Dasatinib targets chronic myeloid leukemia-CD34+ progenitors as effectively as it targets mature cells

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ABSTRACT

Dasatinib is effective in most chronic phase chronic myeloid leukemia patients both in first-line therapy and following imatinib failure. While imatinib uptake into CD34+ cells is low compared to mononuclear cells, few data evaluate how well dasatinib targets primitive CML cells. This study compares intracellular concentration of dasatinib and Bcr-Abl kinase inhibition in CML-CD34+ progenitors and mononuclear cells induced by dasatinib. The intracellular concentrations of dasatinib were similar between CML-CD34+ and mononuclear cells (P=0.8). Similarly, there was no significant difference in the degree of dasatinib-mediated Bcr-Abl kinase inhibition. ABCB1 (MDR1) and ABCG2 inhibitors neither increased dasatinib intracellular concentration nor enhanced dasatinib-mediated Bcr-Abl kinase inhibition. In contrast to nilotinib, we show that dasatinib is not an ABCB1 inhibitor. Thus, dasatinib targets CML-CD34+ progenitors as effectively as it targets mononuclear cells. ABCB1 and ABCG2 efflux pumps do not appear to influence the intracellular dasatinib concentration in CML-CD34+ progenitors.

Introduction

Chronic myeloid leukemia (CML) is characterized by the *BCR-ABL1* oncogene, which translates into constitutively active Bcr-Abl oncoprotein. Imatinib (IM, Novartis, Basel, Switzerland) is a first-line therapy for chronic phase CML (CML-CP) patients.[1] Although IM is highly effective at eradicating the majority of CML cells, residual *BCR-ABL1*+ progenitors persist in CML patients despite undetectable molecular disease.[2,3] These residual progenitors may be responsible for disease persistence, tyrosine kinase inhibitor (TKI) resistance and disease progression. The exact mechanism of refractoriness of these primitive progenitors is largely unknown. However, it has been postulated that inadequate Bcr-Abl kinase inhibition may be a factor.[4] Engler *et al.* demonstrated that IM intracellular uptake and retention (IUR) is significantly lower in CML-CD34+ cells compared to mononuclear cells (MNC) cells,[5] and that this difference was likely due to low organic cation transporter-1 (OCT-1) activity in CML-CD34+ cells compared to mature MNC cells. However, the efflux proteins ABCB1 (also known as multidrug resistance protein 1, MDR1) and ABCG2 (breast cancer resistance protein) may also be contributing to the low intracellular concentration of IM in CML-CD34+ progenitors.[5,6] These data suggest that inadequate IM intracellular concentration in CML-CD34+ and CD34+CD38- progenitors may compromise the ability of IM to eradicate these cells.

Dasatinib, a 2nd generation TKI is effective in many patients with CML-CP as well as in advanced phase patients who failed IM therapy.[7,8] Moreover, in newly diagnosed CML-CP patients, dasatinib is superior to IM in terms of achieving complete cytogenetic response (CCR) and major molecular response (MMR) at 12 months.[9] Despite clinical availability few data assess the effectiveness of dasatinib on CML-CD34+.[4,10] Dasatinib is a substrate of both ABCB1 and ABCG2 efflux proteins[11-13] and multiple studies suggest that ABCB1 and ABCG2 mRNA expression is higher in CML-CD34+ cells compared to MNC.[5,6] Given this, we hypothesize that the intracellular concentration of dasatinib in CML-CD34+ progenitors may be lower than that of MNC, and as a result, dasatinib may not target these progenitors as effectively as MNC.

Design and Methods

Peripheral blood (PB) was obtained from newly diagnosed CP-CML patients before starting TKI therapy. All samples were collected with informed consent in accordance with the Institutional Ethics Committee approved protocols and the Declaration of Helsinki. Details of *Design and Methods* are available in the *Online Supplementary Appendix* and *Online Supplementary Figures S1-S5*.

