International Journal of Basic & Clinical Pharmacology
Maggo S et al. Int J Basic Clin Pharmacol. 2020 Jul;9(7):1175-1179
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20202960

New Drug Update

Avapritinib: novel hope for patients with metastatic gist with PDGFRA exon 18 mutation

Sachin Maggo[1]*, A. P. Dubey[2], Pawan Dhull[3], Nilabh Kumar Singh[4]

[1]Department of Medicine, Army Hospital, Joshimath, Uttarakhand, India
[2]Department of Oncology, Santhosh Medical College, Ghaziabad, Uttar Pradesh, India
[3]Department of Neurology, Command Hospital, Lucknow, Uttar Pradesh, India
[4]Department of Medicine, Army Hospital, Tejpur, Assam, India

Received: 25 April 2020
Accepted: 06 June 2020

***Correspondence:**
Dr. Sachin Maggo,
Email: sachinmaggo2003@gmail.com

ABSTRACT

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gastrointestinal tract associated with high rates of malignant transformation. The activating mutations in platelet-derived growth factor receptor A (PDGFRA) have been linked to the development of GISTs, and up to approximately 10% of GIST cases involve mutations of this gene. Current treatment options for metastatic GIST are minimal, mainly trusting on tyrosine kinase inhibitors (TKIs) such as Imatinib, Sunitinib and Regorafenib. However, eventually, most patients develop resistance to TKIs, usually due to the acquisition of secondary mutations. Moreover, 5-6% of patients with unresectable of metastatic GIST have the primary PDGFRA D842V mutation, which makes it resistant to all approved treatment options. Avapritinib, a potent and selective TKI of KIT and PDGFRA activation loop mutants. The drug demonstrates anti-tumor activity by inhibiting the autophosphorylation of KIT D816V and PDGFRA D842V, thereby terminating the downstream signalling. The drug is available in oral formulation with a recommended dosage of 300 mg once daily. The onset of Avapritinib is fast, shows rapid absorption and linear pharmacokinetics. Most common adverse reactions seen are edema, fatigue, abdominal pain, and neurocognitive defects. Clinical trials for Avapritinib have been positive, and results suggest that the drug may be a new safe and effective option for metastatic GIST treatment. With Blueprint Medicines having already received US FDA approval in January 2020, Avapritinib may soon be an addition to the mounting armoury of drugs against metastatic GIST harbouring PDGFRA exon 18 mutation.

Keywords: Avapritinib, Metastatic GIST, PDGFRA mutation, Tyrosine kinase inhibitors

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) epitomize as one of the most common mesenchymal tumors of the gastrointestinal tract 80%, with an annual incidence of 10–15 cases per million people.[1] Originating from the interstitial cells of Cajal, these tumors have been noted to express CD 117 antigen (C-kit) with a gain of function mutation responsible for proliferation of these tumors.[2,3] Usually these tumors are asymptomatic initially, being detected incidentally during abdominal CT or endoscopy done for other indications. Symptomatic patients may present with nonspecific symptoms of nausea, vomiting, abdominal distension, early satiety, abdominal pain, and rarely as a palpable abdominal mass.[4] As these tumors increase in size, they may present with obstructive symptoms (endophytic growth or exophytic compression) including constipation, obstructive jaundice or signs of peritonitis.[5]

In the current era of advanced oncology, the diagnosis of GISTs are established with histopathology and immunochemistry. While CT enterography is the best modality to identify location of these tumors, any perforation, invasion of these tumors into nearby structures, or metastasis, CT-guided biopsy is required for definitive diagnosis of GISTs.[6,7] Three different histologic findings have been recognized, including spindle 70%, epithelioid 20%, or mixed type 10%. The majority of patients with GIST have activating (gain of function) mutations in KIT 70-80% or platelet derived growth factor receptor alpha, platelet-derived growth factor receptor A (PDGFRA) 10%. These mutations drive ligand-independent constitutive kinase activity and downstream signalling, resulting in increased tumour cell proliferation and survival.[8] With the advent of molecular diagnostics and targeted therapy, there has been a paramount change in management of GIST as the treatment response can be reliably predicted by molecular classification. The discovery of receptor tyrosine kinase inhibitors (TKIs) and role in the pathogenesis of GIST has led to widespread use of TKIs, such as imatinib (standard first line therapy), sunitinib (second line therapy) and regorafenib (third line therapy) in disease management.[9] However, eventually, most patients develop resistance to TKIs, usually due to the acquisition of secondary mutations in KIT that usually arise in the adenosine 5-triphosphate (ATP) - binding pocket (exons 13 and 14) or in the activation loop (exons 17 and 18). Moreover, 5-6% of patients with unresectable of metastatic GIST have the primary PDGFRA D842V mutation, which makes it resistant to all approved treatment options.[10,11]

Avapritinib is a potent and selective tyrosine kinase inhibitor of KIT and PDGFRA activation loop mutants. The drug demonstrates anti-tumor activity by inhibiting the autophosphorylation of KIT D816V and PDGFRA D842V, thereby terminating the downstream signalling. Being available as an oral formulation with a recommended dosage of 300 mg once daily, the drug follows linear pharmacokinetics. With estimable results of multiple clinical trials, the US Food and Drug Administration (FDA) on 9 January 2020 approved blueprint medicines avapritinib (Ayvakit™) for the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations.[12,13] Moreover, the drug is also undergoing regulatory assessment in the USA as a 4th line treatment for GIST and in the EU for the treatment of PDGFRA D842V GIST, regardless of prior therapy.[14,15] The novel drug has proven to be a "breakthrough therapy" in the treatment of metastatic GIST in initial results promising to cater significant unmet needs of both the oncologists and the society.

