

## Review

# What Is the Optimal Dose and Schedule for Dasatinib in Chronic Myeloid Leukemia: Two Case Reports and Review of the Literature

Caroline Jamison,\* Debra Nelson,† Mete Eren,† Dron Gauchan,† Ryan Ramaekers,†  
Max Norvell,† and Mehmet Sitki Copur†

\*University of Nebraska Medical Center College of Pharmacy, Omaha, NE, USA

†Saint Francis Cancer Treatment Center, Grand Island, NE, USA

Efficacy and safety of dasatinib in chronic phase (CP) chronic myelogenous leukemia (CML) patients has been well established. Initially approved dose and schedule of 70 mg twice daily has been changed to 100 mg once daily after demonstration of the same efficacy with less toxicity. Some patients require significant dose reductions to enable continued treatment with dasatinib. Even at a dose of 80 mg once daily, several patients may require further dose reductions due to substantial toxicity while maintaining good control of their disease. We report two CP-CML patients achieving and maintaining major molecular responses while on very low doses of dasatinib, ultimately achieving undetectable levels of BCR-ABL fusion transcript in their peripheral blood. Observations of several CP-CML cases responding remarkably well to dasatinib despite very low dose and frequent dose interruptions challenge our current understanding and the accuracy of the data regarding the optimum dose and schedule of this drug. In selected intolerant patients, low-dose dasatinib therapy may be a safe and effective alternative treatment option before a treatment discontinuation or change considered.

Key words: Chronic myeloid leukemia (CML); Dasatinib; Adverse events; Low-dose treatment; Undetectable BCR-ABL

## INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of blood stem cells characterized by the presence of Philadelphia chromosome (Ph), which contains the oncogenic BCR-ABL fusion gene (1). The majority of patients with CML are diagnosed during the initial chronic phase (CP) and receive first-line treatment with imatinib mesylate (Gleevec; Novartis Pharma, East Hanover, NJ, USA), an inhibitor of BCR-ABL tyrosine kinase activity (2,3). Dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY, USA) is a structurally unrelated compound to imatinib, with 325 times higher potency in inhibiting the growth of BCR-ABL-expressing cells in vitro. Unlike imatinib, it can bind to the BCR-ABL kinase in the functionally relevant, catalytically active conformation (4–6). Nearly all approved tyrosine kinase inhibitors are administered orally and have long half-lives resulting in continuous target inhibition when administered once daily. In contrast, the half-life of dasatinib is only 3 to 5 h.

In the dasatinib phase I program, twice daily schedule of the drug sustained BCR-ABL kinase inhibition throughout a 24-h period. During these initial phase I trials, cytogenetic responses and better tolerance of the drug with once daily dosing, including cases treated with dasatinib once daily 5 days per week, were also observed (7). To confirm preliminary findings that intermittent BCR-ABL inhibition is efficacious and to test whether toxicity could be minimized with less frequent dosing, a randomized phase III study was performed investigating dasatinib administered as once daily and twice daily schedules at two total daily doses (100 mg and 140 mg) in patients with CP-CML after imatinib resistance or intolerance. Dasatinib 100 mg once daily offered the most favorable overall benefit–risk assessment leading to the currently recommended dose of the drug (8). However, even at this dose level and schedule dasatinib discontinuation rate of 16% was been observed mostly due to intolerance of the drug (8). Most commonly reported adverse events

Address correspondence to Mehmet Sitki Copur, M.D., Saint Francis Cancer Treatment Center, 2116 W Faidley Ave, Grand Island, NE 68803, USA.  
Tel: +1-3083985450; Fax: +1-3083985351; E-mail: [mcopur@sfgm-gi.org](mailto:mcopur@sfgm-gi.org)

associated with dasatinib include fluid retention, pleural effusions, peripheral edema, myelosuppression, headache, diarrhea, fatigue, myalgia, rash, nausea, and hemorrhage (8,9). Despite significant dose reductions due to adverse events, several cases of continued efficacy with well-controlled disease have been reported (10–13). Here we present our experience with two cases of CP-CML that required significant dose reductions (as low as 20 mg/day and 50 mg/day, respectively) while maintaining a major molecular response (MMR) ultimately leading to complete molecular response.