Results and Discussion

In contrast to imatinib, there is no significant difference in dasatinib intracellular concentration between CML-CD34+ cells and MNC cells

In contrast to previously published findings of imatinib,[5] there was no significant difference in ^{14}C-dasatinib IUR in CML-CD34+ cells and MNC (Figure 1A). At a therapeutically achievable concentration of dasatinib (100 nM), there was no significant difference in ^{14}C-dasatinib IUR between CML-CD34+ and MNC cells (1.0±0.4 *vs.* 0.96±0.45; P=0.8).

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Radioactivity at 100 nM ^{14}C-dasatinib is low and we were concerned that a subtle difference between two cell populations could be missed; therefore, IUR was compared at higher concentration. At 1 μM, there was a significant difference in ^{14}C-dasatinib IUR between CML-CD34$^+$ and MNC cells (8.2±1.6 *vs.* 8.0±1.1; *P*=0.8). Thus, these *in vitro* data demonstrate that, in contrast to imatinib, there is no significant difference in dasatinib IUR between CML-CD34$^+$ progenitors and mature MNC. These finding were further evaluated by comparing the effect of dasatinib on Bcr-Abl kinase activity in CML-CD34$^+$ and MNC.

Dasatinib blocks Bcr-Abl kinase activity equivalently in CML-CD34$^+$ progenitors and CML-MNC

The phosphorylation of Crkl (p-Crkl) is a reliable, reproducible and widely used surrogate marker of Bcr-Abl kinase activity.[14,15] As shown in Figure 1B, the baseline p-Crkl levels were significantly higher in CML-CD34$^+$ cells as compared to mature MNC (67±4 *vs.* 56±7; *P*=0.001; n=11) (Figure 1B). We believe this is the largest dataset demonstrating higher p-Crkl levels in CML-CD34$^+$ cells compared to MNC. These findings confirm previously published findings on a limited number (n=3) of patients.[4] Other groups have shown higher BCR-ABL mRNA, Bcr-Abl protein, total phosphotyrosine and p-Crkl activity in CML-CD34$^+$CD38$^-$ as compared to CD34$^+$CD38$^+$ and MNC cells.[4,6]

Importantly, there was no significant difference in percentage of inhibition of p-Crkl with 2 nM (58±15 *vs.* 54 ±15; *P*=0.7; n=3), 5 nM (26±12 *vs.* 34±13; *P*=0.4; n=3) and 10 nM (14±7 *vs.* 26±13; *P*=0.7; n=3) dasatinib between CML-CD34$^+$ cells and MNC (Figure 1C). Thus, these findings suggest that equivalent dasatinib IUR and Bcr-Abl kinase inhibition can be achieved in CD34$^+$ progenitors and mature MNC. These *in vitro* data suggest that dasatinib can target CML-CD34$^+$ progenitors as effectively as MNC. The intracellular concentration of a drug achieved is the result of the net balance of cellular influx and efflux. Our group has previously reported that lower OCT-1 activity in CML-CD34$^+$