MECHANISM OF ACTION

A number of known mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive instigation of tyrosine kinase receptors, thereby contributing to tumor cell growth and proliferation. Avapritinib is a potent tyrosine kinase type I inhibitor that specifically targets PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC50s) less than 25 nM. Various in vitro and vivo studies have firmly established that avapritinib inhibits the autophosphorylation of KIT D816V and PDGFRA D842V, mutants associated with resistance to approved kinase inhibitors for GIST, with IC50 of 4 nM and 30 nM, respectively.[16] Also, some other potential targets for the drug which are currently under evaluation include wild type KIT, PDGFRB, and CSFR1.

In addition, avapritinib has shown to weaken the transport function of the ATP-binding cassette (ABC) transporters ABCB1 and ABCG2 in vitro, thereby restoring the sensitivity of ABCB1- and ABCG2-overexpressing multidrug resistance cancer cells at nontoxic concentrations.[17]

CLINICAL PHARMACOLOGY

Avapritinib has high plasma protein binding 98.8% which is independent of concentration, with a mean apparent volume of distribution being 1200L (43%). It is rapidly absorbed from the gastrointestinal tract when given orally with the median time to peak concentration (Tmax) ranging from 2.0 to 4.1 hours following single doses of avapritinib 30 mg to 400 mg (0.1 to 1.33 times the approved recommended dose). The drug is recommended to be taken in fasting state (1 hour before meal) as studies have demonstrated an increase in Cmax (59%) and AUC0-INF (29%) with a high calorie and high fat meal as compared to the fasting state. When given at recommended dosage of 300 mg once daily, Avapritinib reaches steady state concentration in 15 days with a mean accumulation ratio of 3.1 to 4.6. The steady state Cmax and AUC0-24h of the drug are 813 ng/ml and 15400 hng/mL.[18]

The mean plasma elimination half-life of avapritinib is estimated to 32 hours to 57 hours following single doses of 30mg to 400mg (0.1 to 1.33 times the approved recommended dose) with a mean oral clearance of 19.5 L/h. The drug is manly metabolized by CYP3A4 and to a small extent by CYP2C9 with studies demonstrating unchanged avapritinib 49% and its metabolites M690 (hydroxy glucuronide; 35%) and M499 (oxidative deamination; 14%) as the major circulating compounds. Elimination of the compound occurs largely in the faeces 70% with a small quantity being eliminated in urine 18%. The pharmacokinetics of the drug is not affected by age, sex, body weight, mild to moderate renal impairment (creatinine clearance 30-89 ml/minutes) or mild to moderate hepatic impairment. However, the effects of severe renal impairment, end-stage renal disease and severe hepatic impairment on the pharmacokinetics of avapritinib have not been studied.[18]

DOSAGE, CLINICAL EFFICACY AND DRUG INTERACTIONS

Results of various dose response studies recommended a dosage of avapritinib of 300mg taken orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal.[18] No drug modifications are required for mild to moderate hepatic or renal dysfunction. However, the safety of the drug in severe renal or hepatic dysfunction is not yet established.

Coadministration of avapritinib with a strong or moderate CYP3A inhibitor may increase the drug's plasma concentrations (potentially increasing the incidence and severity of avapritinib-associated adverse events) and coadministration of the drug with strong or moderate CYP3A inducers may decrease avapritinib plasma concentrations (potentially decreasing drug efficacy). Therefore, concomitant use of avapritinib with strong or moderate CYP3A inhibitors or inducers should be avoided. Nevertheless, if coadministration of avapritinib with a moderate inhibitor is inevitable, a reduction in avapritinib dose is recommended.[18]

CLINICAL TRIALS

The robust clinical efficacy of avapritinib was demonstrated in navigator (NCT02508532), a multi-center, single arm, open-label clinical trial. The study included patients with a confirmed diagnosis of GIST and an ECOG performance status (PS) of 0 to 2. The drug was administered in a dosage of 300 mg or 400 mg orally once daily until disease progression or unacceptable toxicity. However, the dose was later reduced to the recommended dose of 300 mg due to toxicity. The major efficacy outcome was evaluated as overall response rate (ORR) based on disease assessment radiologically using modified RECIST v1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodules within a pre-existing tumor mass was progression. Secondary outcome measures included duration of response (DOR).[19]

Patients with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation were identified by local or central assessment using a polymerase chain reaction or next gen sequencing -based assay. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA exon 18 mutations was 10.6 months (range: 0.3 to 24.9 months). The study population characteristics were median age of 64 years (range: 29 to 90 years), 67% were male, 67% were White, 93% had an ECOG PS of 0-1, 98% had metastatic disease, 53% had largest target lesion >5 cm, and 86% had prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 5). Efficacy results in patients with GIST harbouring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations enrolled in navigator are summarized (Table 1).[19,20]

Table 1: Efficacy results for patients with GIST harbouring PDGFRA exon 18 mutations in navigator study.

