Article published online: 2021-08-05

Dasatinib—A Generation Ahead

Subramaniam Murali Carthikeyan[1] Perumal Kalaiyarasi Jayachandran[1]

[1]Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence Perumal Kalaiyarasi Jayachandran MD, MRCP (UK), DM, Department of Medical Oncology, Cancer Institute (WIA), 38, Sardar Patel Road, Guindy, Chennai, Tamil Nadu 600036, India (e-mail: dr.pkjayachandran@gmail.com).

Ind J Med Paediatr Oncol 2021;42:172–176.

Abstract

Dasatinib is a highly potent second-generation (2G) tyrosine kinase inhibitor (TKI) used in the management of Philadelphia (Ph) chromosome-positive leukemias, chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). In CML, dasatinib produces higher rates of early and deeper molecular responses compared with imatinib. The drug has its share of toxicities, namely, cytopenias, cardiovascular, and pleural effusion. This review describes the pharmacological aspects of dasatinib, clinically relevant toxicities, and their management.

Keywords

- dasatinib
- second-generation TKI in CML
- chronic myeloid leukemia

Introduction

The Philadelphia (Ph) chromosome which is the shortened chromosome 22 is formed due to the juxtaposition of a part of the Break point cluster region *BCR* gene in chromosome 22 to the Abelson murine leukemia virus *ABL* gene part in chromosome 9.[1] The presence of this characteristic reciprocal translocation t(9, 22) is required for the diagnosis of chronic myeloid leukemia (CML). Imatinib, a tyrosine kinase inhibitor (TKI), was a game changer in the management of CML. However, some patients fail to respond to imatinib or develop resistance over time. There are a few second-generation (2G) TKIs like dasatinib, nilotinib, and bosutinib approved for use in CML. These 2G TKIs are approved for either in the first-line or the second-line. Recently the generic version of dasatinib has been approved for use in India. Hence, we have reviewed the key features of dasatinib which was earlier known as BMS 354825.

Mechanism of Action and Pharmacokinetics

Dasatinib is a potent, orally active, small-molecule inhibitor of multiple kinases, including BCR–ABL, (sarcoma) Src family kinases, c-KIT, and platelet-derived growth factor receptor (PDGFR-β5). It does not require conformational changes in the ABL binding domain in contrast to imatinib and hence is active against imatinib-resistant mutations. The absorption is not affected by the food intake and hence can be taken either before food or after food. Dasatinib is metabolized by cytochrome P450 enzyme 3A4(CYP3A4). The terminal half-life is around 5 to 6 hours. Enzyme inhibitors increase the drug levels, leading to increased toxicity. Concomitant use of proton pump inhibitors decreases the bioavailability of dasatinib while concurrent administration of CYP3A4 inhibitors like azoles can increase bioavailability.[2] Preclinical and clinical studies have demonstrated improved central nervous system penetration of dasatinib (►**Table 1**).[3]

Sensitive and Resistant ABL Kinase Domain Mutation

Approximately 10 to 15% of patients with CML chronic phase (CP) develop resistance to imatinib. One of the mechanisms of imatinib resistance is the development of mutations in the ABL kinase domain. Mutations that are sensitive and resistant to dasatinib are mentioned in ►**Table 2**.

DOI https://doi.org/10.1055/s-0041-1732822
ISSN 0971-5851

Thieme Medical and Scientific Publishers Private Ltd. A-12, Second Floor, Sector -2, NOIDA -201301, India

Table 1 Dose modifications for concurrent use with enzyme inhibitors

Setting	Current dose (mg)	Recommended dose (mg)
Concomitant use with enzyme inhibitors	140	40
	100	20
	70	20

Table 2 Common sensitive and resistant mutations for dasatinib

Sensitive mutation (IC50[a]<2)	Y253F, E279K, D276G, M351T, F359V, H396P, H396R, G398R
Moderately resistant (IC50 2–4)	E255V, Q252H, L384M, L486S
Resistant mutation (IC50 > 10)	T315A, T315I,F317L/I/V/C, V299L

[a]IC50: Half maximal inhibitory concentration.

Food and Drug Administration–Approved Indications

Adults

- First-line TKI in Ph + CML—CP, accelerated phase (AP), or blast phase (BP)—100-mg once daily (OD) in CP and 140 mg OD in AP and BP.
- Second-line TKI in CML in any phase with imatinib resistance or intolerance.
- First-line in Ph + acute lymphoblastic leukemia (ALL) along with intensive therapy, 140 mg OD.