### CASE 1

A 43-year-old male presented with leukocytosis and splenomegaly with further workup leading to a diagnosis of CP-CML. His calculated Sokal risk score was 1.01—intermediate risk. Initial imatinib therapy accomplished a complete hematologic response within the first 3 months and a partial cytogenetic response at 12 months. Due to insurance issues, lack of other drug assistance programs, and ineligibility for bone marrow transplant, imatinib therapy, which was made available through a drug-assistance program, was continued up to as high as 800 mg p.o. daily doses. After 37 months of therapy, a complete cytogenetic response could not be reached. With the availability of dasatinib drug-assistance program, the treatment was changed to second-line tyrosine kinase inhibitor (TKI) therapy with this drug. Dasatinib was started initially at 70 mg p.o. twice daily, the recommended dose of the drug at the time. Within 2 months of the initiation of this second-line TKI treatment, a major cytogenetic response (MCyR) was achieved, and by 9 months a complete cytogenetic response (CCyR) was achieved. Once peripheral blood molecular testing for quantitative BCR-ABL analysis became available in our clinic, a major molecular response (MMR) of 5 log reduction in the BCR-ABL p210 fusion transcript of the patient's peripheral blood

was confirmed. As the treatment continued, dasatinib-related adverse events, mostly arthralgias, myalgias, and peripheral edema, did develop and gradually progressed into cumulative toxicity grades 2–3 levels. These adverse events significantly decreased the tolerability of dasatinib leading to the use of diuretics and opioid analgesics for symptom relief and frequent treatment interruptions. Twenty-four months after beginning of dasatinib, the dose was reduced to 100 mg daily when the new data on dasatinib dosing became available (8). Unresolving grade 2 toxicities led to a further dose reduction to 70 mg once daily with no major improvement and a treatment interruption of 1 month duration. Interestingly, during all this time, his quantitative PCR analysis remained at 4 log reduction, revealing continued MMR. Rechallenge for tolerability at 70 mg daily dose was unsuccessful. With the disease so well controlled, yet with persisting intolerable adverse events, another dose reduction attempt to 50 mg p.o. daily was made without major relief in his intolerance symptoms. Finally, a further rather bold dose reduction to 20 mg p.o. once daily proved to be the most tolerable dose for this particular patient. Interestingly, he did not only maintain his major molecular response at this very low dose level, but after a year of MMR, his quantitative BCR-ABL analysis revealed undetectable levels of BCR-ABL fusion protein. Currently the patient remains on 20 mg p.o. once daily dose of dasatinib and on continued follow-ups with molecular response evaluation remaining undetectable at 6-month intervals (Table 1).

### CASE 2

A 53-year-old female presented with leukocytosis and splenomegaly, and a diagnosis of CP-CML was established. Her calculated Sokal score was 1.08—intermediate risk. Initial treatment with imatinib 400 mg daily resulted in complete cytogenetic response (CCyR) in 18 months but discontinued due to mostly gastrointestinal

**Table 1.** Patient Treatment and Response Characteristics

|   | Case 1  | Case 2   |
|---|---|--|
| Age                                     | 43  | 53   |
| Sex                                     | Male  | Female   |
| Sokal score                             | 1.01 (intermediate)   | 1.08 (intermediate)  |
| Imatinib (mg/day)                       | 800   | 400  |
| Reason for imatinib discontinuation     | Lack of appropriate response                                | GI toxicity, pancreatitis, and heart failure                             |
| Dasatinib starting dose (mg/day)        | 70 mg p.o. bid  | 70 mg p.o. bid   |
| Dasatinib starting dose associated ADRs | Arthralgias, myalgias, headache, edema                      | Painful maculopapular rash, pancreatitis, edema                          |
| Dasatinib final dose (mg/day)           | 20 p.o. once daily  | 50 p.o. once daily   |
| Time to MMR on dasatinib                | 9 months  | 10 months  |
| Interventions during dasatinib therapy  | Dose reductions, drug holidays, diuretics, pain medications | Dose reductions, drug holidays, hospitalizations, antiemetics, IV fluids |
| Current dose                            | 20 mg/day   | 50 mg/day  |
| BCR-ABL fusion transcript               | Undetectable  | Undetectable   |

