systems; MMAS: Morisky Medication Adherence Scale; MPR: medication possession ratio; NA: not applicable; PDC: proportion of days covered; SRA: self-reporting adherence; TKI: tyrosine kinase inhibitor; VAS: visual analog scale.*