Leukemia Research Reports 21 (2024) 100452

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

# Long-term follow-up of efficacy and safety in elderly patients with chronic myeloid leukemia treated with intermittent low dose dasatinib therapy

Masahiro Imamura [a,*], Yusuke Nakamura [b], Daisuke Hidaka [a], Reiki Ogasawara [a], Kohei Okada [a], Junichi Sugita [a], Shuichi Ota [a]

[a] Department of Hematology, Sapporo Hokuyu Hospital, 5-1, 6 Jyo 5 Chome, Higashi-sapporo, Shiroishi-ku, Sapporo, 003-0006, Japan
[b] Department of Pharmacy, Sapporo Hokuyu Hospital, 5-1, 6 Jyo 5 Chome, Higashi-sapporo, Shiroishi-ku, Sapporo, 003-0006, Japan

ARTICLE INFO

*Keywords:*
Chronic myeloid leukemia
Dasatinib
Elderly patients
Intermittent low dose therapy
Long-term follow-up

ABSTRACT

Intermittent low dose dasatinib therapy brought about a beneficial effect in elderly patients with chronic-phase chronic myeloid leukemia (CML-CP) without inducing severe adverse events (AEs). An 85-year-old male patient, who received twice-weekly, thrice-weekly, or four-times-weekly administration of 20 mg/day dasatinib after once-weekly administration, achieved a major molecular response two years after the start of dasatinib treatment and later sometimes achieved a deep molecular response, maintaining the efficacy for 11 years. The mean daily dose ranged from 5.7 mg to 11.4 mg. Furthermore, a 79-year-old male patient, who received thrice-weekly or every other day administration of 20 mg/day dasatinib after once-weekly administration, achieved a deep molecular response at four and half years after the start of dasatinib treatment. The mean daily dose is 8.6 mg. Intermittent low dose dasatinib therapy appears to be feasible in elderly patients with CML-CP. The goal of treatment in elderly patients with CML-CP appears to be different from that in younger patients, since they often suffer from serious AEs in the case of standard dose tyrosine kinase inhibitor therapy, followed by the dose reduction or cessation of treatment.

## 1. Introduction

The advent of *BCR-ABL1*-selective tyrosine kinase inhibitors (TKIs) have changed the treatment landscape for chronic-phase chronic myeloid leukemia (CML-CP), inducing a deep molecular response (DMR) of *BCR-ABL1*$^{IS}$ $\leq$0.01 % in a high proportion of patients. However, elderly patients often suffer from serious complications even by low dose administration of TKIs, and therefore the reduction or discontinuation of treatment is frequently required. In fact, approximately 30 % of elderly patients aged more than 60 years underwent dose reduction of TKIs due to severe adverse events (AEs) [1]. This proportion increases depending on the aging due to the age-related decrease in drug metabolisms. We have experienced two cases who treated with intermittent low dose dasatinib therapy, achieving a favorable outcome for a long time. Here, we discuss the feasibility of intermittent low dose dasatinib therapy in elderly patients with CML-CP, comparing the efficacy and safety reported in the previous studies in which the outcome of lower dose TKI therapy are demonstrated [2–10].

## 2. Case presentation

An 85-year-old male patient with CML-CP (case one) received low-dose (100 to 200 mg/day) imatinib 11 years ago [11] (Table 1). Two weeks later various AEs, such as edema and rash (grade1 of Common Terminology Criteria for Adverse Events version 5 (CTCAE ver. 5)) occurred and thereafter, myalgia and liver dysfunction (CTCAE ver. 5 grade 2) developed, followed by the discontinuation of treatment. Since all symptoms disappeared two months after the cessation of imatinib treatment, the patient received a low dose dasatinib of 20 mg/day. This dosing again caused mild thrombocytopenia (CTCAE ver. 5 grade 2); therefore, dosing schedule was changed from once-daily administration to twice-weekly administration via a short term of thrice-weekly administration. Pharmacokinetics study revealed that delayed but adequate amount of the intracellular concentration of dasatinib (2.57 and 5.61 ng/mL at 1 h and 2 h post administration, respectively) despite quite low plasma concentrations of this agent (<0.05, 4.46, and 9.38 ng/mL at trough, 1 h, and 2 h post administration, respectively) [12].

