Dasatinib Dose Management for the Treatment of Chronic Myeloid Leukemia

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PRECIS

The focus of CML treatment is shifting to dose management, with the goal of maintaining response while improving quality of life. Results obtained from dasatinib dose optimization and discontinuation trials will help practitioners determine the best dose and duration of dasatinib for patients with CML.

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[ABSTRACT]

Chronic myeloid leukemia (CML) has evolved into a chronic disease managed with tyrosine kinase inhibitor (TKI) therapy. Now that long-term survival has been achieved in CML, the focus of treatment shifts to dose optimization, with the goal of maintaining response while improving quality of life. In this review, we discuss optimizing the dose of the second-generation TKI dasatinib. Once-daily dosing regimens for dasatinib in the first and later lines of treatment were established through long-term (5- and 7-year) trials. Recently published data indicate that further dose optimization may maintain efficacy while minimizing adverse events. Results obtained from dose optimization and discontinuation trials currently in progress will help practitioners determine the best dose and duration of dasatinib for patients with CML, as treatment decisions will be made through continued discussions between physicians and patients.

KEYWORDS: Dasatinib; Leukemia, Myelogenous, Chronic, BCR-ABL Positive; Quality of life; Tyrosine kinase inhibitor; Dose optimization

INTRODUCTION

Chronic myeloid leukemia (CML) has evolved into a chronic disease now managed with tyrosine kinase inhibitor (TKI) therapy.[1,2] As a result of the use of TKIs approved for CML, patients diagnosed in 2013 are predicted to lose < 3 life-years compared with those without CML, and thus have life spans approaching those of the general population.[3,4] In the United States, rates for new CML cases have been stable over the past 10 years; however, death rates have been decreasing an average 3.1% each year over 2004 through 2013 (Fig. 1).[5] Sixty-five percent of patients with CML survived 5 years or more during 2006 through 2012, as opposed to the 5-year period ending in 2000, when < 50% of patients survived 5 years or more.

Now that long-term survival has been achieved in CML, the focus of treatment shifts to dose optimization and personalization. Dasatinib is a second-generation BCR-ABL1 kinase inhibitor, currently approved at 2 doses[6]: at 100 mg once daily for patients with CML in chronic phase (CML-CP), newly diagnosed or following resistance or intolerance to a previous therapy, and at 140 mg once daily for patients with CML in accelerated/blast phase (CML-AP/BP) or with Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia who are resistant or intolerant to prior therapy. Optimization of dasatinib dosing should have 2 goals: maintenance of cytogenetic and molecular responses, and minimization of adverse events (AEs). In particular, optimization should describe the minimum daily dose of dasatinib that can sustain remission and achieve a patient's therapeutic goals.

Maintaining or improving quality of life (QoL) for patients with CML over the course of their treatment should be a major part of minimizing AEs. QoL may influence a patient's decision to seek treatment regimens of dasatinib that balance efficacy with the fewest AEs, and also offer the easiest adherence.[7] For example, a drug taken once per day is preferable to one requiring multiple daily doses, and a drug that may be taken regardless of type or timing of food is preferable to one that requires timing with regard to meals or that cannot be taken with certain foods. Younger female patients with CML treated with imatinib have reported lower QoL than

the general population[8]; this finding implies that for those who anticipate being on a TKI for many years, QoL aspects of treatment may be especially important.

Ongoing studies are helping to refine treatment options that may be appropriate for some patients, including dasatinib dose reductions, interruptions, or discontinuation. It is the goal of this review to bring clarity to the field of dasatinib dose optimization by discussing published retrospective analyses and ongoing prospective studies. In particular, we discuss factors that drive selection of the optimal dasatinib dose and duration for the treatment of CML.

OPTIMIZING CURRENTLY APPROVED DOSES FOR DASATINIB

The currently approved doses of dasatinib resulted from 2 long-term pivotal trials aimed at maximizing efficacy while minimizing AEs. The CA180-034 trial enrolled patients with imatinib-resistant or -intolerant CML-CP.[9] This study compared dasatinib 100 or 140 mg per day, and once- or twice-daily schedules, to determine the optimal dosage and regimen. Results showed that dasatinib treatment at a dose of 100 mg once daily demonstrated durable efficacy and a tolerable long-term safety profile. The data obtained from this study should be considered the proof of principle that the daily dose of dasatinib can be lowered, from 70 mg twice per day (a total dose of 140 mg per day) to 100 mg once per day in particular, while maintaining efficacy in patients intolerant of or resistant to imatinib.

The CA180-056 DASISION trial (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) was a study of newly diagnosed patients with CML-CP who received dasatinib 100 mg once daily or imatinib 400 mg once daily for a minimum of 5 years.[10] At the end of DASISION, dasatinib 100 mg once daily continued to show improved efficacy compared with imatinib 400 mg daily in the first line. The safety profile of first-line dasatinib 100 mg once daily was well tolerated over the long term; no new safety signals were reported. Taken together, the results of DASISION confirmed that 100 mg once daily constitutes an optimal dose of dasatinib for patients newly diagnosed with CML-CP.

DASATINIB DOSE REDUCTIONS AND/OR INTERRUPTIONS

Efficacy and Safety

There are published data indicating that modifying the dasatinib dose from 100 mg once daily can mitigate significant AEs yet maintain efficacy over the long term. In the phase II DARIA-01 study, patients with CML-CP were enrolled to determine factors influencing adherence and efficacy when AEs from dasatinib were managed with dose modifications.[11] Patients had their dasatinib doses reduced from 100 mg per day to 50 mg per day when they experienced a grade 2 or worse nonhematologic AE or grade 3 or worse hematologic AE. In this small study, 25% of patients had their doses reduced in the first 3 months, and 34% had their doses reduced in the first 6 months. At 6 months, 25 patients (78%) achieved complete cytogenetic responses (CCyR) and 13 (40%) achieved a major molecular response (MMR). Additionally, pleural effusions were managed effectively through dose modifications while molecular responses were maintained. In a small phase II study, NordCML006, 9 patients who had dasatinib doses reduced (6 to an average of 50 mg per day and 3 to an average of 63 mg per day) had nearly the same median rate of molecular response with 4.5-log reduction of *BCR-ABL1* transcripts ($MR^{4.5}$) as did the 8 patients who were maintained on 100 mg per day ($P = .53$).[12]

Previously, a retrospective analysis of exposure and response to dasatinib in the CA180-034 trial showed that major cytogenetic response (MCyR) was significantly associated with average steady-state dasatinib plasma concentrations.[13] Reducing the daily dose from 70 mg twice daily to 100 mg once daily minimized AEs while maintaining efficacy by exploiting differences in measures of exposure: the 100 mg once-daily arm had the lowest steady-state trough concentration of the 4 dose arms investigated in CA180-034. Although this arm also had the lowest weighted average steady-state dasatinib plasma concentration, it had the highest dose maintenance and efficacy. Moreover, pleural effusion was significantly associated with trough concentration, and thus occurred the least in the 100 mg once-daily arm.

The first-line OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy) trial is currently the only prospective study of dose optimization based on therapeutic drug monitoring.[14] This is a phase II trial with 289 newly diagnosed patients with CML-CP enrolled to validate a dose-optimization strategy using plasma levels of dasatinib. As part of the study, patients with high minimal plasma concentrations (C_{min} ≥ 3 nmol/L) had their dasatinib doses reduced in 20-mg decrements every 15 days to 40 mg per day (if needed) in order to lower C_{min} to < 3 nmol/L. Preliminary results of OPTIMDASATINIB showed that patients allocated to this therapeutic drug monitoring strategy showed reduced risk of pleural effusion without impairment of the kinetics of response. By 24 months, 88% of the patients with high C_{min} values who then had their dasatinib doses lowered achieved MMR, 69% achieved molecular response with 4-log reduction of *BCR-ABL1* transcripts ($MR^{4.0}$), and 39% achieved $MR^{4.5}$, considered a complete molecular response/remission (CMR). Moreover, the dose-optimization strategy reduced the risk of pleural effusion in the study population, consistent with the data obtained by Wang et al in their retrospective analysis described above.[13,14]

Intermittent dosing with dasatinib has been shown to improve tolerability in patients with CML who were resistant to or intolerant of imatinib.[15] A strategy of 3 to 5 days of dasatinib, followed by 2 to 4 days of no drug, reduced toxicity while maintaining efficacy. Overall, 18 of 31 patients (58%) maintained or had improved response while on weekly treatment, and 16 of 18 (89%) achieved MMR or $MR^{4.5}$. A larger study wherein 176 patients with CML received reduced and/or interrupted dosing of dasatinib or nilotinib showed there was no statistically significant difference between rates of MCyR or CCyR.[16] The median lowest dasatinib doses given in this study were 60 mg per day for patients with CML-CP and 80 mg per day for patients with CML-AP.

In addition, several case reports have corroborated the results of the previously discussed studies. In one report, a patient aged 85 years was successfully treated with 20 mg of dasatinib twice weekly after developing liver dysfunction on imatinib and achieved MMR 24

months later.[17] In another report, 2 patients with CML-CP were treated with 20 to 50 mg per day of dasatinib; 1 maintained undetectable *BCR-ABL1* transcripts for up to 1 year and 1 had levels of *BCR-ABL1* transcripts 4 to 5 logs reduced (at times the levels were undetectable).[18]

Predicting Which Patients Will Benefit From Dose Reductions

Early molecular responses to a TKI (within the first 6 months of initiating treatment) are predictive of long-term outcomes in CML, and several studies have shown that TKIs induced fast and deep molecular responses, defined as $MR^{4.0}$ or even $MR^{4.5}$.[19-21] These levels of responses predict durable, stable responses, and are considered prerequisites for either dose reductions or dose interruptions.

Both the European LeukemiaNet (ELN) and National Comprehensive Cancer Care Network (NCCN) recommendations define optimal responders in terms of molecular responses.[19,22,23] Therefore, at least for some patients, if deep molecular responses ($MR^{4.0}$ or $MR^{4.5}$) have been achieved after a treatment period, it should be possible to reduce dasatinib doses (Fig. 2).[19] However, molecular monitoring at fixed intervals is recommended by both the NCCN (every 3-6 months 2 years after the achievement of CCyR)[22] and the ELN (after the achievement of MMR),[23] which may result in missing the optimal time to reduce doses of dasatinib. For example, if a deep response occurs early in this timeframe between tests, the opportunity for a dose reduction may be missed or delayed.

Final study results from the 5-year DASISION trial for patients with CML-CP who received first-line dasatinib confirmed that achieving an early molecular response, *BCR-ABL1* ≤ 10% International Scale (IS) at 3 months, was correlated with significantly higher progression-free survival (PFS) and overall survival (OS) rates (88.9% and 93.8%, respectively, for PFS and OS) compared with patients who achieved *BCR-ABL1* > 10% (IS) at 3 months (71.8% and 80.6%, respectively, for PFS and OS).[10] For patients who received dasatinib after failing or becoming intolerant to imatinib in the 7-year CA180-034 study, those who achieved *BCR-ABL1*

≤ 10% (IS) at 3 months likewise showed significantly higher PFS and OS (56% and 72%, respectively, for PFS and OS) than those who had *BCR-ABL1* > 10% (IS) at 3 months (21% and 56%, respectively, for PFS and OS).[9]

Tools predicting outcome at any time during and after therapy would be useful throughout a patient's treatment regimen. Using data from DASISION and CA180-034,[9,10] investigators predicted responses during treatment with dasatinib based on plotting *BCR-ABL1* transcript levels and PFS or OS of patient populations.[24] Such analyses may allow investigators to predict future outcomes at any time, rather than solely at times of *BCR-ABL1* monitoring. A limitation of these projections would be that they become less precise as more time elapses from initiation of TKI therapy: the number of patients for whom a prediction might be made diminishes, reducing the accuracy of the prediction. Increasing the number of patients in the cohort is one way to negate this limitation, for example by combining suitable datasets.