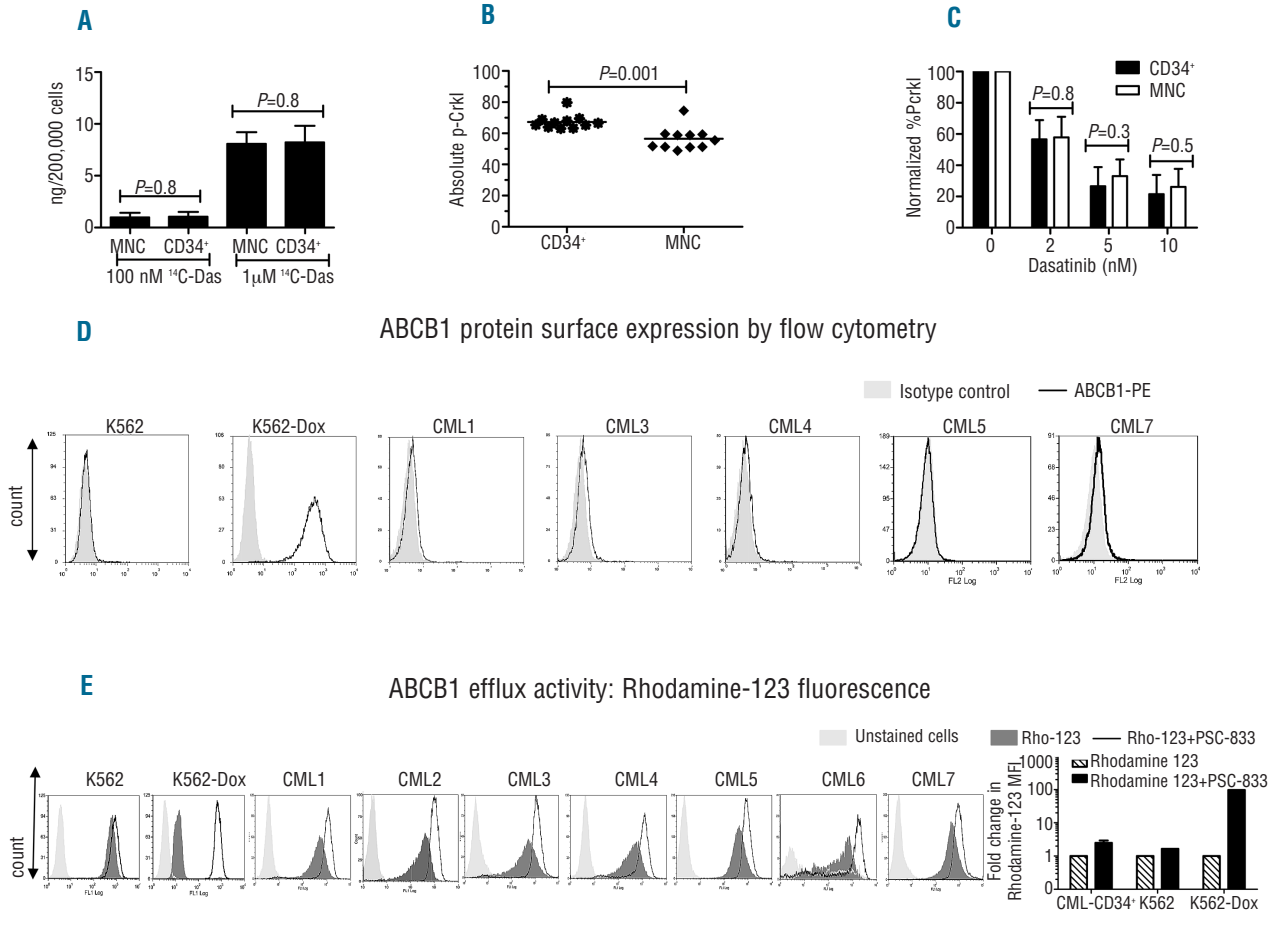

Figure 1. Dasatinib intracellular uptake and retention (IUR) and dasatinib-induced Bcr-Abl kinase inhibition is not significantly different between CML-CD34$^+$ and mononuclear cells (MNC). ABCB1 efflux activity is variable in CML-CD34$^+$ cells. (A) There was no statistically significant difference in dasatinib IUR between CML CD34$^+$ progenitors and MNC (n=6). (B) The baseline p-Crkl level was significantly higher in CML-CD34$^+$ cells compared to MNC (67±4 *vs.* 56±7; *P*=0.001; n=11). (C) p-Crkl inhibition with 2 nM (57±12 *vs.* 57±13; *P*=0.8; n=5), 5 nM (27±12 *vs.* 33±10; *P*=0.3; n=3), and 10 nM (22±12 *vs.* 26±12; *P*=0.5; n=5) dasatinib was not significantly different between CML-CD34$^+$ cells and MNC (D) Surface expression of ABCB1 could not be demonstrated on CML-CD34$^+$ cells of all patients tested (CML1-CML7). K562-Dox (ABCB1 over-expressing cells) and K562 cells were positive and negative control for the assay. (E) Rhodamine-123 fluorescence was significantly lower in K562-Dox cells compared to K562 cells. PSC-833 blocked ABCB1 mediated efflux and increased Rhodamine-123 mean fluorescence intensity (MFI) in K562-Dox cells. CML-CD34$^+$ cells are heterogeneous with some cells having increased ABCB1 activity which can be blocked by PSC-833. In K562 Dox cells PSC-833 increased Rhodamine-123 MFI by 97-fold while in CML-CD34$^+$ and K562 cells it increased only by 2.3 and 1.6-fold, respectively (bar diagram).

