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The Evolution of Dasatinib Dosage Over the Years and Its Relevance to Other Anticancer Medications

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Dasatinib is a multitargeted tyrosine kinase inhibitor (TKI) that is at least 2 logs more potent in vitro against BCR-ABL than imatinib. The recommended dose of dasatinib has evolved since its original approval for different stages of chronic myeloid leukemia (CML) in 2006.[1] Rapidly absorbed, it has a short half-life of approximately 3 to 5 hours, and a twice-daily dosing schedule of 70 mg twice daily was used initially because of the desire to have continued inhibition of BCR-ABL activity, although clinical responses were noted at lower doses administered once daily in earlier phase 1/2 studies.[2] A large randomized study subsequently was performed, and recently updated with 7-year follow-up, that compared doses of 140 mg daily, 70 mg twice daily, 100 mg daily, and 50 mg twice daily in patients in chronic phase who were refractory or intolerant to imatinib.[3] Cytogenetic and molecular responses rates were similar among the groups as was progression-free survival, and a dose of 100 mg daily became the recommended dose because of improved tolerance and, in particular, lower rates of pleural effusion. However, dose reductions were required in >40% of patients, and responses were reported to be maintained at lower doses (sometimes as low as 20 mg/day) in this and other dasatinib clinical trials,[4] as well as anecdotally in the experience of CML clinicians.

In this issue of *Cancer*, investigators from The University of Texas MD Anderson Cancer Center in Houston, extrapolating from these observations, report on the use of 50 mg of dasatinib in 75 patients newly diagnosed with chronic-phase CML.[5] Early cytogenetic and molecular response rates were comparable to the outcomes in similar groups of patients from both the large randomized DASISION trial (Study of Dasatinib vs Imatinib in Patients With Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia), which resulted in the approval of 100 mg of dasatinib as initial therapy for chronic-phase CML,[6] and those from a large US cooperative group randomized study.[7] It is important to note that there appeared to be fewer toxicities compared with the higher doses, with a major reduction in the occurrence of pleural effusions, the most notable “off-target” side effect of dasatinib. Only 1 patient developed a pleural effusion when the 50-mg dose was used compared with a cumulative

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CONFLICT OF INTEREST DISCLOSURES

Charles A. Schiffer has served as a member of the Data Safety and Monitoring Boards for Astellas, Ambit, Pfizer, Takeda, Pharmacyclics, and Juno, has served as a member of the advisory boards of Celgene, Puma, and Genentech; and has received grants to his institution from Celgene, Novartis, Bristol-Myers Squibb, Ariad, Micromedex, and Pharmacyclics for work performed outside of the current study.

incidence of approximately 28% in the DASISION trial[6] and approximately 17% in the cooperative group study.[7]

These are important, credible, and compelling observations that raise the obvious question as to whether these data are sufficient to recommend a change in practice to a 50-mg starting dose. The major limitations of the study by Naqvi et al[5] include the relatively small number of patients (although these were said to be consecutive patients seen at the center), the short duration of follow-up (50 patients followed for > 6 months and only 24 of whom were followed for 12 months), the reliance on a historic control, and the small number (6%) presenting in a higher risk group. That said, there is ample experience with all of the available TKIs demonstrating that early and deep responses are predictive of long-term benefit, with very few episodes of disease progression or loss of response noted in patients who continued to be compliant with their therapy. Only 2 patients treated at a dose of 50 mg failed to respond and approximately 86% had achieved a complete cytogenetic response at 6 months, with 79% reaching a major molecular response at 12 months.

Further follow-up of the full cohort of 75 patients is highly desirable, but I will predict that these early data will “hold up” and that a randomized trial comparing the 2 doses is not necessary, given all that we now know regarding the kinetics and stability of response in patients with chronic-phase disease. I already can hear the cacophony of disagreement from statisticians, perhaps the US Food and Drug Administration, and some CML colleagues, but these results appear persuasive. I would agree that it is uncertain whether the lower dose suffices in patients with higher risk chronic-phase CML; those who have failed to respond adequately to imatinib; or in those with accelerated, blast phase, or Philadelphia chromosome-positive acute lymphoblastic leukemia, for whom I still would use higher doses. Uniquely among the TKIs, dasatinib induces a proliferation of T/natural killer (NK) cells with a possible immunomodulatory effect against CML,[8] and it would be interesting to assess whether this also occurs at the 50-mg dose.

The data-driven downward adjustments of dasatinib dose over time also raise questions regarding the initial choices of dose with both targeted and cytotoxic agents. It is understandable that pharmaceutical companies are wary of choosing doses that might be too low to avoid missing or underestimating the benefits of an otherwise effective drug (although, of course, running the risk of additional toxicity). Nonetheless, I have been impressed with how often dose and schedule selections for large, expensive phase 3 trials are based on the small amount of data derived from a combination of small phase 1 studies followed by phase 2 studies of modest size, using either the phase 1 defined “maximally tolerated dose” or, less often, when the target is well defined, a “biologically effective dose.” Furthermore, there often is a “race” to produce and market the first in a particular class of drugs. This certainly was true in the CML arena, in which there was vigorous, impassioned competition to be the first to complete trials with nilotinib and dasatinib for patients with disease that was refractory or resistant to imatinib.