In addition to molecular responses, effects on CD34+ cells may provide another means to predict responses to dasatinib. A study of newly diagnosed patients with CML-CP showed that the molecular responses at 3 and 6 months depended on the time of dasatinib plasma levels above the IC_{50} for CD34+ cells (dasatinib concentration required to inhibit 50% of CD34+ cells).[25] It was found that patients with longer times (> 12 hours) above the IC_{50} had significantly better prognoses: molecular responses at 3 and < 4 log reductions were 50% and 45%, respectively.

Other Patient Factors

Patient preference should be taken into consideration when deciding to modify dasatinib doses. Reductions and/or interruptions may be preferred by patients when discontinuing dasatinib is not an option; administering a lower dose of dasatinib, after starting treatment at the approved dose, may be preferable to switching to another TKI.[16] Moreover, modifying doses (lowering or interrupting) to mitigate toxicity may help improve adherence.[11]

In addition to minimizing AEs, economic concerns may drive a decision to lower daily doses for some patients.[26] In one study, 41 patients with CML-CP were treated with a mean dose of dasatinib of 92 mg ± 23 mg per day while achieving and maintaining efficacy, although the quality of the responses was not reported.[26] The driving force for reducing doses in this study appears to have been financial, rather than reduction of AEs. Furthermore, as long-term survival of patients with CML is predicted to increase the prevalence of the disease in the near future, the burden of healthcare costs may have to be considered when planning treatment. Thus, economic considerations beyond the personal may play a role in seeking the lowest effective dose of dasatinib or of any TKI.[27] Many of these cost concerns may be mitigated in the future, as approved generic versions of TKIs become available.

Ongoing Trials Investigating Dasatinib Efficacy With Dose Optimization

Nine trials are currently under way, focusing on modifying dasatinib dosing while retaining efficacy; their full titles, registry numbers, and summaries are given in Table 1. Two of these studies, DARIA-01[11] and OPTIMDASATINIB,[28] and have reported preliminary data and are described above.

There are 4 studies under way to determine optimizing dasatinib doses in patients or patient subgroups. A low-dose study in Japan will evaluate efficacy of 50 mg dasatinib per day in patients who are resistant to or intolerant of low-dose imatinib; the primary outcome measure is MMR at 12 months.[29] The CML12 DIRECT (Dasatinib Intensity Regulation to Eliminate Cumulative Toxicities) study will examine dose optimization of dasatinib in patients 60 years and older with CML. In this study, therapeutic daily monitoring will be used to optimize effective doses with minimal toxicity.[30] The DESTINY (De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel) trial will evaluate efficacy at 50 mg per day of dasatinib in treatment-naive patients with CML-CP[31]; its primary outcome is the proportion of patients who maintain MMR on 50 mg per day for 12 months. Patients will then discontinue dasatinib for up to 24 months. The

Therapy of Early Chronic Phase Chronic Myelogenous Leukemia With Dasatinib trial will evaluate whether giving 50 mg dasatinib per day to patients with early CML-CP is as effective as giving 100 mg per day.[32]

Two studies will examine dasatinib efficacy with planned dose interruptions. The DasaHIT trial will evaluate dasatinib holidays for improved drug tolerance in treatment-naive patients with CML and in patients receiving dasatinib as second-line treatment; its primary outcome measures are cumulative toxicity after 2 years and MMR as assessed by monitoring *BCR-ABL1* transcripts at 2 years.[33] The Optimization of TKIs Treatment and Quality of Life trial will evaluate the efficacy of intermittent dasatinib dosing (1 month on, 1 month off vs 1 month on, 1 month off in year 1; 1 month on, 2 months off in year 2; 1 month on, 3 months off in year 3), and the effect on QoL such dosing regimens may have; the primary outcome is changes in QoL at defined times.[34]

Finally, the DasPAQT (Treating Patients With Chronic Myeloid Leukemia in Chronic Phase With Dasatinib) trial is a real-life study to gather data on how CML is managed with dasatinib in practices outside of academic settings, including whether and when dose reductions are used.[35]

DASATINIB DISCONTINUATION

Efficacy

Treatment-free remission (TFR), defined as being free from molecular relapse following TKI discontinuation,[22] is currently an unmet need of CML therapy, as TKIs have increased patients' life spans to be nearly equal to those of the general population.[3,4] To date, there are limited published data on discontinuing dasatinib. In 1 small trial of 34 patients with CML-CP, second-generation TKIs (dasatinib and nilotinib) were safely discontinued.[36] The 12-month probability of maintaining stable MMR was 58%, and no patient progressed to CML-AP or experienced hematologic relapse. The OPTIMDASATINIB trial for newly diagnosed patients with CML also examined dose discontinuations in early responders (those who had *BCR-ABL1* [IS] ≤ 0.0032%

by 3 years).[37] Preliminary results showed that at 12 months, 41% of patients were in TFR. The DADI trial evaluated the effect of dasatinib discontinuation in patients with CML who had been in deep molecular response for at least 1 year.[38] Preliminary results showed that of the 63 patients who discontinued dasatinib, 30 maintained deep molecular responses, and 33 had molecular relapses (all during the first 7 months). The authors concluded that a treatment-free period lasting for > 1 year is feasible. The DASFREE trial is a study for patients with CML-CP receiving either first or subsequent lines of dasatinib who are in stable deep molecular response; the primary endpoint is the MMR rate at 12 months after discontinuation.[39] An interim analysis of 30 patients showed that 1 year after discontinuation, patients had a high TFR success rate (63% had MMR and molecular relapse-free survival at 12 months).[40] There was rescue of molecular responses when dasatinib was reinitiated in all patients who relapsed. The STOP-2G-TKI study by the French CML group assessed maintenance of MMR following treatment discontinuation in patients who received second-generation TKIs (dasatinib or nilotinib) and achieved $MR^{4.5}$ for the previous 2 years or longer.[41] TFR rates at 12 and 48 months were 63% and 54%, respectively.

Predicting Which Patients Will Benefit From Dasatinib Discontinuation

Overall, relatively few patients are eligible for a treatment-free period, and not all successfully maintain a response following discontinuation. For these patients, reducing dasatinib dosing as described above may be the best long-term therapy choice. In deciding which patients to include in current TFR trials, investigators considered performance status, age, molecular response, mutational profile, and adequate organ function (Table 2). For example, the DADI trial examined dasatinib discontinuations in patients who maintained deep molecular response for > 1 year.[38] Patients with performance status of 0 to 2 and with no severe dysfunction of major organ systems were eligible, but patients having *BCR-ABL1* mutations associated with dasatinib resistance, thus putting them at higher risk for relapse, were not eligible. In the real-life setting,

clinicians have been guided by molecular responses (*BCR-ABL1* reduction of at least 4 logs, sustained for ≥ 2 years) and low Sokal risk score. Among Sokal low-risk patients treated with imatinib, 50% to 60% sustained TFR, whereas among high-risk patients, the proportion dropped to 10% to 20%.[42]

Ongoing Trials Investigating Feasibility of Dasatinib Discontinuation

There are several trials focused on efficacy following discontinuation of dasatinib; these are summarized in Table 2 with their full titles and registry numbers. In addition to the trials described above with preliminary results published, the D-NewS trial will assess whether dasatinib can be discontinued without occurrence of molecular relapse in patients with CML-CP in CMR while on dasatinib; the primary outcome is overall probability of maintaining a CMR after discontinuing dasatinib.[43] The D-STOP trial will evaluate discontinuation of dasatinib for patients with CML-CP who maintained CMR for 2 years; the primary outcome measure is the overall probability of maintenance of CMR at 12 months after discontinuation.[44] The DESTINY trial will also evaluate whether patients with CML-CP can discontinue treatment for 24 months while maintaining molecular responses.[31] The Front-line Treatment of BCR-ABL+ CML with Dasatinib (CML1113) trial will follow patients with CML-CP for 5 years after discontinuation of treatment; the primary endpoint is the number of patients who permanently discontinue dasatinib.[45] The LAST (Life After Stopping Tyrosine kinase inhibitors) study will examine the decision-making process for patients with CML-CP and physicians who are considering discontinuing dasatinib; the primary endpoints are the proportion of patients with CML who develop molecular recurrence after discontinuing TKIs, and the patient-reported health status before and after stopping TKIs.[46] The purpose of the TRAD (Treatment-free Remission Accomplished with Dasatinib) trial is to determine whether an operational cure for CML is possible (an operational cure would mean the disease no longer requires treatment); the primary endpoint is molecular remission at 12 months.[47] The EURO-SKI (European Stop Tyrosine Kinase Inhibitor) trial will assess duration of

MMR following cessation of TKI therapy; patients with CML receiving first- or second-line TKI treatment are eligible.[48]

DISCUSSION

The treatment of CML is evolving from a landscape where patients were maintained on a TKI until failure or resistance occurred to one where initial TKI treatment is induction therapy, which in turn may be succeeded by reduced or intermittent dosing as consolidation therapy.[42] As the life expectancy of patients with CML now approaches that of the general population,[3,4] there is considerable interest in modifying doses of TKIs, including dasatinib, to mitigate AEs as well as to reduce cost burdens for patients and healthcare systems.[26] Results of trials designed to optimize dasatinib doses for individual patients will help guide future therapy. Accurate and timely molecular monitoring should be used to guide dose optimization. ELN and NCCN guidelines provide definitions of optimal responses to TKIs and recommendations for molecular monitoring.[22,23] However, what constitutes a CMR may not be an absolute, as more sensitive techniques are validated for future use.[49]

Clinical experience with dasatinib dose optimization is still largely unexplored, and thus there are questions that remain to be answered. Criteria for when doses should be modified have to be established. Currently, the majority of TFR trials require that patients be in molecular remission for at least 1 year. However, patients may have residual disease (Ph+ progenitor cells) and have yet to relapse.[50] In practice, perhaps 50% of patients treated for CML do not achieve MR[4.5]; therefore, it is probably better for patients to receive drug doses that achieve remission, then optimize doses for the long term. It is possible that doses resulting in *BCR-ABL1* transcript levels < 1% will be sufficient for some patients. Among imatinib-resistant patients treated with either dasatinib or nilotinib, patients with *BCR-ABL1* < 1% versus ≥ 1% at 6 months had higher 3-year MMR (83% vs 16%, $P < .001$), PFS (94% vs 84%, $P = .05$), and OS (94% vs

84%, *P* = .05).[51] As trial data mature and are published, the answer to this question should become clearer.

The lowest induction and maintenance doses of dasatinib to achieve optimal responses need to be established. Despite what could be considered a short serum half-life (3-5 hours),[52] lower and intermittent doses of dasatinib are proving to be effective treatment options. Beyond what long-term studies indicate for induction doses,[9,10] patients have been maintained successfully on doses as low as 20 mg per day.[18] A possible explanation for the efficacy of low-dose dasatinib may be attributed to its high potency[53] and prolonged inhibition of targets.[52] For example, it has been reported that the mechanism of cellular apoptosis induced by dasatinib is comparable between continuous low-dose and transient high-dose treatment in vitro; however, the effects on pro-apoptotic molecules (eg, BIM) are prolonged with low-dose (≥6 hours) versus high-dose (20 minutes) exposure.[52]

The level of efficacy patients should maintain following dose modifications also has yet to be determined. Some level of molecular relapse is likely, and re-treatment with a TKI has been used successfully.[42] Future clinical trials should be designed to determine if administering induction followed by maintenance doses of dasatinib is a feasible treatment approach. As a word of caution, very long-term follow-up will be required for patients whose doses are modified, to ensure they do not relapse.