toxicity, pancreatitis, and heart failure symptoms. At this point she was switched to dasatinib 70 mg twice daily (recommended dose at that time) with continued CCyR. After initial 19 months of therapy, dasatinib dose was decreased to 100 mg p.o. once daily due to painful maculopapular rash and pancreatitis. Despite dose reduction she could not tolerate the drug and discontinued after 2 months due to grade 2 pancreatitis symptoms requiring hospitalizations a few times. After 5 months of treatment interruption, she attempted to start at a dose of 50 mg twice daily. Unable to tolerate this dose due to abdominal pain, pancreatitis symptoms, and lower leg edema, she tried a 50 mg p.o. once daily dose. Interestingly again, during all this time, her BCR-ABL p 210 fusion transcript remained between 4 to 5 log reductions to undetectable levels. She is currently on 50 mg p.o. daily dasatinib with undetectable BCR-ABL p210 fusion transcript (Table 1).

### DISCUSSION

Treatment of chronic myeloid leukemia with BCR-ABL tyrosine kinase inhibitors requires full adherence to treatment. Due to poor adherence determined by factors related to the patient, the drug, and the disease, a significant proportion of patients may fail to take full advantage of the exciting new treatment options for CP-CML. While oral TKI agents are far more effective and convenient in CP-CML, the optimization of treatment results ultimately relies on adequate patient compliance to the prescribed therapy. Nonadherence is a relatively common event during long-term treatment with TKIs, increasing the risk for poor treatment outcomes (14). In one study measuring adherence levels during a 3-month period in 87 consecutive CP-CML patients who had received imatinib as first-line therapy, treatment adherence was a critical factor for achieving and maintaining molecular response. While median adherence was very high (98%) in this study, the probability of achieving major and complete molecular responses was significantly better in patients with more than 90% of treatment adherence (15).

Dasatinib is one of the most effective targeted therapies in CML patients who are unresponsive or intolerant to imatinib. Although dasatinib is generally well tolerated, serious toxicities can occur in some patients even at much lower doses than recommended. Lower doses and frequent dose interruptions raise the concerns for compromised therapeutic efficacy and development of early drug resistance. In both of our presented cases, dasatinib was the only available and accessible second-generation TKI at the time, and we were forced to dose reduce to the levels reported here due to intolerable toxicities, which required frequent treatment interruptions. In both cases, issues of concurrent drug and/or diet interaction, noncompliance, improper drug administration, or organ dysfunction to interfere with the metabolism of dasatinib

were convincingly excluded through careful evaluation by oncologist and by our clinical pharmacy team. Both cases were not only able to maintain their major molecular response with better tolerability at the reported very low dose levels, but intriguingly they have both achieved undetectable levels of BCR-ABL fusion transcript at the time of this report.

In vitro transient potent inhibition of BCR-ABL with dasatinib can irreversibly induce apoptosis, challenging the murine model data of imatinib (STI-571) that continuous target inhibition is a prerequisite for effective leukemic cell kill (16-18). This has been supported by the clinical efficacy data of dasatinib on intermittent once daily dose targeting (8,19). Significantly shorter plasma half-life of dasatinib (3 to 5 h) compared to that of imatinib (half-life 19 h) may prevent repetitive subtherapeutic drug exposure, thus circumventing the possibility of promotion of drug resistance (20,21). Furthermore, dasatinib represents a different class of BCR-ABL targeting inhibitors with reduced selectivity and enhanced potency (22-24).

Our experience in utilizing very low doses of dasatinib in these two cases, along with similarly reported handful of cases in the literature, is provocative for exploring an alternative dosing and schedule for this drug. Based on responses seen with very low doses of dasatinib, it can be suggested that the minimum concentration for efficacy of this drug may be much lower than previously reported. A dasatinib dosing strategy that is personalized to the patient may help prevent the occurrence of intolerable side effects while maintaining efficacy. Based on the encouraging results from initial dasatinib daily dose optimization trial (25), this concept is now being tested in a multicenter interventional phase II trial by the French CML Intergroup (FILMC) (26).