cells contributes to a lower IM IUR compared to mature MNC.[5] Dasatinib cellular uptake is predominantly OCT-1 independent; however, it is a substrate of ABCB1 and ABCG2 efflux proteins.[11-13]

ABCB1 and ABCG2 efflux transporter expression and functional activity in CML-CD34⁺ cells

Multiple studies suggest that ABCB1 is differentially expressed in CML progenitors, with higher expression in CML-CD34⁺CD38⁻ cells compared to CD34⁺CD38⁺ cells and more mature MNC.[5,6] However, these studies, including ours,[5] assessed ABCB1 mRNA expression rather than ABCB1 protein expression. In the current study, we assessed ABCB1 surface protein expression using flow cytometry. K562-Dox (ABCB1 over-expressing) and K562 (parental) cell lines were used as positive and negative controls for the assay (Figure 1D) and in the majority of patients CD34⁺ cell purity at the time of the assay was 81-97% (*Online Supplementary Figure S1B*). Flow cytometry did not reveal high ABCB1 protein surface expression on CML-CD34⁺ cells from newly diagnosed CML-CP patients (n=5) (Figure 1D). We then assessed the functional activity of this efflux pump using fluorescence substrate. Rhodamine-123, an ABCB1 fluorescent substrate is widely used to assess the efflux activity of ABCB1 pump. K562-Dox (ABCB1 over-expressing cell line) and K562 (parental cells) were used as positive and negative control for the assay. As expected, Rhodamine-123 mean fluorescence intensity (MFI) was significantly lower in K562-Dox cells compared to K562 cells (MFI 0.9 *vs.* 89.9) (Figure 1E) and PSC-833 (ABCB1 inhibitor) increased the MFI by 97-fold (Figure 1E). CML-CD34⁺ cells have variable Rhodamine-123 efflux activity resulting in widespread Rhodamine-123 fluorescence (n=7) (Figure 1E) but it is substantially lower than K562-Dox cells. PSC-833 increased the Rhodamine-123 MFI by only 2.3-fold (n=7) (Figure 1F) in CML-CD34⁺ cells compared to 97-fold in K562-Dox cells.

Thus, our data show that ABCB1 protein is not over-expressed on CML-CD34⁺ cell surface and has variable ABCB1 efflux activity (as demonstrated by Rhodamine-123 assay). Using a functional assay, other groups have also demonstrated limited ABCB1 efflux activity in CML-CD34⁺.[16,17] The results of this functional assay also suggest that CD34⁺ cells are heterogeneous in terms of ABCB1 activity, and early progenitors (CD34⁺CD38⁻) may have higher ABCB1 activity than CD34⁺CD38⁺ cells. As CD34⁺CD38⁻ cells represent only 1-2% of total CD34⁺ cells, flow cytometry may not be able to detect ABCB1 surface protein expression on these minority cell populations in CD34⁺ bulk cells, while Rhodamine-123 fluorescence assay