How to individualize therapy remains to be explored. As clinical trials do not focus on individualized treatment, it is up to clinicians to take into account the needs of the patient: age, emerging AEs, or other factors may enter into the decision to modify dosing. It has been our experience that a dosing schedule involving weekend holidays (5 days of dasatinib, followed by 2 days off the drug) has helped to mitigate AEs while maintaining efficacy; also, we have had positive experiences with alternate daily dosing. In our collective experience, we have treated > 10 patients with modified doses of dasatinib who then maintained their previous response or improved from MMR to CMR. Most of these patients started dasatinib at 100 mg per day, and

upon achieving MMR, had their daily doses lowered. In some cases, patients started at 70 mg per day and achieved MMR, never having received 100 mg per day. For the majority, the responses have been durable. Our decisions to reduce doses were based on the molecular response achieved by the patient. Even if patients do not yet experience AEs, their doses could be lowered to prevent future AEs. This should be considered for special populations, especially the elderly.[34]

Pharmacogenomics may help determine the optimal dose of dasatinib. As more becomes known regarding how genetics affects responses to dasatinib, pharmacogenomics may be used in the future to prescribe individualized doses. For example, variations in the P-glycoprotein allele *ABCB1* affected transport of dasatinib, imatinib, and nilotinib into cells, and thus have implications for efficacy at a given dose.[54] Another study looked at the influence of genetic polymorphisms in *ABCB1* and *ABCG2* (helps confer multidrug resistance), the transcription factor *Oct1,* risk scores (Sokal, EUTOS, and Hasford), and trough concentrations of imatinib on CCyR.[55] The investigators found that a specific variant in *ABCG2* correlated with increased CCyR and thus increased survival.[55]

Answers to these questions and others will come from prospective clinical trials. Many ongoing trials, as detailed above, are designed to determine how to modify the dose of dasatinib, the optimal time to modify dosing, the patients best suited for dose modifications, and the level of response that should be maintained on a modified dose.

CONCLUSIONS

Available data suggest that administering dasatinib below currently approved doses may minimize AEs and maintain efficacy. Drug holidays (days of treatment respite) as an alternative to dose reductions is another means to mitigate AEs while keeping efficacy high. Maintenance therapy (administering a drug at a different dosing schedule in order to maintain a desired level of response) may be a suitable treatment goal, and data from current trials should aid in

developing guidelines for what maintenance therapy should be. Treatment discontinuation is often a goal of CML treatment and certain patients may be well suited to stop dasatinib therapy. Close follow-up and dose re-escalation, reinitiation, or switching to another TKI would be recommended for patients who demonstrate evidence of disease progression, eg, confirmed increase in *BCR-ABL1* levels by PCR. Ultimately, treatment decisions will be made through discussions between physicians and patients. When to reduce doses, for whom to reduce doses, and by how much to reduce doses cannot be settled until data from prospective studies have been analyzed.

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[FIGURE LEGENDS]

Figure 1. Deaths due to CML relative to approval of TKIs. The number of new CML cases and number of deaths due to CML for the years 1992–2013 are shown, with approval of TKIs used to treat CML indicated. CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitors. (Reproduced from SEER Cancer Stat Facts: Chronic Myeloid Leukemia (CML), National Cancer Institute, Bethesda, MD; http://seer.cancer.gov/statfacts/html/cmyl.html, available in the public domain.[5])

Figure 2. Deciding when to lower dose based on leukemic burden and *BCR-ABL1* transcript levels. *BCR-ABL1* transcript levels are monitored by real-time quantitative PCR. The relationship to transcript levels and possible outcomes is indicated. CCyR, complete cytogenetic responses; IS, International Scale; MMR, major molecular response; $MR^{4.5}$, molecular response with 4.5-log reduction of *BCR-ABL1* transcripts; PCR, polymerase chain reaction. (Reproduced without modification from Morotti A, Fava C, Saglio G. Milestones and monitoring. *Curr Hematol Malig Rep.* 2015;10:167–172. doi 10.1007/s11899-015-0258-1. ©The Authors 2015. Published with open access at Springerlink.com under the terms of Creative Commons Attribution 4.0 International License [CC BY 4.0; https:/ /creativecommons.org/licenses/by/4.0/].[19])

TABLE 1. Ongoing Clinical Trials for Reduced/Interrupted Dosing of Dasatinib

Registry Information	Trial Title	Arm(s) (Number of Patients Enrolled)	Intervention(s)	Endpoints
UMIN000007345 (Japanese Ministry of Health; DARIA-01 study)[11,54]	A phase 2 study of mid-term compliance and effectiveness of dasatinib therapy in patients with chronic myeloid leukemia	Single-arm (N = 32)	Dasatinib 100 mg/d, which was either interrupted or lowered to 50 mg/d	• Compliance with dasatinib therapy at 12 months • Treatment related toxicity • Relationship between serum concentration of dasatinib and clinical result • OS and PFS rates at 1 year
NCT01916785 (OPTIMDASATINIB)[16,28]	OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy)	Two arms, randomized (N = 289)	Dasatinib doses will be optimized based on plasma values (target $C_{min} \geq 3$ nmol/L); dasatinib doses start at 100 mg/d	• Cumulative rate of significant AE[a] • Rate and duration of treatment interruptions • Dose of dasatinib • Cumulative rates of CCyR, CMR, and MMR • Time to molecular response • Correlation between dasatinib plasma levels and efficacy • OS and PFS at 5 years • Lymphocyte counts before and during dasatinib • Rate of sustained major molecular remission after dasatinib discontinuation
UMIN000003499 (Japanese Ministry of Health)[29]	Phase II clinical trial of low dose dasatinib in patients with resistant or intolerant CML who are treated with low dose imatinib	Single-arm (N = 30)[b]	Dasatinib 50 mg/d, then 100 mg/d	MMR after 12 months
ACTRN12616000738426 (Australia; CML12 DIRECT)[30]	The DIRECT study: Individualised dasatinib dosing for elderly patients	Single-arm (N = 80)[b]	Patients aged ≥ 60 years will receive dasatinib at 100 mg/d, 70 mg/d, 50 mg/d, or 50 mg	• Incidence of treatment-related pleural effusion • Molecular responses

	with chronic myelogenous leukaemia		every other day	• Survival • Correlation between dasatinib trough levels, intensity, and response and toxicity • QoL • Proportion of patients eligible for treatment-free remission • Proportion of patients with different mechanisms of resistance • Overall tolerability
NCT01804985 (DESTINY)[31]	De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in Chronic Myeloid Leukaemia	Three arms, open-label (N = 168)[b]	Imatinib, nilotinib or dasatinib, at half the standard dose for 12 months (imatinib, 200 mg/d; nilotinib, 400 mg/d; dasatinib, 50 mg/d)	• Proportion of patients who maintain MMR on half dose for 12 months, then discontinue drug for 24 months • Proportion of patients who regain MMR after reinitiating TKI • QoL • Health economic assessment • Investigation of patients more likely to relapse through lab values
NCT02689440[32]	Therapy of Early Chronic Phase CML With Dasatinib	Single-arm (N = 100)[b]	Dasatinib 50 mg/d	• MMR at 12 months • CCyR at 6 months
LN_CMLSTU_2015_576 (European Leukemia Trial Registry; DasaHIT)[33]	Treatment optimization for patients with CML with treatment naïve disease (1st line) and patients with resistance or intolerance against alternative Abl-Kinase Inhibitors (≥ 2nd line)	Two arms, randomized (N = 306)[b]	NA	• The cumulative toxicity score after 2 years of dasatinib treatment • MMR as assessed by *BCR-ABL1* (IS) monitoring by 24 months
NCT02326311[34]	Optimization of TKIs Treatment and Quality of Life in Ph+ CML Patients	Two arms, randomized (N = 502)[b]	Fixed (1 month on/1 month off) vs progressive (1 month on/1 month off for the 1st year; 1	Change in quality of life from baseline, then at 3, 6, 12, 18, 24, 30, and 36 months

	≥60 Years in Deep Molecular Response		month on/2 months off for the 2nd year; 1 month on/3 months off for the 3rd year) intermittent administration of imatinib, dasatinib, or nilotinib	
NCT02348957 (DasPAQT)[35]	Treating Patients With CML in Chronic Phase With Dasatinib	Observational (N = 300)[b]	This study is designed to collect real-life data on CML treatment with dasatinib, with respect to first- and second-line treatment, and switching from another TKI in first line to dasatinib in second line. (It is anticipated that dose modifications will be part of the real-life setting)	• Distribution of molecular remission status at study entry and after 12 and 24 months • Best possible response • Time to molecular remission and progression • Cytogenetic profile • Hematologic response • Patient adherence • Patient satisfaction • QoL • Safety and tolerability

Abbreviations: AE, adverse event; C_{min}, minimal plasma concentration; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CMR, complete molecular response; IS, International Scale; MMR, major molecular response (*BCR-ABL1* [IS] < 0.1%); NA, not available; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor.
[a]Defined by grade 3 to 4 fluid retention, all-grade pleural effusion, hematological grade 3 to 4 AEs related to dasatinib, and/or all AE leading to dasatinib discontinuation within the first year of therapy.
[b]Estimated enrollment.

TABLE 2. Ongoing Clinical Trials for Discontinuations of Dasatinib

Registry Information	Trial Title	Arm(s) (Number of Patients Enrolled)	Inclusion Criteria	Description	Primary Endpoint(s)
NCT01916785 (OPTIMDASATINIB)[28,37]	OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy)	2 arms, randomized (N = 289)	• CML-CP • ECOG PS 0-2 • Adequate organ function • Dasatinib ≥ 3 years • $MR^{4.5}$ for 2 years	In addition to optimizing dasatinib dosing based on plasma values, this study is evaluating dasatinib discontinuation in early molecular responders	Cumulative rate of significant AE[a]
UMIN000005130 (Japanese Ministry of Health; DADI)[38]	Dasatinib Discontinuation trial	Single-arm (N = 88)	• Imatinib-resistant/intolerant CML-CP • ECOG PS 0-2 • No severe dysfunction of major organs • No *BCR-ABL1* mutations associated with dasatinib resistance • Dasatinib ≥ 1 year • $MR^{4.0}$ for 1 year	Patients with CML in sustained deep molecular response for at least 1 year to be monitored for treatment-free remission	Proportion of patients with treatment-free remission at 6 months after discontinuation (time from discontinuation to molecular relapse)
NCT01850004 (DASFREE)[39,40]	Open-Label Study Evaluating Dasatinib Therapy Discontinuation in Patients With Chronic Phase CML With Stable Complete Molecular Response	Single-arm, open-label (N = 71)	• CML-CP • ECOG PS 0-1 • Dasatinib ≥ 2 years • $MR^{4.5}$ ≥ 1 year	Patients with CML in $MR^{4.5}$ discontinue dasatinib to see if response is maintained	MMR at 12 months
STOP-2G-TKI study[41]	STOP second generation (2G)–tyrosine kinase inhibitor (TKI) study	Single-arm (N = 100)	• Treatment with second-generation TKI (dasatinib or nilotinib) ≥ 3 years • $MR^{4.5}$ ≥ 2 years	Aim is to evaluate treatment-free remission following discontinuation of first-line or subsequent lines of dasatinib or nilotinib in patients with	Treatment-free remission (no loss of MMR) at 12 months

				CML with long-lasting and deep molecular responses	
NCT01887561 (D-NewS)[43]	Dasatinib for Patients Achieving Complete Molecular Response for Cure D-NewS Trial	Single-arm (N = 100)[b]	• Newly diagnosed CML-CP • ECOG PS 0-2 • Adequate organ function • CMR	Patients in CMR following dasatinib treatment discontinue therapy to see if response is maintained	Overall probability of maintenance of CMR after discontinuing dasatinib
NCT01627132 (D-STOP)[44]	Discontinuation of Dasatinib in Patients With Chronic Myeloid Leukemia-CP Who Have Maintained Complete Molecular Remission for Two Years; Dasatinib Stop Trial	Single-arm, open-label (N = 50)[b]	• CML-CP • ECOG PS 0-2 • Adequate organ function • CMR for 2 years	Patients with CML in CMR on 100 mg/d dasatinib will discontinue drug	Overall probability of maintenance of CMR at 12 months after stopping dasatinib
NCT01804985 (DESTINY)[31]	De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in Chronic Myeloid Leukaemia	Three arms, open-label (N = 168)[b]	• CML-CP • TKI treatment ≥ 3 years • ≥ MMR for 1 year	Imatinib, nilotinib, or dasatinib, given at half the standard dose for 12 months, followed by discontinuation for a further 2 years	Proportion of patients who maintain MMR on half dose for 12 months, then discontinue drug for 24 months
NCT01761890 (CML1113)[45]	Front-line Treatment of BCR-ABL+ Chronic Myeloid Leukemia (CML) With Dasatinib	Observational (N = 133)[b]	• CML-CP • Dasatinib for 2 years	Real-life study of patients given first-line dasatinib who discontinue drug after 2 years of treatment	Number of patients who discontinue dasatinib permanently after 2 years
NCT02269267 (The LAST Study)[46]	The Life After Stopping Tyrosine Kinase Inhibitors Study	Single-arm, open-label (N = 173)[b]	• CML-CP • TKI treatment ≥ 3 years • Currently on imatinib, dasatinib, nilotinib, or bosutinib • Documented $MR^{4.0}$ ≥ 2 years	Patients will discontinue TKI, be monitored for molecular recurrence, and report quality of life using standard assessment tools	• Proportion of patients with CML who develop molecular recurrence after discontinuing TKIs • Patient-reported health status of patients before and after stopping