Pediatrics

- First-line TKI in CML CP (≥ 1 year of age), 60 to 80 mg/m^2 OD.
- Newly diagnosed Ph + ALL in combination with chemotherapy, 80 mg/m^2 OD.
- Other Indications (Off-Label)
- Gastrointestinal stromal tumor with PDGFRA D842V mutation, 50 mg twice daily (BD).[4,5]

Common Toxicity and Dose Adjustments

1. Hematological toxicities are among the most common side effects of dasatinib. Cytopenias are common during therapy and occur at increased frequency in those of Ph + ALL and accelerated/blast phase of CML than in the CP. Higher rates of cytopenias are also reported following switching to dasatinib after imatinib failure. Cytopenias are more common in the first few weeks or months of treatment and improve once the leukemic clones are cleared. Hematological monitoring with complete blood count (CBC) is recommended weekly for the first 4 to 6 weeks. In the absence of cytopenias, CBC can be monitored once in every 2 weeks or monthly until month 3. In patients with advanced phase CML, more frequent monitoring is advised (►**Tables 3** and **4**).
2. Dasatinib can inhibit platelet aggregation and can cause bleeding manifestations like gastrointestinal bleeding (5%). Dasatinib should be used with caution in patients receiving aspirin or anticoagulants.[6-8]
3. Pleural effusion: The mechanism of pleural effusion is believed to be immune mediated. Other mechanisms include off-target inhibition of PDGFR-β and SRC family kinase. PDGFR-β inhibition leads to reduced interstitial fluid pressure and inhibition of SRC leads to change in vascular permeability. The effusion is exudative and lymphocyte rich. The risk factors associated with increased risk of pleural effusion include older age (>65 years),[9] previous history of cardiovascular disease, hypertension, twice daily schedule, higher dose, and advanced-phase CML. It can happen at any time during treatment, the median time in the DASISION trial being 114 weeks. The median duration of pleural effusion is around 4 weeks. Around 60% of those who develop pleural effusion can have recurrence of effusion. The management of effusion depends on the symptoms, presence of risk factors, and the extent of hematological response achieved. Diuretics and steroids have been used in the management, although the rationale for their use is not established. Only a minority of

Table 3 Incidence of common toxicities[6,7]

Toxicity	Incidence	
	All grade (%)	Grades 3, 4 (%)
Haematology		
Anemia	90	10
Neutropenia	65	21
Febrile neutropenia	4	
Thrombocytopenia	70	19
Fluid retention		
Superficial edema	22	
Pleural effusion	28	5
Cardiovascular		
Pericardial effusion	3	1
Pulmonary hypertension	<1	5
Pulmonary edema	2	
Congestive cardiac failure	2	1
Cardiac Ischemia	3.9	
Cardiac arrhythmias	7	
Bleeding diathesis		
Gastrointestinal bleed	2	
Central nervous system bleed	<1	
Other toxicities		
Rash	14	
Fatigue	8	
Myalgia	23	
Diarrhea	17	1

patients require treatment discontinuation due to pleural effusion (6% patients in DASISION trial). The management of pleural effusion is shown in **Table 5**.

4. Cardiac toxicity is briefed below:
   - Prolongation of cardiac ventricular repolarization (QTc; 1%), dysrhythmias can occur. Electrolyte imbalances (hypokalemia or hypomagnesemia) should be corrected before starting treatment. Caution should be exerted while using drugs that prolong the QTc interval as it may predispose to life-threatening arrhythmias. All patients should get baseline electrocardiogram (ECG). In case of QTc > 440 ms or prolongation of >30 ms from baseline, weekly monitoring of ECG is preferred. Dasatinib should be stopped in case of QTc > 500 ms or prolongation of >50 ms from baseline and ECG monitored weekly. Dasatinib is resumed when QTc ≤ 450 ms in two consecutive ECGs.[11]
   - Congestive heart failure (2%) can occur or worsen due to fluid retention.
   - Pulmonary arterial hypertension (PAH; <1%) warrants discontinuation of the drug. It is reversible in most cases once the drug is stopped.[11]
   - Pericardial effusion (1%) due to fluid retention.
5. Gastrointestinal toxicity can occur in the form of diarrhea (22%), nausea (8%), vomiting (5%), and abdominal pain. These toxicities usually occur in the initial weeks of therapy and resolve with symptomatic treatment.[11]
6. Dose modifications for hepatic and renal dysfunction: patients with severe hepatic impairment (Child–Pugh C) and severe renal impairment (creatinine more than three times the upper limit of normal) have not been included in trials and there are no specific clinical trials for the use of dasatinib in patients with renal and hepatic impairment. However, the amount of dasatinib and its metabolites excreted through kidney is low and hence, no dose modifications are recommended for patients with hepatic and renal dysfunction.