* Corresponding author at: Department of Hematology, Sapporo Hokuyu Hospital, 5-1, Higashi-sapporo, 5-1, 6 Jyo 5 Chome, Shiroishi-ku, Sapporo, 003-0006, Japan.
*E-mail address:* masahiro-imamura@outlook.jp (M. Imamura).

https://doi.org/10.1016/j.lrr.2024.100452
Received 25 January 2024; Accepted 22 February 2024
Available online 23 February 2024

**Table 1**
Long-term follow-up of patients with chronic-phase chronic myeloid leukemia treated with low-dose dasatinib therapy.

| Treatment day | Used TKI Dose Schedule (mg/day) (days/week) | | Molecular response AMP-CML *BCR-ABL1*$^{IS}$ (copies/ (%) 0.5 μgRNA) | Adverse events (CTCAE version 5.0) |
|---|---|---|---|---|
| Case one: an 85-year-old male | | | | |
| -8 | None | | >625 | |
| 0 | IM 100 | | | |
| | 7 | | | |
| 63 | Cessation of IM | | | Grade1 edema and skin rash Grade 2 myalgia, liver dysfunction, and thrombocytopenia |
| 133 | DA 20 | 7 | >525 | |
| 153 | DA 20 | 3 | | Grade 2 thrombocytopenia |
| 167 | DA 20 | 2 | | |
| 509 | DA 20 | 2 | 86 | |
| 874 | DA 20 | 2 | <5 (≈ <0.01) | |
| 1199 | DA 20 | 2 | 0.0250 | |
| 1546 | DA 20 | 2 | 0.0336 | |
| 1716 | DA 20 | 3 | | |
| 1795 | DA 20 | 2 | | Grade 2 liver dysfunction |
| 1851 | DA 20 | 2 | 0.1427 | |
| 1905 | DA 20 | 4 | 0.0560 | |
| 1954 | DA 20 | 4 | 0.0300 | |
| 2290 | DA 20 | 4 | 0.0045 | |
| 2709 | DA 20 | 4 | 0.0100 | |
| 3072 | DA 20 | 4 | 0.0130 | |
| 3438 | DA 20 | 4 | 0.0200 | |
| 3802 | DA 20 | 4 | 0.0062 | |
| 4068 | DA 20 | 4 | 0.0192 | |
| 4152 | DA 20 | 4 | 0.0245 | |
| Case two: a 79-year-old male | | | | |
| -14 | None | | | |
| 0 | DA 20 | 7 | 121.5240 | |
| 21 | DA 20 | 3 | | Grade 2 thrombocytopenia |
| 56 | DA 20 | 3 | 1.0171 | |
| 140 | DA 20 | 3 | 0.4430 | |
| 252 | DA 20 | 3 | 0.2497 | |
| 308 | DA 20 | | | |
| | Every 2 | | | |
| 336 | DA 20 | | 0.0948 | |
| | Every 2 | | | |
| 364 | DA 20 | | 0.1450 | |
| | Every 2 | | | |
| 413 | DA 20 | 7 | 0.1790 | |
| 469 | DA 20 | | 0.1847 | |
| | Every 2 | | | |
| 665 | DA 20 | | 0.1108 | |
| | Every 2 | | | |
| 711 | DA 20 | | 0.1128 | |
| | Every 2 | | | |
| 907 | DA 20 | | 0.0417 | |
| | Every 2 | | | |
| 1102 | DA 20 | | 0.0310 | |
| | Every 2 | | | |
| 1296 | DA 20 | | 0.0252 | |
| | Every 2 | | | |
| 1410 | DA 20 | | 0.0163 | |
| | Every 2 | | | |
| 1634 | DA 20 | | 0.0096 | |
| | Every 2 | | | |

Abbreviations: AMP-CML, transcription mediated amplification method; *BCR-ABL*$^{IS}$, the breakpoint cluster region-Abelson 1 transcript level on the International Scale; CTCAE, Common Terminology Criteria for Adverse Events; DA, dasatinib; IM, imatinib; RNA, ribonucleic acid; TKI, tyrosine kinase inhibitor.