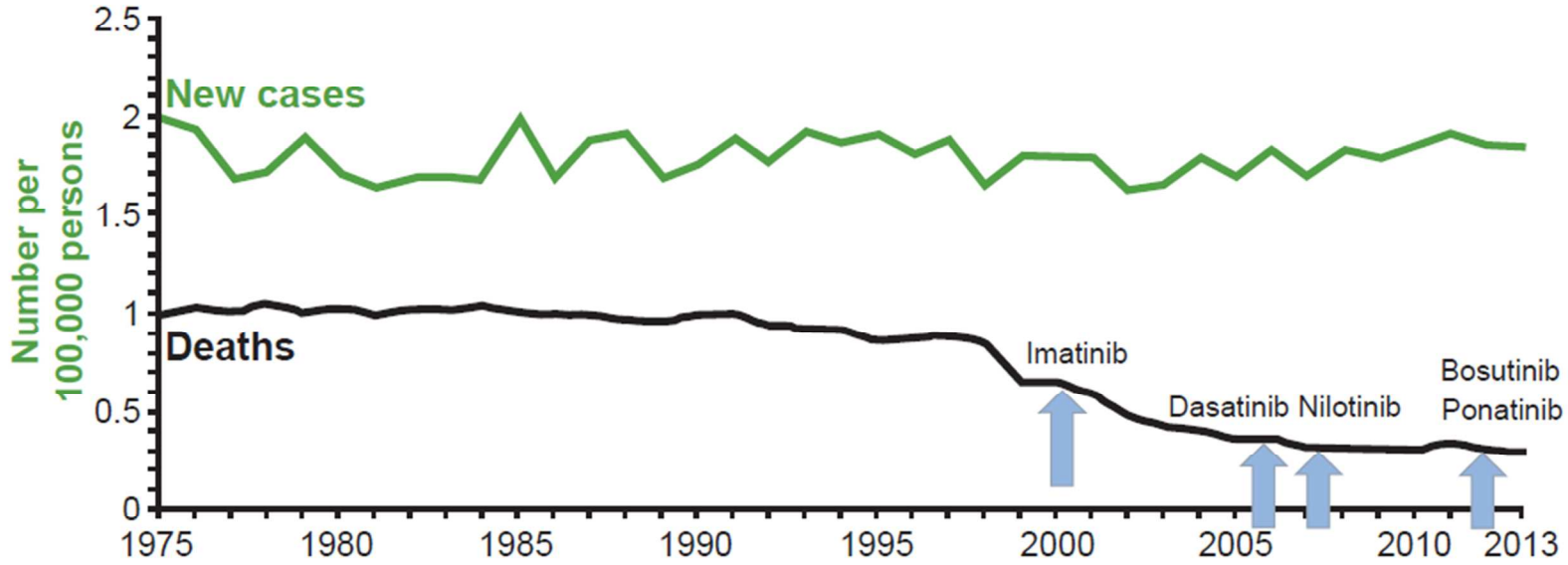
					TKI
NCT02268370 (TRAD)[47]	Treatment-free Remission Accomplished With Dasatinib in Patients With CML	Single-arm, open-label (N = 135)[b]	• CML-CP • Imatinib treatment ≥ 3 years • ECOG PS ≤ 2 • Adequate organ liver and renal functions • $MR^{4.5}$	Patients will take their own supply of imatinib for 3 months to ensure stable responses, then imatinib will be stopped and patients monitored for relapses. If patient has a relapse, then patient will receive dasatinib for up to 2 years. If response is achieved after 1 year and maintained for another year, patient has option to discontinue drug, with continued monitoring	Molecular remission (change from baseline in molecular profile at 12 months)
NCT01596114 (EURO-SKI)[48]	European Stop Tyrosine Kinase Inhibitor Study	Single-arm, open-label (N = 800)[b]	• CML-CP • First- or second-line TKI for ≥ 3 years • $MR^{4.0}$ ≥ 1 year	Main goal is assessment of duration of MMR after stopping TKI therapy	Molecular relapse-free survival

Abbreviations: AE, adverse event; CML, chronic myeloid leukemia; CML-CP, chronic myeloid leukemia in chronic phase; CMR, complete molecular response; ECOG PS, Eastern Cooperative Oncology Group performance status; IS, International Scale; MMR, major molecular response; MR, molecular response (*BCR-ABL1* [IS] < 0.1%); $MR^{4.0}$, molecular response with 4.0-log reduction of *BCR-ABL1* transcripts (*BCR-ABL1* [IS] < 0.01%); $MR^{4.5}$, molecular response with 4.5-log reduction of *BCR-ABL1* transcripts (*BCR-ABL1* [IS] ≤ 0.0032%); TKI, tyrosine kinase inhibitor.

[a]Defined by grade 3 to 4 fluid retention, all-grade pleural effusion, hematological grade 3 to 4 AEs related to dasatinib and/or all AEs leading to dasatinib discontinuation within the first year of therapy.

[b]Estimated enrollment.

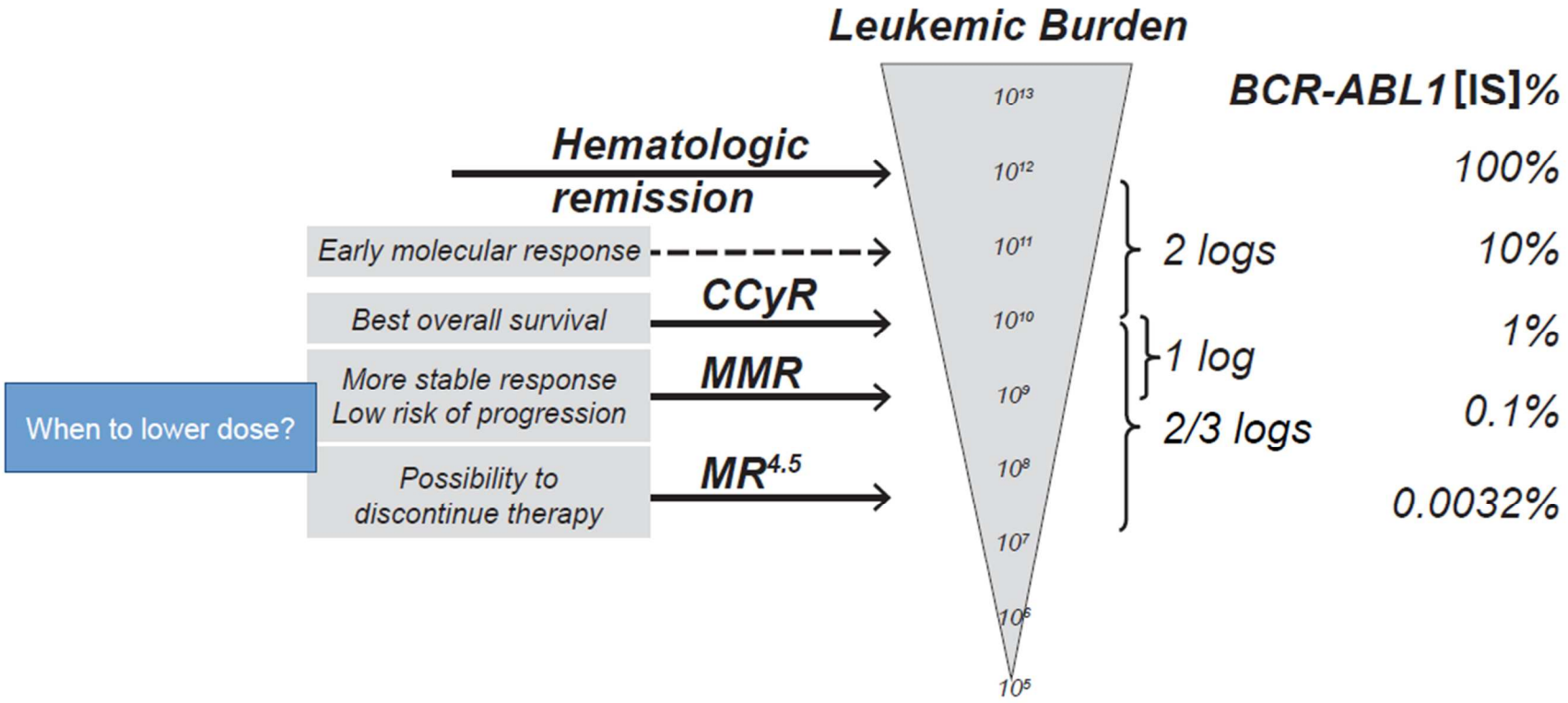
Figure 1.



Year	1975	1980	1985	1990	1995	2000	2004	2008	2012[a]
5-year relative survival	17.2%	28.3%	22.8%	32.0%	34.2%	47.2%	54.5%	64.4%	65.1%

[a]5-year relative survival not yet available; value for 2012 is a 4-year relative survival.

Figure 2.



Dasatinib Dose Management for the Treatment of Chronic Myeloid Leukemia

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AUTHOR CONTRIBUTIONS

All authors take full responsibility for the content of this publication and confirm that it reflects their viewpoints and medical expertise. All authors were involved in reviewing and editing the manuscript, and approved the final draft for submission.

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PRECIS

The focus of CML treatment is shifting to dose management, with the goal of maintaining response while improving quality of life. Results obtained from dasatinib dose optimization and discontinuation trials will help practitioners determine the best dose and duration of dasatinib for patients with CML.

Word counts: 4,450~~316~~ (limit: 6000 including title page, abstract, text, tables, and references); abstract: 133 (limit: ~ 250 words)

Text pages: 3~~4~~3

Number of references: ~~54~~ 56

Tables: 2

Figures: 2

[ABSTRACT]

Chronic myeloid leukemia (CML) has evolved into a chronic disease managed with tyrosine kinase inhibitor (TKI) therapy. Now that long-term survival has been achieved in CML, the focus of treatment shifts to dose optimization, with the goal of maintaining response while improving quality of life. In this review, we discuss optimizing the dose of the second-generation TKI dasatinib. Once-daily dosing regimens for dasatinib in the first and later lines of treatment were established through long-term (5- and 7-year) trials. Recently published data indicate that further dose optimization may maintain efficacy while minimizing adverse events. Results obtained from dose optimization and discontinuation trials currently in progress will help practitioners determine the best dose and duration of dasatinib for patients with CML, as treatment decisions will be made through continued discussions between physicians and patients.

KEYWORDS: Dasatinib; Leukemia, Myelogenous, Chronic, BCR-ABL Positive; Quality of life; Tyrosine kinase inhibitor; Dose optimization

INTRODUCTION

Chronic myeloid leukemia (CML) has evolved into a chronic disease now managed with tyrosine kinase inhibitor (TKI) therapy.[1,2] As a result of the use of TKIs approved for CML, patients diagnosed in 2013 are predicted to lose < 3 life-years compared with those without CML, and thus have life spans approaching those of the general population.[3,4] In the United States, rates for new CML cases have been stable over the past 10 years; however, death rates have been decreasing an average 3.1% each year over 2004 through 2013 (Fig. 1).[5] Sixty-five percent of patients with CML survived 5 years or more during 2006 through 2012, as opposed to the 5-year period ending in 2000, when < 50% of patients survived 5 years or more.