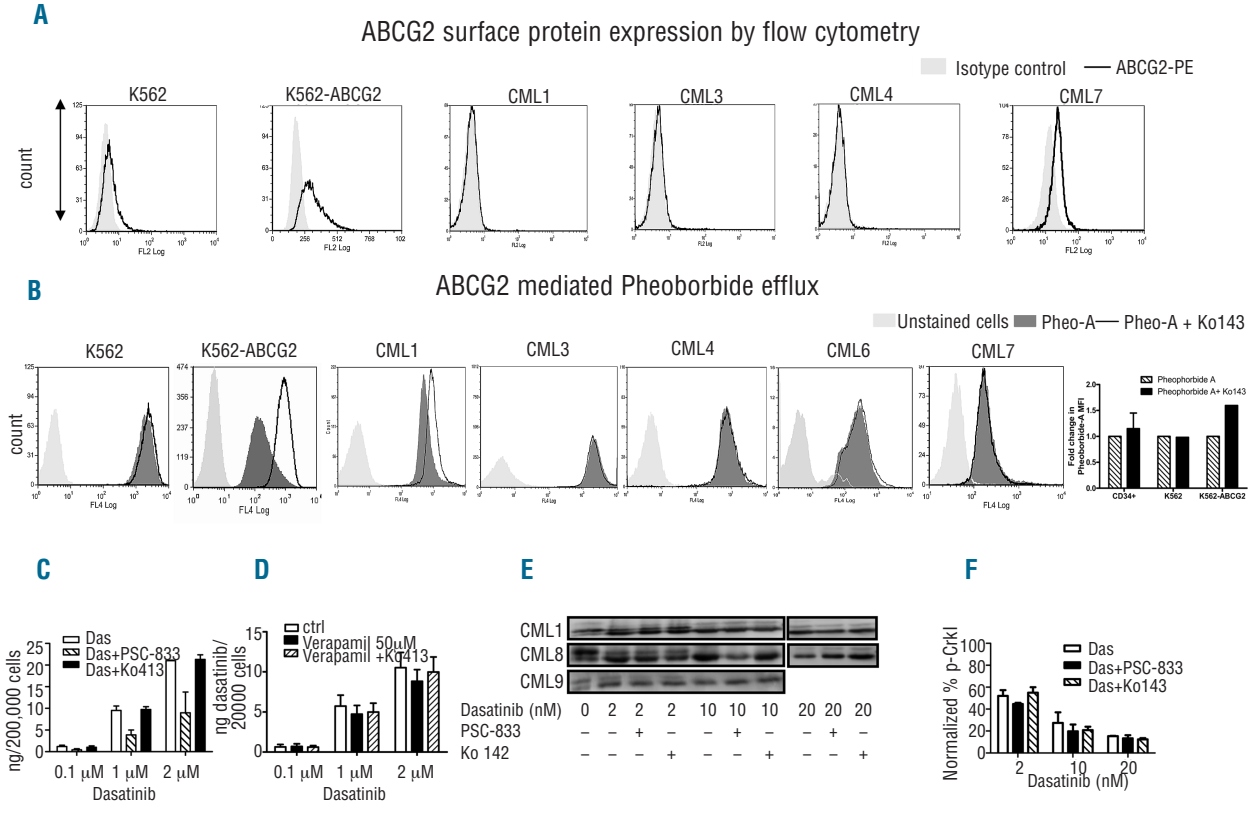

Figure 2. Blocking of ABCB1 or ABCG2 did not enhance the effect of dasatinib in CML-CD34⁺ cells. (A) Flow cytometry did not detect high expression of ABCG2 on CML-CD34⁺ cells (n=4). K562-ABCG2 and K562 cells were employed as positive and negative control. (B) K562-ABCG2 cells effluxed Pheophorbide-A effectively which was blocked by Ko143. CML-CD34⁺ cells (n=5) did not show increased ABCG2 activity and Ko143 did not change Pheophorbide-A fluorescence significantly. Ko143 increased Pheophorbide-A MFI by 1.15, 0.9 and 1.6-fold in CML-CD34⁺, K562 and K562-ABCG2 cells. (C) Neither PSC-833 nor Ko143 increased dasatinib IUR in CML-CD34⁺ cells, on the contrary PSC-833 reduced dasatinib IUR. (D) Similarly, verapamil (another ABCB1 inhibitor) did not change dasatinib IUR significantly. Combined blockade of ABCB1 and ABCG2 by verapamil and Ko143 did not increase dasatinib IUR in CML-CD34⁺ cells (n=3). (E-F) CML-CD34⁺ cells were cultured with dasatinib (2, 10 and 20 nM) with or without PSC-833 or Ko143 and inhibition of Crkl phosphorylation was assessed by Western blot. Neither PSC-833 nor Ko143 enhanced dasatinib mediated Bcr-Abl kinase inhibition.

may be able to detect efflux activity of these 1-2% cells in bulk CD34+ cells. However, due to limitation of cell numbers this has not been tested.