Although the dose seems to be an important factor, as our first case was intolerant of 50 mg daily but not of 20 mg, our two cases may suggest the possibility that some toxicities may be related to continuous drug exposure. Despite dose interruptions, lack of the development of resistance in either case begs the question of whether sustained target inhibition should remain a driving principle or whether intermittent target inhibition strategy with drug holidays may have a role in dasatinib use for CP-CML patients. In a retrospective analysis, alternate scheduling of low-dose dasatinib with weekend holidays has been shown to increase the compliance along with successful long-term disease control (13). Authors attributed their findings to two factors: first, continued treatment lasting weeks or sometimes months without toxicity-triggered interruptions, and second, high enough daily dosing of dasatinib to achieve potent transient inhibition of BCR-ABL to irreversibly induce apoptosis. These hypothesis-generating findings remain to be confirmed by prospectively designed larger studies.

Most patients with chronic myeloid leukemia (CML) treated with imatinib will relapse if treatment is withdrawn. A prospective clinical trial of imatinib withdrawal in 40 chronic-phase CML patients who had sustained undetectable minimal residual disease for at least 2 years showed that at 24 months, the actuarial estimate of stable treatment-free remission was 47.1%. Most relapses occurred within 4 months of stopping imatinib, and no relapses beyond 27 months were seen (27). While it has been proposed that imatinib can be discontinued without molecular relapse at least in some CML patients, little is known about whether this assumption could be exploitable for the second-generation ABL-tyrosine kinase inhibitors like dasatinib. A prospective, multicenter clinical trial to assess whether dasatinib could be discontinued without occurrence of molecular relapse in CML patients showed that this could be possible in a proportion of CML patients with stable complete molecular response for at least 1 year, provided that frequent molecular monitoring is performed (28). Similar to imatinib study, patients in the dasatinib study who lost complete molecular response after dasatinib discontinuation still maintained good sensitivity to the reintroduction of drug. These findings are consistent with our two cases' observed response patterns and their continued sensitivity to the restart of dasatinib after treatment discontinuations.

### CONCLUSION

Our two cases lend support to previous reports of comparable efficacy of low-dose dasatinib to standard dose dasatinib with more tolerable side effects. Dasatinib given at much lower doses than currently recommended can be a safe and effective strategy before resorting to expensive second-line or third-line choices. Hopefully, this may also lead to decreased drug costs at lower dose levels. Despite the successful clinical responses in both of our patients, conclusions that can be drawn from this experience should be interpreted with caution and considered tentative until larger prospective controlled studies define the minimum effective dose and schedule for this drug. If the lower doses are prescribed due to intolerable side effects, close molecular monitoring is strongly recommended.