Table 4 Dose modifications for hematological toxicity[7]

Setting	Hematologic toxicity	Recommendations
CML CP 100-mg OD	ANC <500 or platelet <50,000	1. Interrupt dasatinib until ANC >1,000 and platelets >50,000 and resume at the original starting dose. 2. For recurrence, interrupt dose, resume dasatinib at 80-mg OD and then for further recurrence, reduce dose to 50-mg OD.
CML AP, BP, Ph + ALL	ANC <500 or platelet <10,000	1. Check if toxicity is disease related. 2. If not related to disease interrupt dasatinib until ANC > 1,000 and platelets >20,000 and resume the original dose. 3. For recurrence, interrupt dose, resume dasatinib at 100-mg OD (second episode) or 80-mg OD (third episode).

Abbreviations: BP, blast phase; ALL, acute lymphoblastic leukemia; AP, accelerated phase; CP, chronic phase; CML, chronic myeloid leukemia; OD, once daily; Ph, Philadelphia; ANC, absolute neutrophil count.

Table 5 Recommendations for the management of pleural effusion[10]

Grade	Management	Dose interruption/dose reduction
Grade 1	1. Observe. 2. Repeat chest X-ray once in 3 months for 1 year.	Nil
Grade 2	1. Steroids—prednisolone 40 mg/day for 4–5 days. 2. Diuretics.	1. Interrupt dose until effusion resolves to grade1. 2. Resume at a 20% reduced dose.
Grades 3 and 4	1. Thoracentesis if required. 2. Steroids and diuretics.	1. Interrupt dose until effusion resolves to Grade1. 2. Resume at a 20% reduced dose. 3. Consider stopping the drug for recurrent effusions (grade 3 or 4) even after 2 dose reductions.

Monitoring during Therapy

CBCs should be monitored once in 2 weeks for CP and once weekly for advanced phase CML for the first 2 months and then once in 3 months. In case of Ph-positive ALL, the CBC is done according to the recommendations of the protocol used.

Liver function tests and renal function tests should be done once in 2 weeks for the first 2 months and then whenever clinically indicated. In Ph-positive ALL, these tests may be required more frequently as per the protocol used.

Chest X-ray and ECG are recommended only if clinically indicated.

Points to Ponder in Dosing

OD is preferred, as it is found to be as efficacious as BD dosing with lesser adverse events, especially pleural effusion and also requires lesser dose interruptions.[12] The dasatinib is available in tablet formulations in the following strengths 20, 50, 70, and 100 mg. The tablets should be consumed whole and should not be crushed or cut.

A lower dose of dasatinib (50-mg OD) in CP, CML is found to be more efficacious in a single phase-2 study from the MD Anderson Cancer Centre when compared with the historical cohort of the DASISION study. The rates of molecular responses were higher than historical controls who received a dose of 100 mg (major molecular remission [MMR or MR3] at 1 year was 81%; four log reductions [MR4] at 1 year was 55%). Randomized controlled trials are needed to confirm the above results.[13]

Table 6 Key trials with the use of dasatinib

Study	Setting	Design	Result
DASISION[15]	CML–CP, first line *n* = 519	Dasatinib 100 vs. imatinib 400 mg OD	1 year CCyR 77 vs. 66% ($p = 0.007$) 5-year MMR 76 vs. 64% ($p < 0.0022$
CCCG-ALL2015[16]	Newly diagnosed pediatric Ph-positive ALL *n* =189	Dasatinib 80 mg/m^2 vs. imatinib 300 mg/m^2/day	4 year EFS 71 vs. 48.9% ($p = 0.005$) 4-year OS 88.4 vs. 69.4% ($p = 0.004$)
CA180–034[17]	CML–CP second line after imatinib failure or intolerance *n* = 670	Dasatinib 100 mg OD vs. 50 mg BD vs. 140 mg OD vs. 70 mg BD	MMR at 7 years 100 mg OD: 43.7% 50 mg BD: 41.6% 140 mg OD: 40.7% 70 mg BD: 41.07%
CA180–035[18]	CML AP/BP *n* = 317	Dasatinib 140 mg OD vs. 70 mg BD	1 year MMR 66 vs. 68% Pleural effusion 20 vs. 39%, ($p < 0.001$)

Abbreviations: OS, overall survival; ALL, acute lymphoblastic leukemia; AP, accelerated phase; BD, twice daily; BP, blast phase; CP, chronic phase; CML, chronic myeloid leukemia; MMR, major molecular remission; OD, once daily; Ph, Philadelphia; CCyR, complete cytogenetic response, EFS, Event free survival.