Using ABCG2 over-expressing cell lines, we and others have previously demonstrated that dasatinib is an ABCG2 substrate.[11-13] Therefore, we assessed ABCG2 surface expression and functional activity in CML-CD34+ cells. K562-ABCG2 and K562 cells were used as a control. Flow cytometry analysis suggested that ABCG2 protein was not over-expressed in CML-CD34+ cells (n=4) (Figure 2A). Functional activity of ABCG2 efflux pump was assessed by using Pheophorbide-A, a fluorescent ABCG2 substrate. MFI of was substantially lower in K562-ABCG2 cells compared to K562 cells (MFI 209.5 *vs.* 348) (Figure 2B). Ko143, an ABCG2 inhibitor, blocked ABCG2-mediated efflux and increased Pheophorbide-A MFI in K562-ABCG2 cells (209.5 *vs.* 334.5) (Figure 2B). In CML-CD34+ cells, Ko143 increased the Pheophorbide MFI by only 1.2±0.3-fold (n=5) (Figure 2B) suggesting that, in this cohort of patients, ABCG2 activity in CML-CD34+ cells is not high. Similarly, using BODIPY-prazosin, another ABCG2 substrate, Davies *et al.* also reported low ABCG2 activity in CML-CD34+ cells.[17]

Blocking ABCB1 or ABCG2 activity did not potentiate the effect of dasatinib in CML CD34+ cells

In ABCB1 over-expressing K562-Dox cells, PSC-833 (ABCB1 inhibitor) significantly increased dasatinib IUR and reduced the $IC50^{dasatinib}$.[11] However, PSC-833 did not increase dasatinib IUR (100 nM, 1μM, and 2 μM dasatinib) in CML-CD34+ progenitors (Figure 2C); on the contrary, there was reduction in dasatinib IUR. Therefore, experiments were repeated using another ABCB1 inhibitor, verapamil. Verapamil made no significant change to dasatinib IUR (at 0.1, 1 and 2 μM of dasatinib) in CML-CD34+ cells (n=3) (Figure 2D).

We then assessed the effect of PSC-833 on dasatinib-mediated Bcr-Abl kinase activity in CML-CD34+ cells and MNC. In CML-CD34+ cells, PSC-833 did not augment Crkl phosphorylation inhibition mediated by 2 nM (52±5 *vs.* 44.6±1), 10 nM (27.4±9.6 *vs.* 19.7±6) and 20 nM (15.4±0.2 *vs.* 13.3±2.8) dasatinib (Figure 2E and F).

Nilotinib inhibited ABCB1-mediated Rhodamine-123 efflux in K562-Dox cells (*Online Supplementary Figure S2A* and *B*) which is consistent with previously published findings[18,19] and increases dasatinib IUR in K562-Dox cells.[20] However, in CML-CD34+ cells, nilotinib did not increase the IUR of 100 nM (0.9±0.4 *vs.* 0.9±0.3; n=4) and 1 μM (8±1.1 *vs.* 8±1; n=4) ^{14}C-Das (*Online Supplementary Figure S2C*). Similarly, we did not observe any effect of nilotinib on ^{14}C-das IUR in CML-MNC (P>0.5) (*Online Supplementary Figure S2D*).

We have previously reported that Ko143, an ABCG2 inhibitor, significantly increases dasatinib IUR and significantly reduces $IC50^{dasatinib}$ in the K562-ABCG2 (ABCG2 over-expressing) cell line.[11] However, in CML-CD34+ cells, Ko143 did not increase the IUR of 100 nM (1.1±0.3 *vs.* 1.0±0.3; n=3), 1 μM (9.5 μM ±1 *vs.* 9.7±0.6; n=3) and 2 μM (21±0.13 *vs.* 21.2±1.0; n=3) of ^{14}C-Das (Figure 2C). Ko143 did not enhance Bcr-Abl kinase inhibition mediated by 2 nM (52±5 *vs.* 55±5; n=3), 10 nM (27±10 *vs.* 20 ±3; n=3) and 20 nM (15 ±0.2 *vs.* 12±1; n=3) of dasatinib (Figure 2E-F).