Now that long-term survival has been achieved in CML, the focus of treatment shifts to dose optimization and personalization. Dasatinib is a second-generation BCR-ABL1 kinase inhibitor, currently approved at 2 doses[6]: at 100 mg once daily for patients with CML in chronic phase (CML-CP), newly diagnosed or following resistance or intolerance to a previous therapy, and at 140 mg once daily for patients with CML in accelerated/blast phase (CML-AP/BP) or with Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia who are resistant or intolerant to prior therapy. Optimization of dasatinib dosing should have 2 goals: maintenance of cytogenetic and molecular responses, and minimization of adverse events (AEs). In particular, optimization should describe the minimum daily dose of dasatinib that can sustain remission and achieve a patient's therapeutic goals.

Maintaining or improving quality of life (QoL) for patients with CML over the course of their treatment should be a major part of minimizing AEs. QoL may influence a patient's decision to seek treatment regimens of dasatinib that balance efficacy with the fewest AEs, and also offer the easiest adherence.[7] For example, a drug taken once per day is preferable to one requiring multiple daily doses, and a drug that may be taken regardless of type or timing of food is preferable to one that requires timing with regard to meals or that cannot be taken with certain foods. Younger female patients with CML treated with imatinib have reported lower QoL than

the general population[8]; this finding implies that for those who anticipate being on a TKI for many years, QoL aspects of treatment may be especially important.

Ongoing studies are helping to refine treatment options that may be appropriate for some patients, including dasatinib dose reductions, interruptions, or discontinuation. It is the goal of this review to bring clarity to the field of dasatinib dose optimization by discussing published retrospective analyses and ongoing prospective studies. In particular, we discuss factors that drive selection of the optimal dasatinib dose and duration for the treatment of CML.

OPTIMIZING CURRENTLY APPROVED DOSES FOR DASATINIB

The currently approved doses of dasatinib resulted from 2 long-term pivotal trials aimed at maximizing efficacy while minimizing AEs. The CA180-034 trial enrolled patients with imatinib-resistant or -intolerant CML-CP.[9] This study compared dasatinib 100 or 140 mg per day, and once- or twice-daily schedules, to determine the optimal dosage and regimen. Results showed that dasatinib treatment at a dose of 100 mg once daily demonstrated durable efficacy and a tolerable long-term safety profile. The data obtained from this study should be considered the proof of principle that the daily dose of dasatinib can be lowered, from 70 mg twice per day (a total dose of 140 mg per day) to 100 mg once per day in particular, while maintaining efficacy in patients intolerant of or resistant to imatinib.

The CA180-056 DASISION trial (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) was a study of newly diagnosed patients with CML-CP who received dasatinib 100 mg once daily or imatinib 400 mg once daily for a minimum of 5 years.[10] At the end of DASISION, dasatinib 100 mg once daily continued to show improved efficacy compared with imatinib 400 mg daily in the first line. The safety profile of first-line dasatinib 100 mg once daily was well tolerated over the long term; no new safety signals were reported. Taken together, the results of DASISION confirmed that 100 mg once daily constitutes an optimal dose of dasatinib for patients newly diagnosed with CML-CP.

DASATINIB DOSE REDUCTIONS AND/OR INTERRUPTIONS

Efficacy and Safety

There are published data indicating that modifying the dasatinib dose from 100 mg once daily can mitigate significant AEs yet maintain efficacy over the long term. In the phase II DARIA-01 study, patients with CML-CP were enrolled to determine factors influencing adherence and efficacy when AEs from dasatinib were managed with dose modifications.[11] Patients had their dasatinib doses reduced from 100 mg per day to 50 mg per day when they experienced a grade 2 or worse nonhematologic AE or grade 3 or worse hematologic AE. In this small study, 25% of patients had their doses reduced in the first 3 months, and 34% had their doses reduced in the first 6 months. At 6 months, 25 patients (78%) achieved complete cytogenetic responses (CCyR) and 13 (40%) achieved a major molecular response (MMR). Additionally, pleural effusions were managed effectively through dose modifications while molecular responses were maintained. In a small phase II study, NordCML006, 9 patients who had dasatinib doses reduced (6 to an average of 50 mg per day and 3 to an average of 63 mg per day) had nearly the same median rate of molecular response with 4.5-log reduction of *BCR-ABL1* transcripts ($MR^{4.5}$) as did the 8 patients who were maintained on 100 mg per day ($P = .53$).[12]

Previously, a retrospective analysis of exposure and response to dasatinib in the CA180-034 trial showed that major cytogenetic response (MCyR) was significantly associated with average steady-state dasatinib plasma concentrations.[13] Reducing the daily dose from 70 mg twice daily to 100 mg once daily minimized AEs while maintaining efficacy by exploiting differences in measures of exposure: the 100 mg once-daily arm had the lowest steady-state trough concentration of the 4 dose arms investigated in CA180-034. Although this arm also had the lowest weighted average steady-state dasatinib plasma concentration, it had the highest dose maintenance and efficacy. Moreover, pleural effusion was significantly associated with trough concentration, and thus occurred the least in the 100 mg once-daily arm.

The first-line OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy) trial is currently the only prospective study of dose optimization based on therapeutic drug monitoring.[14] This is a phase II trial with 289 newly diagnosed patients with CML-CP enrolled to validate a dose-optimization strategy using plasma levels of dasatinib. As part of the study, patients with high minimal plasma concentrations (C_{min} ≥ 3 nmol/L) had their dasatinib doses reduced in 20-mg decrements every 15 days to 40 mg per day (if needed) in order to lower C_{min} to < 3 nmol/L. Preliminary results of OPTIMDASATINIB showed that patients allocated to this therapeutic drug monitoring strategy showed reduced risk of pleural effusion without impairment of the kinetics of response. By 24 months, 88% of the patients with high C_{min} values who then had their dasatinib doses lowered achieved MMR, 69% achieved molecular response with 4-log reduction of *BCR-ABL1* transcripts ($MR^{4.0}$), and 39% achieved $MR^{4.5}$, considered a complete molecular response/remission (CMR). Moreover, the dose-optimization strategy reduced the risk of pleural effusion in the study population, consistent with the data obtained by Wang et al in their retrospective analysis described above.[13,14]

Intermittent dosing with dasatinib has been shown to improve tolerability in patients with CML who were resistant to or intolerant of imatinib.[15] A strategy of 3 to 5 days of dasatinib, followed by 2 to 4 days of no drug, reduced toxicity while maintaining efficacy. Overall, 18 of 31 patients (58%) maintained or had improved response while on weekly treatment, and 16 of 18 (89%) achieved MMR or $MR^{4.5}$. A larger study wherein 176 patients with CML received reduced and/or interrupted dosing of dasatinib or nilotinib showed there was no statistically significant difference between rates of MCyR or CCyR.[16] The median lowest dasatinib doses given in this study were 60 mg per day for patients with CML-CP and 80 mg per day for patients with CML-AP.

In addition, several case reports have corroborated the results of the previously discussed studies. In one report, a patient aged 85 years was successfully treated with 20 mg of dasatinib twice weekly after developing liver dysfunction on imatinib and achieved MMR 24

months later.[17] In another report, 2 patients with CML-CP were treated with 20 to 50 mg per day of dasatinib; 1 maintained undetectable *BCR-ABL1* transcripts for up to 1 year and 1 had levels of *BCR-ABL1* transcripts 4 to 5 logs reduced (at times the levels were undetectable).[18]

~~It has been our experience that a dosing schedule involving weekend holidays (5 days of dasatinib, followed by 2 days off the drug) has helped to mitigate AEs while maintaining efficacy; also, we have had positive experiences with alternate daily dosing. In our collective experience, we have treated > 10 patients with modified doses of dasatinib who then maintained their previous response or improved from MMR to complete molecular response (CMR). Most of these patients started dasatinib at 100 mg per day, and upon achieving MMR, had their daily doses lowered. In some cases, patients started at 70 mg per day and achieved MMR, never having received 100 mg per day. For the majority, the responses have been durable. Our decisions to reduce doses were based on the molecular response achieved by the patient.~~

Predicting Which Patients Will Benefit From Dose Reductions

Early molecular responses to a TKI (within the first 6 months of initiating treatment) are predictive of long-term outcomes in CML, and several studies have shown that TKIs induced fast and deep molecular responses, defined as $MR^{4.0}$ or even $MR^{4.5}$.[19-21] These levels of responses predict durable, stable responses, and are considered prerequisites for either dose reductions or dose interruptions.

Both the European LeukemiaNet (ELN) and National Comprehensive Cancer Care Network (NCCN) recommendations define optimal responders in terms of molecular responses.[19,22,23] Therefore, at least for some patients, if deep molecular responses ($MR^{4.0}$ or $MR^{4.5}$) have been achieved after a treatment period, it should be possible to reduce dasatinib doses (Fig. 2).[19] However, molecular monitoring at fixed intervals is recommended by both the NCCN (every 3-6 months 2 years after the achievement of CCyR)[22] and the ELN (after the achievement of MMR) ~~recommend molecular monitoring at fixed intervals~~,[~~22,~~23] which may result

in missing the optimal time to reduce doses of dasatinib. For example, if a deep response occurs early in this timeframe between tests, the opportunity for a dose reduction may be missed or delayed.

Final study results from the 5-year DASISION trial for patients with CML-CP who received first-line dasatinib confirmed that achieving an early molecular response, *BCR-ABL1* ≤ 10% International Scale (IS) at 3 months, was correlated with significantly higher progression-free survival (PFS) and overall survival (OS) rates (88.9% and 93.8%, respectively, for PFS and OS) compared with patients who achieved *BCR-ABL1* > 10% (IS) at 3 months (71.8% and 80.6%, respectively, for PFS and OS).[10] For patients who received dasatinib after failing or becoming intolerant to imatinib in the 7-year CA180-034 study, those who achieved *BCR-ABL1* ≤ 10% (IS) at 3 months likewise showed significantly higher PFS and OS (56% and 72%, respectively, for PFS and OS) than those who had *BCR-ABL1* > 10% (IS) at 3 months (21% and 56%, respectively, for PFS and OS).[9]

Tools predicting outcome at any time during and after therapy would be useful throughout a patient's treatment regimen. Using data from DASISION and CA180-034,[9,10] investigators predicted responses during treatment with dasatinib based on plotting *BCR-ABL1* transcript levels and PFS or OS of patient populations.[24] Such analyses may allow investigators to predict future outcomes at any time, rather than solely at times of *BCR-ABL1* monitoring. A limitation of these projections would be that they become less precise as more time elapses from initiation of TKI therapy: the number of patients for whom a prediction might be made diminishes, reducing the accuracy of the prediction. Increasing the number of patients in the cohort is one way to negate this limitation, for example by combining suitable datasets.

In addition to molecular responses, effects on CD34+ cells may provide another means to predict responses to dasatinib. A study of newly diagnosed patients with CML-CP showed that the molecular responses at 3 and 6 months depended on the time of dasatinib plasma levels above the IC_{50} for CD34+ cells (dasatinib concentration required to inhibit 50% of CD34+

cells).[25] It was found that patients with longer times (> 12 hours) above the IC_{50} had significantly better prognoses: molecular responses at 3 and < 4 log reductions were 50% and 45%, respectively.

Other Patient Factors

Patient preference should be taken into consideration when deciding to modify dasatinib doses. Reductions and/or interruptions may be preferred by patients when discontinuing dasatinib is not an option; administering a lower dose of dasatinib, after starting treatment at the approved dose, may be preferable to switching to another TKI.[16] Moreover, modifying doses (lowering or interrupting) to mitigate toxicity may help improve adherence.[11]

In addition to minimizing AEs, economic concerns may drive a decision to lower daily doses for some patients.[26] In one study, 41 patients with CML-CP were treated with a mean dose of dasatinib of 92 mg ± 23 mg per day while achieving and maintaining efficacy, although the quality of the responses was not reported.[26] The driving force for reducing doses in this study appears to have been financial, rather than reduction of AEs. Furthermore, as long-term survival of patients with CML is predicted to increase the prevalence of the disease in the near future, the burden of healthcare costs may have to be considered when planning treatment. Thus, economic considerations beyond the personal may play a role in seeking the lowest effective dose of dasatinib or of any TKI.[27] Many of these cost concerns may be mitigated in the future, as approved generic versions of TKIs become available.