Table 7 Key trials evaluating the role of treatment-free remission

DADI[19]	setting: 1/2 L after imatinib failure. *n* = 63	Criteria for stop: MR4 for 1 year. Criteria for restart: loss of MR4	3-year TFR 36%
DASFREE[20]	setting: 1L/subsequent lines *n* = 84	Criteria for stop: MR 4.5 for 1 year Criteria for restart: loss of MMR	2-year TFR 46%

Abbreviations: MMR, major molecular remission; MR4, four log reductions; TFR, treatment- free remission; L, line of treatment.

Stopping Tyrosine Kinase Inhibitor

Treatment-free remission (TFR) has evolved as a treatment goal in patients with a sustained deep molecular response (DMR). It helps to avoid the toxicity associated with long-term TKI use and also decreases the financial burden of long-term medication. This strategy requires motivated patients and close monitoring of BCR–ABL transcript levels. Patients usually regain molecular responses following treatment reinitiation, in case of loss of MMR during the stop phase. TFR as a goal is possible with imatinib and 2G TKIs. With the use of 2G TKIs, more proportion of patients can achieve a deep molecular response and such responses happen earlier compared with the use of imatinib. Hence more patients are eligible for the TFR strategy. Selected trials on the use of TKI discontinuation with dasatinib are shown in ►**Table 7**.

Dasatinib in Pregnancy and Breastfeeding

There is a paucity of clinical data on the safety of dasatinib in pregnancy. Pregnancy-related issues include miscarriage, intrauterine growth retardation, and placental abruption. Fetal effects include the development of hydrops fetalis, skeletal malformations, and cytopenias. Dasatinib should be avoided during pregnancy and lactation.[14] There is limited data on the pregnancy outcome of female partners of men who are taking dasatinib.

Conclusion

Dasatinib is a potent 2G TKI with better responses in the management of chronic myeloid leukemia. With the availability of generic dasatinib, the cost of treatment has considerably come down, thereby increasing the reach of the drug to the poor and downtrodden.

Funding

There were no external sources of funding for this project.

Conflict of Interest

None of the authors have any relevant conflicts of interest to declare.

References

1 Nowell PC. The minute chromosome (Phl) in chronic granulocytic leukemia. Blut 1962;8(2):65–66
2 van Leeuwen RWF, van Gelder T, Mathijssen RHJ, Jansman FGA. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol 2014;15(8):e315–e36
3 Porkka K, Koskenvesa P, Lundán T, Rimpilä J, Mustjoki S, Smykla R, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008;112(4):1005–12
4 Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14(18):5749–5758
5 Li J, Zhou Y, Zhang X, et al. Safety and efficacy of dasatinib in patients with advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib: A single arm, multicenters, phase 2 trial. J Clin Oncol 2019;37(4, suppl):138–138
6 Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010;362(24):2260–2270
7 Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021986s021lbl.pdf. Accessed June 30, 2021
8 Jabbour E, Deininger M, Hochhaus A. Management of adverse events associated with tyrosine kinase inhibitors

in the treatment of chronic myeloid leukemia. Leukemia 2011;25(2):201–210
9 Hughes TP, Laneuville P, Rousselot P, et al. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica 2019;104(1):93–101
10 Cortes JE, Jimenez CA, Mauro MJ, Geyer A, Pinilla-Ibarz J, Smith BD. Pleural effusion in dasatinib-treated patients with chronic myeloid leukemia in chronic phase: identification and management. Clin Lymphoma Myeloma Leuk 2017;17(2):78–82
11 Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 2016;30(8):1648–1671
12 Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood 2009;113(25):6322–6329
13 Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2020;126(1):67–75
14 Cortes JE, Abruzzese E, Chelysheva E, Guha M, Wallis N, Apperley JF. The impact of dasatinib on pregnancy outcomes. Am J Hematol 2015;90(12):1111–1115
15 Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-Naïve chronic myeloid leukemia patients trial. J Clin Oncol 2016;34(20):2333–2340
16 Shen S, Chen X, Cai J, et al. Effect of dasatinib vs imatinib in the treatment of pediatric philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. JAMA Oncol 2020;6(3):358–366
17 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(9):869–874
18 Ottmann O, Saglio G, Apperley JF, et al. Long-term efficacy and safety of dasatinib in patients with chronic myeloid leukemia in accelerated phase who are resistant to or intolerant of imatinib. Blood Cancer J 2018;8(9):88
19 Okada M, Imagawa J, Tanaka H, et al. DADI Trial Group, Japan. Final 3-year results of the dasatinib discontinuation trial in patients with chronic myeloid leukemia who received dasatinib as a second-line treatment. Clin Lymphoma Myeloma Leuk 2018;18(5):353–360.e1
20 Shah NP, García-Gutiérrez V, Jiménez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma 2020;61(3):650–659