Moreover, simultaneous ABCB1 and ABCG2 blockade with verapamil and Ko143 did not increase dasatinib IUR (0.1, 1 and 2 μM of dasatinib) significantly in CML-CD34+ cells (Figure 2D). Together these results suggest that blockade of ABCB1 and ABCG2 does not increase dasatinib IUR nor potentiate dasatinib-mediated Bcr-Abl kinase inhibition in CML-CD34+ cells (Figure 2E and F). Davies and colleagues reported that blocking of ABCB1 and ABCG2 did not augment the effect of nilotinib on CML-CD34+ cells.[17] Similarly Hatziieremia *et al.* reported that blocking of ABCB1 efflux pump did not augment IM effect on CML-CD34+ cells and the authors concluded that ABCB1 is expressed at too low a level to be of functional significance in these cells.[16]

Dasatinib does not block efflux of ABCB1 substrates

Although multiple studies have demonstrated that dasatinib is an ABCB1 substrate,[11-13] none have assessed whether dasatinib interferes with the cellular efflux of other ABCB1 substrates. As ABCB1 proteins are detected in numerous organs, such as the adrenals, kidneys, liver, colon, small intestine, brain, heart, placenta and testes, drug-drug interaction with these proteins might influence the cellular concentration of other medications administered simultaneously. Therefore, in the present study, we assessed the effect of dasatinib on other ABCB1 substrates. At therapeutically relevant concentrations, dasatinib did not inhibit Rhodamine-123 efflux in K562-Dox cell line and K562 cells (*Online Supplementary Figure S2A* and *B*), suggesting that it does not block ABCB1-mediated efflux of Rhodamine-123. Similarly, dasatinib did not increase IUR of 1 μM and 2 μM ^{14}C-IM in K562-Dox cells and VBL-100 cells (ABCB1 over-expressing cells) and their parental cells, K562 and CCRF-CEM respectively, (*Online Supplementary Figure S2E-J*). Together these data suggest that, unlike nilotinib,[18] therapeutically achievable concentrations of dasatinib does not block ABCB1-mediated efflux. Dhose *et al.* suggested that dasatinib is an ABCB1 inhibitor, but only at a very high concentration (10 μM) which is not achievable at therapeutic dosing schedule and, therefore, probably not clinically relevant.[19] Understanding these interactions can be clinically relevant for monitoring the drug level, dosing schedule and drug-drug interactions.

Conclusion

This study demonstrates that, in contrast to imatinib, dasatinib intracellular concentration is similar in CML-CD34+ cells and MNC. Moreover, there was no significant difference in dasatinib-mediated Bcr-Abl kinase inhibition between CML-CD34+ progenitors and MNC. Thus, these *in vitro* data suggest that dasatinib targets CML-CD34+ progenitors as effectively as it targets mature cells. Although dasatinib is an ABCB1 and ABCG2 substrate, ABCB1 and ABCG2 inhibitors neither increased dasatinib intracellular concentration nor enhanced the dasatinib-mediated Bcr-Abl kinase inhibition in CML-CD34+ progenitors. This suggests that, in newly diagnosed CML-CP patients, ABCB1 and ABCG2 efflux pump activities do not appear to influence the intracellular dasatinib concentration in CML-CD34+ progenitors.