Ongoing Trials Investigating Dasatinib Efficacy With Dose Optimization

Nine trials are currently under way, focusing on modifying dasatinib dosing while retaining efficacy; their full titles, registry numbers, and summaries are given in Table 1. Two of these studies, DARIA-01[11] and OPTIMDASATINIB,[28] and have reported preliminary data and are described above.

There are 4 studies under way to determine optimizing dasatinib doses in patients or patient subgroups. A low-dose study in Japan will evaluate efficacy of 50 mg dasatinib per day in patients who are resistant to or intolerant of low-dose imatinib; the primary outcome measure is MMR at 12 months.[29] The CML12 DIRECT (Dasatinib Intensity Regulation to Eliminate Cumulative Toxicities) study will examine dose optimization of dasatinib in patients 60 years and older with CML. In this study, therapeutic daily monitoring will be used to optimize effective doses with minimal toxicity.[30] The DESTINY (De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel) trial will evaluate efficacy at 50 mg per day of dasatinib in treatment-naive patients with CML-CP[31]; its primary outcome is the proportion of patients who maintain MMR on 50 mg per day for 12 months. Patients will then discontinue dasatinib for up to 24 months. The Therapy of Early Chronic Phase Chronic Myelogenous Leukemia With Dasatinib trial will evaluate whether giving 50 mg dasatinib per day to patients with early CML-CP is as effective as giving 100 mg per day.[32]

Two studies will examine dasatinib efficacy with planned dose interruptions. The DasaHIT trial will evaluate dasatinib holidays for improved drug tolerance in treatment-naive patients with CML and in patients receiving dasatinib as second-line treatment; its primary outcome measures are cumulative toxicity after 2 years and MMR as assessed by monitoring *BCR-ABL1* transcripts at 2 years.[33] The Optimization of TKIs Treatment and Quality of Life trial will evaluate the efficacy of intermittent dasatinib dosing (1 month on, 1 month off vs 1 month on, 1 month off in year 1; 1 month on, 2 months off in year 2; 1 month on, 3 months off in year 3), and the effect on QoL such dosing regimens may have; the primary outcome is changes in QoL at defined times.[34]

Finally, the DasPAQT (Treating Patients With Chronic Myeloid Leukemia in Chronic Phase With Dasatinib) trial is a real-life study to gather data on how CML is managed with dasatinib in practices outside of academic settings, including whether and when dose reductions are used.[35]

DASATINIB DISCONTINUATION

Efficacy

Treatment-free remission (TFR), defined as being free from molecular relapse following TKI discontinuation,[22] is currently an unmet need of CML therapy, as TKIs have increased patients' life spans to be nearly equal to those of the general population.[3,4] To date, there are limited published data on discontinuing dasatinib. In 1 small trial of 34 patients with CML-CP, second-generation TKIs (dasatinib and nilotinib) were safely discontinued.[36] The 12-month probability of maintaining stable MMR was 58%, and no patient progressed to CML-AP or experienced hematologic relapse. The OPTIMDASATINIB trial for newly diagnosed patients with CML also examined dose discontinuations in early responders (those who had *BCR-ABL1* [IS] ≤ 0.0032% by 3 years).[37] Preliminary results showed that at 12 months, 41% of patients were in TFR. The DADI trial evaluated the effect of dasatinib discontinuation in patients with CML who had been in deep molecular response for at least 1 year.[38] Preliminary results showed that of the 63 patients who discontinued dasatinib, 30 maintained deep molecular responses, and 33 had molecular relapses (all during the first 7 months). The authors concluded that a treatment-free period lasting for > 1 year is feasible. The DASFREE trial is a study for patients with CML-CP receiving either first or subsequent lines of dasatinib who are in stable deep molecular response; the primary endpoint is the MMR rate at 12 months after discontinuation.[39] An interim analysis of 30 patients showed that 1 year after discontinuation, patients had a high TFR success rate (63% had MMR and molecular relapse-free survival at 12 months).[40] There was rescue of molecular responses when dasatinib was reinitiated in all patients who relapsed. The STOP-2G-TKI study by the French CML group assessed maintenance of MMR following treatment discontinuation in patients who received second-generation TKIs (dasatinib or nilotinib) and achieved $MR^{4.5}$ for the previous 2 years or longer.[41] TFR rates at 12 and 48 months were 63% and 54%, respectively.

Predicting Which Patients Will Benefit From Dasatinib Discontinuation

Overall, relatively few patients are eligible for a treatment-free period, and not all successfully maintain a response following discontinuation. For these patients, reducing dasatinib dosing as described above may be the best long-term therapy choice. In deciding which patients to include in current TFR trials, investigators considered performance status, age, molecular response, mutational profile, and adequate organ function (Table 2). For example, the DADI trial examined dasatinib discontinuations in patients who maintained deep molecular response for > 1 year.[38] Patients with performance status of 0 to 2 and with no severe dysfunction of major organ systems were eligible, but patients having *BCR-ABL1* mutations associated with dasatinib resistance, thus putting them at higher risk for relapse, were not eligible. In the real-life setting, clinicians have been guided by molecular responses (*BCR-ABL1* reduction of at least 4 logs, sustained for ≥ 2 years) and low Sokal risk score. Among Sokal low-risk patients treated with imatinib, 50% to 60% sustained TFR, whereas among high-risk patients, the proportion dropped to 10% to 20%.[42]

Ongoing Trials Investigating Feasibility of Dasatinib Discontinuation

There are several trials focused on efficacy following discontinuation of dasatinib; these are summarized in Table 2 with their full titles and registry numbers. In addition to the trials described above with preliminary results published, the D-NewS trial will assess whether dasatinib can be discontinued without occurrence of molecular relapse in patients with CML-CP in ~~complete molecular remission~~CMR while on dasatinib; the primary outcome is overall probability of maintaining CMR after discontinuing dasatinib.[43] The D-STOP trial will evaluate discontinuation of dasatinib for patients with CML-CP who maintained CMR for 2 years; the primary outcome measure is the overall probability of maintenance of CMR at 12 months after discontinuation.[44] The DESTINY trial will also evaluate whether patients with CML-CP can discontinue treatment for 24 months while maintaining molecular responses.[31] The Front-line

Treatment of BCR-ABL+ CML with Dasatinib (CML1113) trial will follow patients with CML-CP for 5 years after discontinuation of treatment; the primary endpoint is the number of patients who permanently discontinue dasatinib.[45] The LAST (Life After Stopping Tyrosine kinase inhibitors) study will examine the decision-making process for patients with CML-CP and physicians who are considering discontinuing dasatinib; the primary endpoints are the proportion of patients with CML who develop molecular recurrence after discontinuing TKIs, and the patient-reported health status before and after stopping TKIs.[46] The purpose of the TRAD (Treatment-free Remission Accomplished with Dasatinib) trial is to determine whether an operational cure for CML is possible (an operational cure would mean the disease no longer requires treatment); the primary endpoint is molecular remission at 12 months.[47] The EURO-SKI (European Stop Tyrosine Kinase Inhibitor) trial will assess duration of MMR following cessation of TKI therapy; patients with CML receiving first- or second-line TKI treatment are eligible.[48]

DISCUSSION

The treatment of CML is evolving from a landscape where patients were maintained on a TKI until failure or resistance occurred to one where initial TKI treatment is induction therapy, which in turn may be succeeded by reduced or intermittent dosing as consolidation therapy.[42] As the life expectancy of patients with CML now approaches that of the general population,[3,4] there is considerable interest in modifying doses of TKIs, including dasatinib, to mitigate AEs as well as to reduce cost burdens for patients and healthcare systems.[26] Results of trials designed to optimize dasatinib doses for individual patients will help guide future therapy. Accurate and timely molecular monitoring should be used to guide dose optimization. ELN and NCCN guidelines provide definitions of optimal responses to TKIs and recommendations for molecular monitoring.[22,23] However, what constitutes a ~~complete molecular response~~CMR may not be an absolute, as more sensitive techniques are validated for future use.[49]

Clinical experience with dasatinib dose optimization is still largely unexplored, and thus there are questions that remain to be answered. Criteria for when doses should be modified have to be established. Currently, the majority of TFR trials require that patients be in molecular remission for at least 1 year. However, patients may have residual disease (Ph+ progenitor cells) and have yet to relapse.[50] In practice, perhaps 50% of patients treated for CML do not achieve MR[4.5]; therefore, it is probably better for patients to receive drug doses that achieve remission, then optimize doses for the long term. It is possible that doses resulting in *BCR-ABL1* transcript levels < 1% will be sufficient for some patients. Among imatinib-resistant patients treated with either dasatinib or nilotinib, patients with *BCR-ABL1* < 1% versus ≥ 1% at 6 months had higher 3-year MMR (83% vs 16%, *P* < .001), PFS (94% vs 84%, *P* = .05), and OS (94% vs 84%, *P* = .05).[51] As trial data mature and are published, the answer to this question should become clearer.

The lowest induction and maintenance doses of dasatinib to achieve optimal responses need to be established. Despite what could be considered a short serum half-life (3-5 hours),[52] lower and intermittent doses of dasatinib are proving to be effective treatment options. Beyond what long-term studies indicate for induction doses,[9,10] patients have been maintained successfully on doses as low as 20 mg per day.[18] A possible explanation for the efficacy of low-dose dasatinib may be attributed to its high potency[53] and prolonged inhibition of targets.[52] For example, it has been reported that the mechanism of cellular apoptosis induced by dasatinib is comparable between continuous low-dose and transient high-dose treatment in vitro; however, the effects on pro-apoptotic molecules (eg, BIM) are prolonged with low-dose (≥6 hours) versus high-dose (20 minutes) exposure.[52]

The level of efficacy patients should maintain following dose modifications also has yet to be determined. Some level of molecular relapse is likely, and re-treatment with a TKI has been used successfully.[42] Future clinical trials should be designed to determine if administering induction followed by maintenance doses of dasatinib is a feasible treatment approach. As a

word of caution, very long-term follow-up will be required for patients whose doses are modified, to ensure they do not relapse.

How to individualize therapy remains to be explored. As clinical trials do not focus on individualized treatment, it is up to clinicians to take into account the needs of the patient: age, emerging AEs, or other factors may enter into the decision to modify dosing. It has been our experience that a dosing schedule involving weekend holidays (5 days of dasatinib, followed by 2 days off the drug) has helped to mitigate AEs while maintaining efficacy; also, we have had positive experiences with alternate daily dosing. In our collective experience, we have treated > 10 patients with modified doses of dasatinib who then maintained their previous response or improved from MMR to CMR. Most of these patients started dasatinib at 100 mg per day, and upon achieving MMR, had their daily doses lowered. In some cases, patients started at 70 mg per day and achieved MMR, never having received 100 mg per day. For the majority, the responses have been durable. Our decisions to reduce doses were based on the molecular response achieved by the patient. Even if patients do not yet experience AEs, their doses could be lowered to prevent future AEs. This should be considered for special populations, especially the elderly.[34]

Pharmacogenomics may help determine the optimal dose of dasatinib. As more becomes known regarding how genetics affects responses to dasatinib, pharmacogenomics may be used in the future to prescribe individualized doses. For example, variations in the P-glycoprotein allele *ABCB1* affected transport of dasatinib, imatinib, and nilotinib into cells, and thus have implications for efficacy at a given dose.[52-54] Another study looked at the influence of genetic polymorphisms in *ABCB1* and *ABCG2* (helps confer multidrug resistance), the transcription factor *Oct1,* risk scores (Sokal, EUTOS, and Hasford), and trough concentrations of imatinib on CCyR.[53-55] The investigators found that a specific variant in *ABCG2* correlated with increased CCyR and thus increased survival.[53,55]

Answers to these questions and others will come from prospective clinical trials. Many ongoing trials, as detailed above, are designed to determine how to modify the dose of dasatinib, the optimal time to modify dosing, the patients best suited for dose modifications, and the level of response that should be maintained on a modified dose.