And indeed, the doses of other TKIs have had to be modified as experience accumulated. The ENESTnd study compared 2 doses of nilotinib with imatinib in patients who were newly diagnosed, with overall results similar to those of the upfront trials using dasatinib,

with the exception of the unexpected finding of high rates of clinically significant thrombotic cardiovascular complications that exceeded 10% at the higher dose of 400 mg administered twice daily.[9] Rates were lower but still appreciable at the now recommended dose of 300 mg twice daily, and one can only speculate whether effectiveness can be maintained with less toxicity at even lower doses.

Similar observations were made using ponatinib, which most likely is the most potent of the BCR-ABL-targeted TKIs, in which initial phase 2 studies using a dose of 45 mg/day produced a catastrophic rate of thrombotic events of >25%.[10,11] Because this is the only TKI that is active against the T315I mutation, studies currently are underway starting at lower doses or using rapid dose de-escalation in an attempt to decrease the frequency of these complications. It can be argued that these vascular side effects would have been missed even with larger early-phase trials, but these observations reinforce the desirability of better defining the lowest effective dose, particularly for drugs that are intended to be given for many years and perhaps for life.

There also are important cost implications when using lower doses of dasatinib. In many ways, CML served as the prototype for the “financial toxicity” associated with anticancer treatment as exemplified by the sneaky and gradual company-driven increase in the price of imatinib from approximately $30,000 per year to > $100,000 over the years.[12] Unlike some oral drugs, such as lenalidomide and ponatinib, for which enigmatically all doses have the same price, halving the dose of dasatinib would result in an approximately 50% reduction in price, although the cost still would be formidable ($8000-$9000/month). Multiple versions of generic imatinib currently are available and although the initial prices for the generic were the same or sometimes higher than the branded version in the United States, economic sanity eventually should prevail, with prices falling toward what the rest of the world enjoys (well less than $10,000/year). Furthermore, long-term outcomes are nearly identical when patients with chronic-phase disease initiate treatment with either imatinib or second-generation TKIs,[6,7,9] and hence imatinib should continue to be the preferred initial treatment of the majority of patients in chronic phase, particularly given the much lower rates of long-term effects on other organ systems with imatinib.[13]

It is likely that lower doses will be as effective and perhaps less toxic with other molecularly targeted agents including some monoclonal antibodies, which can persist in the circulation months after their administration and for which the doses and schedules were derived empirically, as well as immunomodulatory agents such as lenalidomide for multiple myeloma. For obvious reasons, pharmaceutical companies do not have strong motivation to perform such studies. It also takes a certain amount of “courage” to deviate from “proven” regimens, but in many circumstances, as with dasatinib, clinical experience can provide observations that lower doses can remain effective and should be tested further. For example, intermittent dosing of imatinib in patients with a good cytogenetic response has been shown to be a safe approach in elderly patients with CML[14] The article by Naqvi et al[5] should stimulate further evaluations of this sort in patients with CML and other types of cancer.

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REFERENCES

1. Wang X, Roy A, Hochhaus A, Kantarjian HM, Chen TT, Shah NP. Differential effects of dosing regimen on the safety and efficacy of dasatinib: retrospective exposure-response analysis of a Phase III study. Clin Pharmacol. 2013;5:85–97. [PubMed: 23788844]
2. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006;354:2531–2541. [PubMed: 16775234]
3. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180–034. Am J Hematol. 2016;91:869–874. [PubMed: 27192969]
4. Cortes J, Hochhaus A, Kantarjian H, et al. Impact of dose reductions on 5-year efficacy in newly diagnosed patients with chronic myeloid leukemia in chronic phase (CML-CP) from DASISION [abstract]. J Clin Oncol. 2017;35 (suppl; abstr 7051).
5. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2018;124: 2740–2747. [PubMed: 29723397]
6. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients trial. J Clin Oncol. 2016; 34:2333–2340. [PubMed: 27217448]
7. Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood. 2012;120: 3898–3905. [PubMed: 22915637]
8. Schiffer CA, Cortes JE, Hochhaus A, et al. Lymphocytosis after treatment with dasatinib in chronic myeloid leukemia: effects on response and toxicity. Cancer. 2016;122:1398–1407. [PubMed: 26998677]
9. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044–1054. [PubMed: 26837842]
10. Dalzell MD. Ponatinib pulled off market over safety issues. Manag Care. 2013;22:42–43.
11. Cortes JE, Talpaz M, Kantarjian H. Ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2014;370:577.
12. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121:4439–4442. [PubMed: 23620577]
13. Schiffer CA. First-line treatment for patients with CML in chronic phase: why imatinib is an appropriate choice. Oncology (Williston Park). 2013;27:780, 825. [PubMed: 24133825]
14. Russo D, Martinelli G, Malagola M, et al. Effects and outcome of a policy of intermittent imatinib treatment in elderly patients with chronic myeloid leukemia. Blood. 2013;121:5138–5144. [PubMed: 23678005]