Here, the intracellular concentration (5.61 ng/mL) at 2 h post administration in this patient was close to that (5.94 ng/mL) in a patient with CML-CP who achieved a major molecular response (MMR) treated with once-daily administration of the standard dose (100 mg/day) dasatinib. In this control patient, the plasma concentration at trough, 1 h, and 2 h was 6.62, 127.8, and 63.2 ng/mL, respectively. In general, the efficacious trough and peak plasma concentrations in once-daily administration of 100 mg/day was supposed to be 2.61 and 54.6 ng/mL, respectively [13]. Thus, such a unique pharmacokinetics in this patient indicated a possibility of alteration in drug transporter function. The analysis in single nucleotide polymorphisms (SNPs) of drug transporter genes showed a certain correlation between the efficacy and the genotypes [14]. Resultantly, it turned out that this patient possessed the SNPs related to the AEs of imatinib and the efficacy of dasatinib. Since the *BCR-ABL1* kinase domain dependent- and independent-mechanisms, and other mechanisms regulate the efficacy of TKIs, the analysis of SNPs alone may not be sufficient to predict the effect of TKIs. More comprehensive analyses may be necessary, whereas the occurrence of AEs is predictable by the analysis of SNPs. In elderly patients with CML, administration of the standard dose of TKIs is sometimes intolerable due to severe AEs. Therefore, the analysis of SNPs in conjunction of pharmacokinetics study can provide useful information to determine the adequate dosing and administration schedule, avoiding the development of severe AEs and achieving a favorable molecular response. According to findings in case one, accomplishment of an early molecular response in elderly patients with CML-CP appears to be not always required dissimilar to younger patients who are expected to achieve a treatment-free response. As shown in Table 1, case one achieved an MMR of *BCR-ABL1* $^{IS}\leq$0.1 % almost two years after the start of dasatinib treatment. The *BCR-ABL1* $^{IS}$ between three and four years after the start of dasatinib treatment varied from 0.0336 % to 0.0250 % and thereafter slightly increased. Therefore, we changed the dosing schedule to four-times-weekly administration. The *BCR-ABL1* $^{IS}$ between five and eleven years after the start of dasatinib treatment fluctuated from 0.056 % to 0.0045 %, showing the efficacy frequently beyond MMR and occasionally close to DMR. The intermittent low dose dasatinib therapy in elderly patients with CML-CP is feasible, achieving an MMR or a DMR for 11 years. Now, he is 96 years old and enjoying calm and ordinary lives. The mean daily dose of dasatinib is only 5.7 to 11.4 mg.

In addition, we treated another 79-year-old male patient (case two) with CML-CP who administered intermittent low dose (thrice-weekly administration or every other day administration of 20 mg; the mean daily dose of 8.6 to 10 mg) dasatinib. The efficacy judged by the level of *BCR-ABL1* $^{IS}$ gradually decreased from 121.5240 % and achieved a DMR (*BCR-ABL1* $^{IS}$ of 0.0096 %) at four and half years after the start of dasatinib treatment. Although mild thrombocytopenia (CTCAE ver. 5 grade 2) developed, he had no severe AEs (Table 1). The trough and peak (1 h post administration) plasma concentrations on day fifty-five treated with thrice-weekly administration of 20 mg/day were 1.45 and 30.19 ng/mL, respectively. Although the peak concentration is slightly lower than that (54.6 ng/mL) in the patient treated with once-daily administration of the standard dose (100 mg/day) of dasatinib, one should notice the fact that the mean daily dose was 8.6 mg in this patient treated with thrice-weekly administration of 20 mf/day of dasatinib.

## 3. Discussion

In elderly patients, aggressive treatment is not always tolerable; therefore, a sustained chronic phase is acceptable. The goal of treatment in elderly patients with CML-CP seems to differ from that in younger patients. In the case of imatinib, intermittent (one week on and one week off for the first month; two weeks on and two weeks off for the second and third months; one month on and one month off for the fourth month to the twelve month and thereafter) standard dose therapy was not successful in terms of improving the clinical outcome while affected cytogenetic and molecular response [15]; therefore, it is important to validate whether the induction of efficacy in intermittent low dose therapy is dasatinib-specific and limited to the individual who possesses unique features of drug transporter gene polymorphisms like case one.