### REFERENCES

1. Sawyers, C. L. Chronic myeloid leukemia. *N. Engl. J. Med.* 340:1330–1340; 1999.
2. Hehlmann, R.; Berger, U.; Hochhaus, A. Chronic myeloid leukemia: A model for oncology. *Ann. Hematol.* 84:487–497; 2005.
3. Quintas-Cardama, A.; Cortes, J. E. Chronic myeloid leukemia: Diagnosis and treatment. *Mayo Clin. Proc.* 81:973–988; 2006.
4. Tokarski, J. S.; Newitt, J. A.; Chang, C. Y.; Cheng, J. D.; Wittekind, M.; Kiefer, S. E.; Kish, K.; Lee, F. Y.; Borzilleri, R.; Lombardo, L. J.; Xie, D.; Zhang, Y.; Klei, H. E. The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants. *Cancer Res.* 66:5790–5797; 2006.
5. Shah, N. P. Dasatinib. *Drugs Today (Barc).* 43:5–12; 2007.
6. Hochhaus, A.; Kantarjian, H. M.; Baccarani, M.; Lipton, J. H.; Apperley, J. F.; Druker, B. J.; Facon, T.; Goldberg, S. L.; Cervantes, F.; Niederwieser, D.; Silver, R. T.; Stone, R. M.; Hughes, T. P.; Muller, M. C.; Ezzeddine, R.; Countouriotis, A. M.; Shah, N. P. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 109:2303–2309; 2007.
7. Talpaz, M.; Shah, N. P.; Kantarjian, H.; Donato, N.; Nicoll, J.; Paquette, R.; Cortes, J.; O'Brien, S.; Nicaise, C.; Bleickardt, E.; Blackwood-Chirchir, M. A.; Iyer, V.; Chen, T. T.; Huang, F.; Decillis, A. P.; Sawyers, C. L. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N. Engl. J. Med.* 354:2531–2541; 2006.
8. Shah, N. P.; Kantarjian, H. M.; Kim, D. W.; Réa, D.; Dorlhiac-Llacer, P. E.; Milone, J. H.; Vela-Ojeda, J.; Silver, R. T.; Khoury, H. J.; Charbonnier, A.; Khoroshko, N.; Paquette, R. L.; Deininger, M.; Collins, R. H.; Otero, I.; Hughes, T.; Bleickardt, E.; Strauss, L.; Francis, S.; Hochhaus, A. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib resistant and intolerant chronic phase chronic myeloid leukemia. *J. Clin. Oncol.* 26:3204–3212; 2008.
9. Wong, S. F. New dosing schedules of dasatinib for CML and adverse event management. *J. Hematol. Oncol.* 2:10–13; 2009.
10. Serpa, M.; Sanabani, S. S.; Bendit, I.; Seguro, F.; Xavier, F.; Barroso, C. B.; Conchon, M.; Dorlhiac-Llacer, P. E. Efficacy and tolerability after unusually low doses of dasatinib in chronic myeloid leukemia patients intolerant to standard-dose dasatinib therapy. *Clin. Med. Insights Oncol.* 4:155–162; 2010.
11. Visani, G.; Breccia, M.; Gozzini, A.; Specchia, G.; Montefusco, E.; Morra, E.; Annunziata, M.; Camera, A.; Cavazzini, F.; Stagno, F.; Pregno, P.; Usala, E.; Santini, V.; Piccaluga, P. P.; Isidori, A. Dasatinib even at low doses is an effective second-line therapy for chronic myeloid leukemia patients resistant or intolerant to imatinib. Results from a real life-based Italian multicenter prospective study on 114 patients. *Am. J. Hematol.* 85:960–963; 2010.
12. Porrini, R.; Montefusco, E.; Breccia, M.; Paolo Vigneri, P.; Luciano, L.; Gozzini, A.; Castagnetti, F.; Ulisciani, S.; Cavazzini, F.; Annunziata, M.; Sora, F.; Rossi, A. R.; Pregno, P.; Trawinska, M. M.; Crisa, E.; Musto, P.; Tiribelli, M.; Binotto, G.; Occhini, U.; Feo, C.; Martino, B.; Avanzini, P.; Spina, E.; Pane, F.; Santini, V.; Rosti, G.; Cambrin, G. R.; Alimena, G. Low-dose dasatinib as front-line therapy for elderly patients with CML. *ASH Meeting, Abstract 2293; December 2010.* Retrieved from <https://ash.confex.com/ash/2010/webprogram/Paper32124.html>
13. La Rosee, P.; Martiat, P.; Leitner, A.; Klag, T.; Müller, M. C.; Erben, P.; Schenk, T.; Saussele, S.; Hochhaus, A. Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib. *Ann. Hematol.* 92:1345–1350; 2013.
14. Noens, L.; van Lierde, M. A.; De Bock, R.; Verhoef, G.; Zachee, P.; Berneman, Z.; Martiat, P.; Mineur, P.; Van Eygen, K.; MacDonald, K.; De Geest, S.; Albrecht, T.; Abraham, I.

- Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia the ADAGIO study. *Blood* 113(22):5401–5411; 2009.
15. Marin, D.; Bazeos, A.; Mahon, F. X.; Eliasson, L.; Milojkovic, D.; Bua, M.; Apperley, J. F.; Szydlo, R.; Desai, R.; Kozlowski, K.; Paliompeis, C.; Latham, V.; Foroni, L.; Molimard, M.; Reid, A.; Rezvani, K.; de Lavallade, H.; Guallar, C.; Goldman, J.; Khorashad, J. S. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J. Clin. Oncol.* 28(14):2381–2388; 2010.
  16. Wollff, N. C.; Ilaria, R. L. Establishment of a murine model for therapy-treated chronic myelogenous leukemia using the tyrosine kinase inhibitor ST1571. *Blood* 98:2808–2016; 2001.
  17. Snead, J. L.; O'Hare, T.; Adrian, L. T.; Eide, C. A.; Lange, T.; Druker, B. J.; Deininger, M. W. Acute dasatinib exposure commits Bcr-Abl-dependent cells to apoptosis. *Blood* 114:3459–3463; 2009.
  18. Shah, N. P.; Kasap, C.; Weier, C.; Balbas, M.; Nicoll, J. M.; Bleickardt, E.; Nicaise, C.; Sawyers, C. L. Transient potent BCRABL inhibition is sufficient to commit chronic myeloid leukemia cells irreversibly to apoptosis. *Cancer Cell* 14:485–493; 2008.
  19. Kantarjian, H.; Cortes, J.; Kim, D. W.; Dorlhiac-Llacer, P.; Pasquini, R.; DiPersio, J.; Müller, M. C.; Radich, J. P.; Khoury, H. J.; Khoroshko, N.; Bradley-Garelik, M. B.; Zhu, C.; Tallman, M. S. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-Month median follow-up. *Blood* 113:6322–6329; 2009.
  20. Peng, B.; Lloyd, P.; Schran, H. Clinical pharmacokinetics of imatinib. *Clin. Pharmacokinet.* 44:879–894; 2005.
  21. Brave, M.; Goodman, V.; Kaminskas, E.; Farrell, A.; Timmer, W.; Pope, S.; Harapanhalli, R.; Saber, H.; Morse, D.; Bullock, J.; Men, A.; Noory, C.; Ramchandani, R.; Kenna, L.; Booth, B.; Gobburu, J.; Jiang, X.; Sridhara, R.; Justice, R.; Pazdur, R. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. *Clin. Cancer Res.* 14:352–359; 2008.
  22. O'Hare, T.; Walters, D. K.; Stoffregen, E. P.; Jia, T.; Manley, P. W.; Mestan, J.; Cowan-Jacob, S. W.; Lee, F. Y.; Heinrich, M. C.; Deininger, M. W.; Druker, B. J. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res.* 65:4500–4505; 2005.
  23. le Coutre, P.; Mologni, L.; Cleris, L.; Marchesi, E.; Buchdunger, E.; Giardini, R.; Formelli, F.; Gambacorti-Passerini, C. In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. *J. Natl. Cancer Inst.* 91:163–168; 1999.
  24. Shah, N. P.; Tran, C.; Lee, F. Y.; Chen, P.; Norris, D.; Sawyers, C. L. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 305:399–401; 2004.
  25. Dasatinib Daily Dose Optimization Based on Residual Drug Levels Resulted in Reduced Risk of Pleural Effusions and High Molecular Response Rates: Final Results of the Randomized OPTIM Dasatinib Trial. European Hematology Association, Abstract ABSSUB-5297; 2014. Retrieved from <http://www.peerviewpress.com/dasatinib-dose-optimisation-strategy-reduces-pleural-effusion>
  26. OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy). ClinicalTrials.gov Identifier: NCT01916785. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT01916785>
  27. Ross, D. M.; Branford, S.; Sevmour, J. F.; Schwarzer, A. P.; Arthur, C.; Yeung, D. T.; Dang, P.; Goyne, J. M.; Slader, C.; Filshie, R. J.; Mills, A. K.; Melo, J. V.; White, D. L.; Grigg, A. P.; Hughes, T. P. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood* 122:515–522; 2013.
  28. Tanaka, H.; Imagawa, J.; Okada, M.; Nakamae, H.; Hino, M.; Murai, K.; Ishida, Y.; Kumagai, T.; Sato, S.; Ohashi, K.; Sakamaki, H.; Wakita, H.; Uoshima, N.; Nakagawa, Y.; Minami, Y.; Ogasawara, M.; Takeoka, T.; Akasaka, H.; Morita, S.; Sakamoto, J.; Kimura, S. Discontinuation of dasatinib in patients with CML who have maintained complete molecular response for at least one year: Results from a prospective discontinuation (DADI) trial. American Society of Hematology Abstract 3998; 2013. Retrieved from <https://ash.confex.com/ash/2013/webprogram/Paper58644.html>