CONCLUSIONS

Available data suggest that administering dasatinib below currently approved doses may minimize AEs and maintain efficacy. Drug holidays (days of treatment respite) as an alternative to dose reductions is another means to mitigate AEs while keeping efficacy high. Maintenance therapy (administering a drug at a different dosing schedule in order to maintain a desired level of response) may be a suitable treatment goal, and data from current trials should aid in developing guidelines for what maintenance therapy should be. Treatment discontinuation is often a goal of CML treatment and certain patients may be well suited to stop dasatinib therapy. Close follow-up and dose re-escalation, reinitiation, or switching to another TKI would be recommended for patients who demonstrate evidence of disease progression, eg, confirmed increase in *BCR-ABL1* levels by PCR. Ultimately, treatment decisions will be made through discussions between physicians and patients. When to reduce doses, for whom to reduce doses, and by how much to reduce doses cannot be settled until data from prospective studies have been analyzed.

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[FIGURE LEGENDS]

Figure 1. Deaths due to CML relative to approval of TKIs. The number of new CML cases and number of deaths due to CML for the years 1992–2013 are shown, with approval of TKIs used to treat CML indicated. CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitors. (Reproduced from SEER Cancer Stat Facts: Chronic Myeloid Leukemia (CML), National Cancer Institute, Bethesda, MD; http://seer.cancer.gov/statfacts/html/cmyl.html, available in the public domain.[5])

Figure 2. Deciding when to lower dose based on leukemic burden and *BCR-ABL1* transcript levels. *BCR-ABL1* transcript levels are monitored by real-time quantitative PCR. The relationship to transcript levels and possible outcomes is indicated. CCyR, complete cytogenetic responses; IS, International Scale; MMR, major molecular response; $MR^{4.5}$, molecular response with 4.5-log reduction of *BCR-ABL1* transcripts; PCR, polymerase chain reaction. (Reproduced without modification from Morotti A, Fava C, Saglio G. Milestones and monitoring. *Curr Hematol Malig Rep.* 2015;10:167–172. doi 10.1007/s11899-015-0258-1. ©The Authors 2015. Published with open access at Springerlink.com under the terms of Creative Commons Attribution 4.0 International License [CC BY 4.0; https:/ /creativecommons.org/licenses/by/4.0/].[19])

TABLE 1. Ongoing Clinical Trials for Reduced/Interrupted Dosing of Dasatinib

Registry Information	Trial Title	Arm(s) (Number of Patients Enrolled)	Intervention(s)	Endpoints
UMIN000007345 (Japanese Ministry of Health; DARIA-01 study)[11,54]	A phase 2 study of mid-term compliance and effectiveness of dasatinib therapy in patients with chronic myeloid leukemia	Single-arm (N = 32)	Dasatinib 100 mg/d, which was either interrupted or lowered to 50 mg/d	• Compliance with dasatinib therapy at 12 months • Treatment related toxicity • Relationship between serum concentration of dasatinib and clinical result • OS and PFS rates at 1 year
NCT01916785 (OPTIMDASATINIB)[16,28]	OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy)	Two arms, randomized (N = 289)	Dasatinib doses will be optimized based on plasma values (target $C_{min} \geq 3$ nmol/L); dasatinib doses start at 100 mg/d	• Cumulative rate of significant AE[a] • Rate and duration of treatment interruptions • Dose of dasatinib • Cumulative rates of CCyR, CMR, and MMR • Time to molecular response • Correlation between dasatinib plasma levels and efficacy • OS and PFS at 5 years • Lymphocyte counts before and during dasatinib • Rate of sustained major molecular remission after dasatinib discontinuation
UMIN000003499 (Japanese Ministry of Health)[29]	Phase II clinical trial of low dose dasatinib in patients with resistant or intolerant CML who are treated with low dose imatinib	Single-arm (N = 30)[b]	Dasatinib 50 mg/d, then 100 mg/d	MMR after 12 months
ACTRN12616000738426 (Australia; CML12 DIRECT)[30]	The DIRECT study: Individualised dasatinib dosing for elderly patients	Single-arm (N = 80)[b]	Patients aged ≥ 60 years will receive dasatinib at 100 mg/d, 70 mg/d, 50 mg/d, or 50 mg	• Incidence of treatment-related pleural effusion • Molecular responses

	with chronic myelogenous leukaemia		every other day	• Survival • Correlation between dasatinib trough levels, intensity, and response and toxicity • QoL • Proportion of patients eligible for treatment-free remission • Proportion of patients with different mechanisms of resistance • Overall tolerability
NCT01804985 (DESTINY)[31]	De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in Chronic Myeloid Leukaemia	Three arms, open-label (N = 168)[b]	Imatinib, nilotinib or dasatinib, at half the standard dose for 12 months (imatinib, 200 mg/d; nilotinib, 400 mg/d; dasatinib, 50 mg/d)	• Proportion of patients who maintain MMR on half dose for 12 months, then discontinue drug for 24 months • Proportion of patients who regain MMR after reinitiating TKI • QoL • Health economic assessment • Investigation of patients more likely to relapse through lab values
NCT02689440[32]	Therapy of Early Chronic Phase CML With Dasatinib	Single-arm (N = 100)[b]	Dasatinib 50 mg/d	• MMR at 12 months • CCyR at 6 months
LN_CMLSTU_2015_576 (European Leukemia Trial Registry; DasaHIT)[33]	Treatment optimization for patients with CML with treatment naïve disease (1st line) and patients with resistance or intolerance against alternative Abl-Kinase Inhibitors (≥ 2nd line)	Two arms, randomized (N = 306)[b]	NA	• The cumulative toxicity score after 2 years of dasatinib treatment • MMR as assessed by *BCR-ABL1* (IS) monitoring by 24 months
NCT02326311[34]	Optimization of TKIs Treatment and Quality of Life in Ph+ CML Patients	Two arms, randomized (N = 502)[b]	Fixed (1 month on/1 month off) vs progressive (1 month on/1 month off for the 1st year; 1	Change in quality of life from baseline, then at 3, 6, 12, 18, 24, 30, and 36 months

	≥60 Years in Deep Molecular Response		month on/2 months off for the 2nd year; 1 month on/3 months off for the 3rd year) intermittent administration of imatinib, dasatinib, or nilotinib	
NCT02348957 (DasPAQT)[35]	Treating Patients With CML in Chronic Phase With Dasatinib	Observational (N = 300)[b]	This study is designed to collect real-life data on CML treatment with dasatinib, with respect to first- and second-line treatment, and switching from another TKI in first line to dasatinib in second line. (It is anticipated that dose modifications will be part of the real-life setting)	• Distribution of molecular remission status at study entry and after 12 and 24 months • Best possible response • Time to molecular remission and progression • Cytogenetic profile • Hematologic response • Patient adherence • Patient satisfaction • QoL • Safety and tolerability

Abbreviations: AE, adverse event; C_{min}, minimal plasma concentration; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CMR, complete molecular response; IS, International Scale; MMR, major molecular response (*BCR-ABL1* [IS] < 0.1%); NA, not available; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor.
[a]Defined by grade 3 to 4 fluid retention, all-grade pleural effusion, hematological grade 3 to 4 AEs related to dasatinib, and/or all AE leading to dasatinib discontinuation within the first year of therapy.
[b]Estimated enrollment.

TABLE 2. Ongoing Clinical Trials for Discontinuations of Dasatinib

Registry Information	Trial Title	Arm(s) (Number of Patients Enrolled)	Inclusion Criteria	Description	Primary Endpoint(s)
NCT01916785 (OPTIMDASATINIB)[28,37]	OPTIMDASATINIB (Optimized Tyrosine Kinase Inhibitors Monotherapy)	2 arms, randomized (N = 289)	• CML-CP • ECOG PS 0-2 • Adequate organ function • Dasatinib ≥ 3 years • $MR^{4.5}$ for 2 years	In addition to optimizing dasatinib dosing based on plasma values, this study is evaluating dasatinib discontinuation in early molecular responders	Cumulative rate of significant AE[a]
UMIN000005130 (Japanese Ministry of Health; DADI)[38]	Dasatinib Discontinuation trial	Single-arm (N = 88)	• Imatinib-resistant/intolerant CML-CP • ECOG PS 0-2 • No severe dysfunction of major organs • No *BCR-ABL1* mutations associated with dasatinib resistance • Dasatinib ≥ 1 year • $MR^{4.0}$ for 1 year	Patients with CML in sustained deep molecular response for at least 1 year to be monitored for treatment-free remission	Proportion of patients with treatment-free remission at 6 months after discontinuation (time from discontinuation to molecular relapse)
NCT01850004 (DASFREE)[39,40]	Open-Label Study Evaluating Dasatinib Therapy Discontinuation in Patients With Chronic Phase CML With Stable Complete Molecular Response	Single-arm, open-label (N = 71)	• CML-CP • ECOG PS 0-1 • Dasatinib ≥ 2 years • $MR^{4.5}$ ≥ 1 year	Patients with CML in $MR^{4.5}$ discontinue dasatinib to see if response is maintained	MMR at 12 months
STOP-2G-TKI study[41]	STOP second generation (2G)–tyrosine kinase inhibitor (TKI) study	Single-arm (N = 100)	• Treatment with second-generation TKI (dasatinib or nilotinib) ≥ 3 years • $MR^{4.5}$ ≥ 2 years	Aim is to evaluate treatment-free remission following discontinuation of first-line or subsequent lines of dasatinib or nilotinib in patients with	Treatment-free remission (no loss of MMR) at 12 months

				CML with long-lasting and deep molecular responses	
NCT01887561 (D-NewS)[43]	Dasatinib for Patients Achieving Complete Molecular Response for Cure D-NewS Trial	Single-arm (N = 100)[b]	• Newly diagnosed CML-CP • ECOG PS 0-2 • Adequate organ function • CMR	Patients in CMR following dasatinib treatment discontinue therapy to see if response is maintained	Overall probability of maintenance of CMR after discontinuing dasatinib
NCT01627132 (D-STOP)[44]	Discontinuation of Dasatinib in Patients With Chronic Myeloid Leukemia-CP Who Have Maintained Complete Molecular Remission for Two Years; Dasatinib Stop Trial	Single-arm, open-label (N = 50)[b]	• CML-CP • ECOG PS 0-2 • Adequate organ function • CMR for 2 years	Patients with CML in CMR on 100 mg/d dasatinib will discontinue drug	Overall probability of maintenance of CMR at 12 months after stopping dasatinib
NCT01804985 (DESTINY)[31]	De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in Chronic Myeloid Leukaemia	Three arms, open-label (N = 168)[b]	• CML-CP • TKI treatment ≥ 3 years • ≥ MMR for 1 year	Imatinib, nilotinib, or dasatinib, given at half the standard dose for 12 months, followed by discontinuation for a further 2 years	Proportion of patients who maintain MMR on half dose for 12 months, then discontinue drug for 24 months
NCT01761890 (CML1113)[45]	Front-line Treatment of BCR-ABL+ Chronic Myeloid Leukemia (CML) With Dasatinib	Observational (N = 133)[b]	• CML-CP • Dasatinib for 2 years	Real-life study of patients given first-line dasatinib who discontinue drug after 2 years of treatment	Number of patients who discontinue dasatinib permanently after 2 years
NCT02269267 (The LAST Study)[46]	The Life After Stopping Tyrosine Kinase Inhibitors Study	Single-arm, open-label (N = 173)[b]	• CML-CP • TKI treatment ≥ 3 years • Currently on imatinib, dasatinib, nilotinib, or bosutinib • Documented $MR^{4.0}$ ≥ 2 years	Patients will discontinue TKI, be monitored for molecular recurrence, and report quality of life using standard assessment tools	• Proportion of patients with CML who develop molecular recurrence after discontinuing TKIs • Patient-reported health status of patients before and after stopping