Previous studies showed the efficacy of lower dose (40 mg/day to 80 mg/day, mostly 50 mg/day) dasatinib therapy [2–9] (Table 2). In

**Table 2**
Efficacy and safety of low dose tyrosine kinase inhibitors in patients with chronic-phase chronic myeloid leukemia.

| No of cases | Median Age (Range) | TKI dose mg/day | Efficacy P value/ 95% CI | Adverse events | Ref. |
|---|---|---|---|---|---|
| 21 | 76 (65-83) | DA >20-≤50 (n=6) | MR4 at any time: 100%<br>6-M MR4:17%<br>1-Y MR4:34%<br>2-Y MR4: 50%<br>MR4.5 at any time: 50%<br>2-Y MR4.5:17% | Grade 1/2 PE: 29<br>Grade 3/4 AEs: 15% | Itamura et al. 2017 |
| | | DA ≤20 (n=15) | MR4 at any time: 74%<br>6-M MR4: 20%<br>1-Y MR4: 47%<br>2-Y MR4: 67%<br>MR4.5 at any time:67%<br>2-Y MR4.5: 34% | | |
| 9 | 73 (64-87) | DA 50 | MMR at 12-M: 5/9<br>DMR at 18-M: 3/9 | Mild-to-moderate PE:1/9 | Iriyama et al. 2018 |
| 83 | | DA 50 | 3-Y MMR: 92% 0.23<br>3-Y MR4: 77% 0.04<br>3-Y MR4.5: 77% 0.02<br>4-Y FFS: 89% 0.04<br>4-Y EFS: 95% 0.06<br>4-Y OS: 97% 0.78 | Grade 3/4 AEs: 27%<br>Grade 3/4 PE: 3% | Jabbour et al. 2022 |
| 150 | | DA 100 | 3-Y MMR: 84%<br>3-Y MR4: 66%<br>3-Y MR4.5: 62%<br>4-Y FFS: 77%<br>4-Y EFS: 92%<br>4-Y OS: 96% | Grade 3/4 AEs: 32%<br>Grade 3/4 PE: 10% | |
| 83 | 47 (20-84) | DA 50 | 5-Y CCyR:98%<br>5-Y MMR: 95%<br>5-Y DMR: 82%<br>5-Y OS:96%<br>5-Y EFS: 90% | Grade 3/4 AEs: 18%<br>Grade 3/4 PE: 2% | Gener-Ricos et al. 2023 |
| 49 | 40 (19-73) | DA 50 | 6-M BCR-ABLIS$^{a}$≤1%: 87% 0.04<br>1-Y MMR:68%<br>1-Y MR4: 20%<br>1-Y MR4.5: 12%<br>2-Y EFS: 85.9% 0.031<br>2-Y OS: 96.2% | Grade 3 AEs: 2% | Ahmed et al. 2023 |
| | | IM 400 | 6-M BCR-ABLIS$^{a}$≤1%: 63.3%<br>1-Y MMR 66.6%<br>1-Y MR4: 5.5%<br>1-Y MR4.5: 0%<br>2-Y EFS: 48.9%<br>2-Y OS: 95% | Grade 3/4 AEs: 0% | |
| 3 | 31 | DA 80-100, 50 | BCR-ABLIS%: 0.01% | Grade 4 thrombocytopenia at high dose | Serpa et al. 2010 |
| | 46 | DA 70-100, 80 | BCR-ABLIS%: 0.8% | Grade 4 thrombocytopenia and grade 3 neutropenia at high dose | |
| | 58 | DA 40-100, 20/40 alternate-day treatment | BCR-ABLIS%: 0.018% | Grade 4 pancreatitis at high dose | |
| 2 | 43 | IM 800 | MMR at 9 M | | Jamieson et al. 2016 |
| | | DA 140, 20 | DMR at later time | Grade 2/3 arthralgia, myalgia, headache, and edema at high dose | |
| | 53 | IM 400 | MMR at 10 M | Grade 2/3 painful maculopapular rash, pancreatitis, and edema at high dose | |
| | | DA 140, 50 | DMR at later time | | |
| 90 | | IM | 92.8% (95% CI, 85.3-96.6%) | Not applicable | Claudiani et al. 2021 |
| | 50 (18-86) | IM 300 | 2-Y MRFS: 94.4% | | |
| | 44 (19-72) | IM 200 | 2-Y MRFS: 89.8% | | |
| 88 | | DA | 94% (95% CI: 86.7-97.4%) | | |
| | 46 (24-68) | DA 70 | 2-Y MRFS: 100% | | |
| | 50 (20-73) | DA 50 | 2-Y MRFS: 96.9% | | |
| | 59 (20-79) | DA 40 | 2-Y MRFS: 91.7% | | |
| | 54 (18-90) | DA ≤20 | 2-Y MRFS: 88.5% | | |
| 81 | | NI | 91.6% (95% CI, 81.4-96.4%) | | |
| | 47 (18-83) | NI 400 | 2-Y MRFS: 92.5% | | |
| | 43 (21-64) | NI 300 | 2-Y MRFS: 85.7% | | |
| | 41 (29-55) | NI ≤200 | 2-Y MRFS: 90.9% | | |