Authorship and Disclosures

Information on authorship, contributions, and financial and other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355(23):2408-17.
2. Chomel JC, Bonnet ML, Sorel N, Bertrand A, Meunier MC, Fichelson S, et al. Leukemic stem cell persistence in chronic myeloid leukemia patients with sustained undetectable molecular residual disease. Blood. 2011;118(13):3657-60.
3. Chu S, McDonald T, Lin A, Chakraborty S, Huang Q, Snyder DS, et al. Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood. 2011;118 (20):5565-72.
4. Copland M, Hamilton A, Elrick LJ, Baird JW, Allan EK, Jordanides N, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood. 2006;107(11):4532-9.
5. Engler JR, Frede A, Saunders VA, Zannettino AC, Hughes TP, White DL. Chronic myeloid leukemia CD34+ cells have reduced uptake of imatinib due to low OCT-1 activity. Leukemia. 2010;24(4):765-70.
6. Jiang X, Zhao Y, Smith C, Gasparetto M, Turhan A, Eaves A, et al. Chronic myeloid leukemia stem cells possess multiple unique features of resistance to BCR-ABL targeted therapies. Leukemia. 2007;21(5):926-35.
7. Kantarjian H, Cortes J, Kim DW, Dorlhiac-Llacer P, Pasquini R, DiPersio J, et al. 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. 2009;113(25): 6322-9.
8. Muller MC, Cortes JE, Kim DW, Druker BJ, Erben P, Pasquini R, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009;114(24):4944-53.
9. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-70.
10. Konig H, Copland M, Chu S, Jove R, Holyoake TL, Bhatia R. Effects of dasatinib on SRC kinase activity and downstream intracellular signaling in primitive chronic myelogenous leukemia hematopoietic cells. Cancer Res. 2008;68(23):9624-33.
11. Hiwase DK, Saunders V, Hewett D, Frede A, Zrim S, Dang P, et al. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. Clin Cancer Res. 2008;14(12):3881-8.
12. Giannoudis A, Davies A, Lucas CM, Harris RJ, Pirmohamed M, Clark RE. Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): implications for the treatment of imatinib-resistant chronic myeloid leukemia. Blood. 2008;112(8):3348-54.
13. Hegedus C, Ozvegy-Laczka C, Apati A, Magocsi M, Nemet K, Orfi L, et al. Interaction of nilotinib, dasatinib and bosutinib with ABCB1 and ABCG2: implications for altered anti-cancer effects and pharmacological properties. Br J Pharmacol. 2009;158(4):1153-64.
14. ten Hoeve J, Arlinghaus RB, Guo JQ, Heisterkamp N, Groffen J. Tyrosine phosphorylation of CRKL in Philadelphia+ leukemia. Blood. 1994;84(6):1731-6.
15. Oda T, Heaney C, Hagopian JR, Okuda K, Griffin JD, Druker BJ. Crkl is the major tyrosine-phosphorylated protein in neutrophils from patients with chronic myelogenous leukemia. J Biol Chem. 1994;269(37):22925-8.
16. Hatziieremia S, Jordanides NE, Holyoake TL, Mountford JC, Jorgensen HG. Inhibition of MDR1 does not sensitize primitive chronic myeloid leukemia CD34+ cells to imatinib. Exp Hematol. 2009;37(6):692-700.
17. Davies A, Jordanides NE, Giannoudis A, Lucas CM, Hatziieremia S, Harris RJ, et al. Nilotinib concentration in cell lines and primary CD34(+) chronic myeloid leukemia cells is not mediated by active uptake or efflux by major drug transporters. Leukemia. 2009;23(11):1999-2006.
18. Tiwari AK, Sodani K, Wang SR, Kuang YH, Ashby CR Jr, Chen X, et al. Nilotinib (AMN107, Tasigna) reverses multidrug resistance by inhibiting the activity of the ABCB1/Pgp and ABCG2/BCRP/MXR transporters. Biochem Pharmacol. 2009;78(2): 153-61.
19. Dohse M, Scharenberg C, Shukla S, Robey RW, Volkmann T, Deeken JF, et al. Comparison of ATP-binding cassette transporter interactions with the tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib. Drug Metab Dispos. 2010;38(8):1371-80.
20. Hiwase DK, White D, Zrim S, Saunders V, Melo JV, Hughes TP. Nilotinib-mediated inhibition of ABCB1 increases intracellular concentration of dasatinib in CML cells: implications for combination TKI therapy. Leukemia. 2010;24(3):658-60.