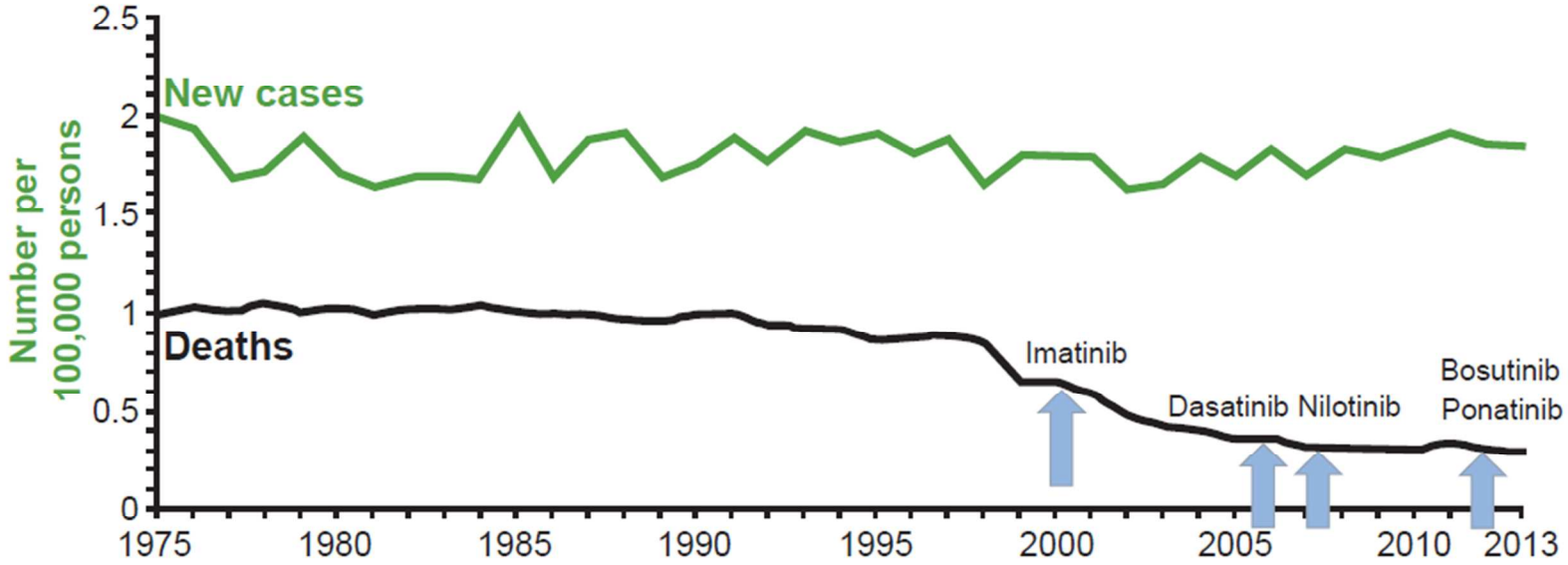
					TKI
NCT02268370 (TRAD)[47]	Treatment-free Remission Accomplished With Dasatinib in Patients With CML	Single-arm, open-label (N = 135)[b]	• CML-CP • Imatinib treatment ≥ 3 years • ECOG PS ≤ 2 • Adequate organ liver and renal functions • $MR^{4.5}$	Patients will take their own supply of imatinib for 3 months to ensure stable responses, then imatinib will be stopped and patients monitored for relapses. If patient has a relapse, then patient will receive dasatinib for up to 2 years. If response is achieved after 1 year and maintained for another year, patient has option to discontinue drug, with continued monitoring	Molecular remission (change from baseline in molecular profile at 12 months)
NCT01596114 (EURO-SKI)[48]	European Stop Tyrosine Kinase Inhibitor Study	Single-arm, open-label (N = 800)[b]	• CML-CP • First- or second-line TKI for ≥ 3 years • $MR^{4.0}$ ≥ 1 year	Main goal is assessment of duration of MMR after stopping TKI therapy	Molecular relapse-free survival

Abbreviations: AE, adverse event; CML, chronic myeloid leukemia; CML-CP, chronic myeloid leukemia in chronic phase; CMR, complete molecular response; ECOG PS, Eastern Cooperative Oncology Group performance status; IS, International Scale; MMR, major molecular response; MR, molecular response (*BCR-ABL1* [IS] < 0.1%); $MR^{4.0}$, molecular response with 4.0-log reduction of *BCR-ABL1* transcripts (*BCR-ABL1* [IS] < 0.01%); $MR^{4.5}$, molecular response with 4.5-log reduction of *BCR-ABL1* transcripts (*BCR-ABL1* [IS] ≤ 0.0032%); TKI, tyrosine kinase inhibitor.

[a]Defined by grade 3 to 4 fluid retention, all-grade pleural effusion, hematological grade 3 to 4 AEs related to dasatinib and/or all AEs leading to dasatinib discontinuation within the first year of therapy.

[b]Estimated enrollment.

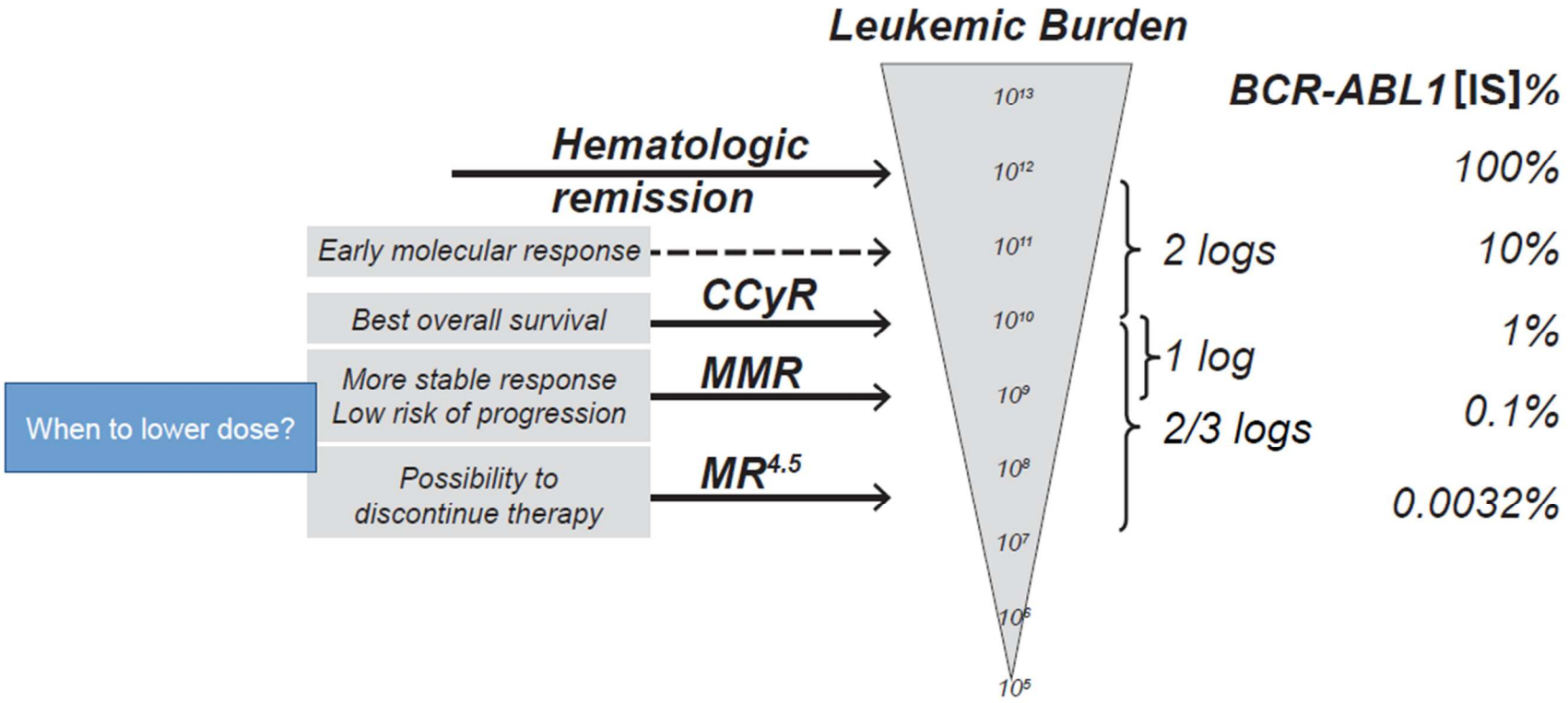
Figure 1.

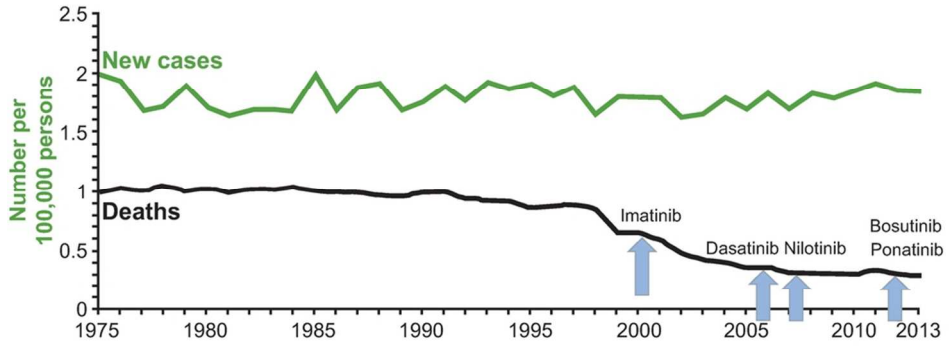


Year	1975	1980	1985	1990	1995	2000	2004	2008	2012[a]
5-year relative survival	17.2%	28.3%	22.8%	32.0%	34.2%	47.2%	54.5%	64.4%	65.1%

[a]5-year relative survival not yet available; value for 2012 is a 4-year relative survival.

Figure 2.





Year	1975	1980	1985	1990	1995	2000	2004	2008	2012[a]
5-year relative survival	17.2%	28.3%	22.8%	32.0%	34.2%	47.2%	54.5%	64.4%	65.1%

[a]5-year relative survival not yet available; value for 2012 is a 4-year relative survival.

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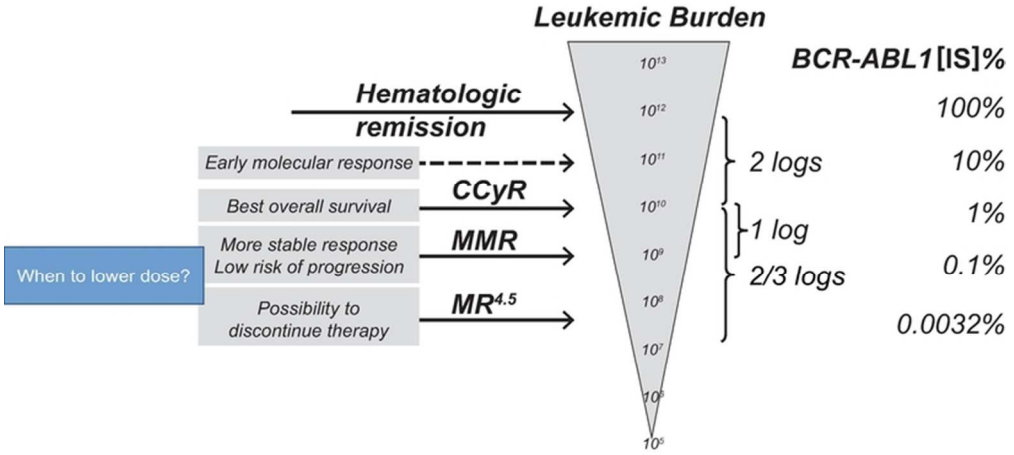

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69x31mm (300 x 300 DPI)