(*continued on next page*)

**Table 2** (*continued*)

| No of cases | Median Age (Range) | TKI dose mg/day | Efficacy P value/ 95% CI | Adverse events | Ref. |
|---|---|---|---|---|---|
| 39 | | BO | 96.0% (95% CI, 80.6-99.3%) | | |
| | 49 (26-63) | BO 300 | 2-Y MRFS: 100% | | |
| | 49 (32-79) | BO 200 | 2-Y MRFS: 100% | | |
| | 56 (22-68) | BO <200 | 2-Y MRFS: 85.7% | | |
| 52 | 78 (74-84) | DA 20 | 1-Y MMR: 60%<br>1-Y MR4: 27%<br>1-Y MR4.5: 13% | Grade 3/4 AEs: 23%<br>Grade 3/4 neutropenia: 6% | Murai et al. 2021 |

Abbreviations: AEs, adverse events; BO, bosutinib; *BCR-ABL1*$^{IS}$, the breakpoint cluster region-Abelson 1 transcript level on the International Scale; CCyR, complete cytogenetic response; CI, confidence interval; DA. Dasatinib; DMR, deep molecular response; EFS, event-free survival; FFS, failure-free survival; IM, imatinib; M, month; MR, molecular response; MMR, major molecular response; MRFS, molecular recurrence-free survival; n, number; NI, nilotinib; P, provability; PE, pleural effusion; Ref., reference; TKI, tyrosine kinase inhibitor; OS, overall survival; Y, year.

addition, further lower doses (e.g., 20 mg/day or ≤20 mg/day) induced favorable outcomes [2–6] (Table 2). Itamura et al. reported that among 21 elderly patients with CML-CP, 91 % of patients administered the mean dasatinib dose of ≤50 mg/day achieved a molecular response of MR3 (*BCR-ABL1* $^{IS}$ < 0.1 %), MR4 (*BCR-ABL1* $^{IS}$ < 0.01 %), and MR4.5 (*BCR-ABL1* $^{IS}$ < 0.0032 %) in 96 %, 77 %, and 62 %, respectively, while 72 % of patients administered the mean dasatinib dose of ≤20 mg/day achieved a molecular response of MR3 and MR4 in 94 % and 74 %, respectively [2]. Similarly, Iriyama et al. demonstrated that nine elderly patients with CML-CP administered 50 mg/day of dasatinib achieved an MMR in 5 of 9 at 12 months and a DMR in 3 of 9 at 18 months [3]. Jabbour et al. showed that the efficacy of 50 mg/day of dasatinib ($n$ = 83) was comparable to that of 100 mg/day of dasatinib ($n$ = 150), while the frequency of pleural effusion was lower in the 50 mg/day cohort than in the 100 mg/day cohort [4]. Gener-Ricos et al. and Ahmed et al. confirmed that the efficacy of 50 mg/day of dasatinib was feasible [5,6]. However, since even this dose sometimes caused grade 3 to 4 AEs, especially in elderly patients, they required more reduced doses of dasatinib. Serpa et al. reported that a patient administered alternate day dasatinib of 20 mg and 40 mg every other day achieved an MMR [7]. Jamieson et al. demonstrated that the dasatinib administration of 20 mg/day as well as 50 mg/day induced a DMR [8]. Claudiani et al. showed that the two-year molecular recurrence-free survival (MRFS) in patients received dasatinib of 70 mg/day, 50 mg/day, 40 mg/day, and ≤20 mg/day was 100 %, 96.9 %, 91.7 %, and 88.5 %, respectively, suggesting that the efficacy of lower doses of dasatinib treatment is favorable [9]. In the same study, they showed that lower doses of other TKIs such as imatinib, nilotinib, and bosutinib were also acceptable in their efficacy. In imatinib cohort, the two-year MRFS was 94.4 %, and 89.8 % for 300 mg/day and 200 mg/day, respectively. In nilotinib cohort, the two-year MRFS was 92.5 %, 85.7 %, and 90.9 % for 400 mg/day, 300 mg/day, and ≤200 mg/day, respectively. In bosutinib cohort, the two-year MRFS was 100 %, 100 %, and 85.7 % for 300 mg/day, 200 mg/day, and ≤200 mg/day, respectively. These results clearly indicate that lower doses of TKIs can be efficacious in patients with CML-CP who are intolerant or resistant to the standard dose of a certain TKI. Murai et al. reported that the administration of 20 mg/day of dasatinib was effective in elderly patients with CML-CP [10].

However, there are no previous studies of long-term follow-up in elderly patients with CML-CP treated with intermittent low dose dasatinib therapy. Therefore, it is worthwhile to validate the efficacy of low dose therapy including intermittent administration of TKIs based on a larger clinical study. In that case, we need to pay attention to the induction of gene mutations related to drug resistance in the case of intermittent low dose TKI therapy as compared with continuous standard dose TKI therapy.

## 4. Conclusion

Intermittent low dose dasatinib therapy is efficacious in elderly patients with CML-CP without inducing serious AEs. In the future, a prospective randomized clinical study is required to ascertain its true efficacy.

## Funding

There was no specific funding for this manuscript.

## Data availability

The data are available from the corresponding author upon reasonable request.

## Consent to participate

Informed consent was obtained from the patients.

## CRediT authorship contribution statement

**Masahiro Imamura:** Conceptualization, Data curation, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Yusuke Nakamura:** Formal analysis, Methodology, Writing – review & editing. **Daisuke Hidaka:** Writing – review & editing. **Reiki Ogasawara:** Data curation, Writing – review & editing. **Kohei Okada:** Writing – review & editing. **Junichi Sugita:** Writing – review & editing. **Shuichi Ota:** Writing – review & editing.

## Declaration of competing interest

R.O., K.O., and S.O. received honoraria from Bristol Myers Squibb. K. O., J.S., and M.I. received honoraria from Novartis. The other authors declare no conflict of interest.

## References

[1] S. Ota, T. Matsukawa, S. Yamamoto, S. Ito, M. Shindo, K. Sato, T. Kondo, K. Kohda, H. Sakai, A. Mori, T. Takahashi, H. Ikeda, H. Kuroda, Y. Haseyama, M. Yamamoto, T. Sarashina, M. Yoshida, R. Kobayashi, M. Nishio, T. Ishihara, Y. Hirayama, Y. Kakinoki, H. Kobayashi, T. Fukuhara, M. Imamura, M. Kurosawa, Severe adverse events by tyrosine kinase inhibitors decrease survival rates in patients with newly diagnosed chronic-phase chronic myeloid leukemia, Eur. J. Haematol 101 (2018) 95–105.

[2] H. Itamura, Y. Kubota, T. Shindo, T. Ando, K. Kojima, S. Kimura, Elderly patients with chronic myeloid leukemia benefit from a dasatinib dose as low as 20mg, Clin. Lymphoma Myeloma Leuk. 17 (2017) 370–374.

[3] N. Iriyama, K. Ohashi, S. Hashino, S. Kimura, C. Nakaseko, H. Takano, M. Hino, M. Uchiyama, S. Morita, J. Sakamaoto, H. Sakamaki, K. Inokuchi, The efficacy of reduced-dose dasatinib as a subsequent therapy in patients with chronic myeloid leukemia in the chronic phase: the LD-CML study of the Kanto CML study group, Intern. Med. 57 (2018) 17–23.

[4] E. Jabbour, K. Sasaki, F.G. Haddad, G.C. Issa, J. Skinner, S. Dellasala, M. Yilmaz, A. Ferrajoli, P. Bose, P. Thompson, Y. Alvarado, N. Jain, G. Garcia-Manero, K. Takahashi, G. Borthakur, N. Pemmaraju, S. Pierce, H. Kantarjian, Low-dose dasatinib 50mg/day versus standard-dose dasatinib 100mg/day as frontline

therapy in chronic mueloid leukemia in chronic phase: a prospective score analysis, Am. J. Hematol. 97 (2022) 1413–1418.
[5] G. Gener-Ricos, F.G. Haddad, K. Sasaki, G.C. Issa, J. Skinner, L. Masarova, G. Borthakur, Y. Alvarado, G. Garcia-Manero, E. Jabbour, H. Kantarjian, Low-dose dasatinib (50mg daily) frontline therapy in newly diagnosed chronic phase chronic myeloid leukemia: 5-year follow-up results, Clin. Lymphoma Myeloma Leuk. 23 (2023) 742–748.
[6] R. Ahmed, R. Singh, J. Kapoor, P.C. Patra, N. Agrawal, D. Bhurani, R. Halder, Attenuated dose dasatinib in newly diagnosed chronic myeloid leukemia chronic phase patients in India, Clin. Lymphoma Myeloma Leuk 23 (2023) e71–e77.
[7] M. Serpa, S.S. Sanabani, I. Bendit, F. Seguro, F. Xavier, C.B. Barroso, M. Conchon, P.E. Dorlhiac-Llacer, 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 (2020) 155–162.
[8] C. Jamieson, D. Nelson, M. Eren, D. Gauchan, R. Ramaekers, M. Norvell, M. S. Copur, What is the optimal dose and schedule for dasatinib in chronic myeloid leukemia: two case reports and review of the literature, Oncol. Res. 23 (2016) 1–5.
[9] S. Claudiani, J.F. Apperley, R. Szydlo, A. Khan, G. Nesr, C. Hayden, A.J. Innes, K. Dominy, P. Foskett, L. Foroni, J. Khorashad, D. Milojkovic, TKI dose reduction can effectively maintain major molecular remission in patients with chronic myeloid leukaemia, Br. J. Haematol. 193 (2021) 346–355.
[10] K. Murai, H. Ureshino, T. Kumagai, H. Tanaka, K. Nishiwaki, S. Wakita, K. Inokuchi, T. Fukushima, C. Yoshida, N. Uoshima, T. Kiguchi, M. Mita, J. Aoki, S. Kimura, K. Karimata, K. Usuki, J. Shimono, Y. Chinen, J. Kuroda, Y. Matsuda, K. Nakao, T. Ono, K. Fujimaki, H. Shibayama, C. Mizumoto, T. Takeoka, K. Io, T. Kondo, M. Miura, Y. Minami, T. Ikezoe, J. Imagawa, A. Takamori, A. Kawaguchi, J. Sakamoto, S. Kimura, Low-dose dasatinib in older patients with chronic myeloid leukemia in chronic phase (DAVLEC): a single-arm, multicentre phase 2 trial, Lancet Haematol. 8 (2021) e902–e911.
[11] M. Imamura, Efficacy of intermittently administered dasatinib with a reduced dose in an elderly patient with chronic myeloid leukemia, Geriatr. Gerontol. Int 16 (2016) 768–770.
[12] M. Imamura, Y. Nakamura, M. Sugawara, Plasma and intracellular concentrations in an elderly patient with leukemia receiving low-dose dasatinib therapy, Geriatr. Gerontol. Int. 18 (2018) 505–507.
[13] X. Wang, A. Roy, A.M. Hochhaus, H.M. Kantarjian, T.-T. Chen, N.P. Shah, Differential effects of dosing regimen on the safety and efficacy of a phase III study, Clin. Pharmacol. 5 (2013) 85–97.
[14] Y. Nakamura, D. Hidaka, R. Ogasawara, K. Okada, J. Sugita, A. Sukehata, K. Kitagawa, S. Ota, M. Imamura, Analysis of drug transporter gene polymorphisms in an elderly patient with chronic myeloid leukemia successfully treated with intermittent low dose dasatinib, Geriatr. Gerontol. Int. 23 (2023) 965–966.
[15] D. Russo, G. Martinelli, M. Malagola, C. Skert, S. Soverini, I. Iacobucci, A. De Vivo, N. Testoni, F. Castagnetti, G. Gugliotta, D. Turri, M. Bergamaschi, P. Pregno, E. Pungolino, F. Stagno, M. Breccia, B. Martino, T. Intermesoli, C. Fava, E. Abruzzese, M. Tiribelli, C. Bigazzi, B.M. Cesana, G. Rosti, M. Baccarani, Effects and outcome of a policy of intermittent imatinib treatment in elderly patients with chronic myeloid leukemia, Blood 121 (2013) 5138–5144.