Efficacy parameter	PDGFRA exon 18[1] (n=43)	PDGFRA D842V (n=38)
Overall response rate (95% CI)	84% (69%, 93%)	89% (75%, 97%)
Complete response, n (%)	3 (7%)	3 (8%)
Partial response, n (%)	33 (77%)	31 (82%)
Duration of response	n=36	n=34
Median in months (range)	NR (1.9+, 20.3+)	NR (1.9+, 20.3+)
Patients with DOR ≥6 months, n (%)	22 (61%)	20 (59%)

Abbreviations: CI = confidence interval; NR = not reached; NE = not estimable; [+]denotes ongoing response; [1]exon 18 mutations other than D842V included in this population are: deletion of D842_H845 (n=3); D842Y (n=1); and deletion of D842_H845 with insertion of V (n=1). [*]11 patients with an ongoing response were followed <6 months from onset of response.

In addition, a randomized, open-label, multicentre, phase 3 voyager (NCT03465722) study is comparing the efficacy of avapritinib with regorafenib in patients who have previously received imatinib and 1 or 2 other TKIs for the treatment of GIST. The study has recruited 476 patients and is expected to be completed by April 2023; the primary outcome is PFS and secondary outcomes include ORR, OS and health related quality of life (HR-QOL) measures.[21]

SAFETY AND ADVERSE DRUG REACTIONS

The safety of avapritinib in patients with unresectable or metastatic GIST was evaluated in phase 3 clinical trial (navigator study). Among patients receiving the drug, 56% were exposed for 6 months or longer and 44% were exposed for greater than one year. However, the study excluded patients with history of cerebrovascular accident or transient ischemic attacks, known risk of intracranial bleeding, and metastases to the brain.

The most common adverse reactions occurring in ≥10% of patients treated with Avapritinib (300 mg or 400 mg) are summarized (Table 2). Serious adverse reactions occurring in ≥1% of patients who received the drug were anemia 9%, abdominal pain 3%, pleural effusion 3%, sepsis 3%, gastrointestinal haemorrhage 2%, vomiting 2%, acute kidney injury 2%, pneumonia 1% and tumour haemorrhage 1%. Fatal adverse reactions occurred in 3.4% of patients. Modification of dosage (dose reduction

or dosing interruption) due to an adverse reaction was done in 49% of patients who received the drug with a median time to dose reduction being 9 weeks.[19-21]

Table 2: Adverse reactions (≥10 %) in patients receiving avapritinib in navigator study.

Adverse reactions	Avapritinib N=204	
	All grades %	Grade ≥3 %
General		
Edema[a]	72	2
Fatigue/asthenia	61	9
Pyrexia	14	0.5
Gastrointestinal		
Nausea	64	2.5
Vomiting	38	2
Diarrhea	37	4.9
Abdominal pain[b]	31	6
Constipation	23	1.5
Dyspepsia	16	0
Nervous system		
Cognitive impairment[c]	48	4.9
Dizziness	22	0.5
Headache	17	0.5
Sleep disorders[d]	16	0
Taste effects[e]	15	0
Mood disorders[f]	13	1
Metabolism and nutrition		
Decreased appetite	38	2.9
Eye		
Increased lacrimation	33	0
Skin and subcutaneous tissue		
Rash[g]	23	2.1
Hair colour changes	21	0.5
Alopecia	13	-
Respiratory, thoracic and mediastinal		
Dyspnea	17	2.5
Pleural effusion	12	2
Investigations		
Weight decreased	13	1

*Per national cancer institute common terminology criteria for adverse events (CTCAE) version 4.03 and 5.0. [a]Edema includes face swelling, conjunctival edema, eye edema, eyelid edema, orbital edema, periorbital edema, face edema, mouth edema, pharyngeal edema, peripheral edema, edema, generalized edema, localized edema, peripheral swelling, testicular edema. [b]Abdominal pain includes abdominal pain, upper abdominal pain, abdominal discomfort, lower abdominal pain, abdominal tenderness, and epigastric discomfort. [c]Cognitive impairment includes memory impairment, cognitive disorder, confusional state, disturbance in attention, amnesia, mental impairment, mental status changes, encephalopathy, dementia, abnormal thinking, mental disorder, and retrograde amnesia. [d]Sleep disorders includes insomnia, somnolence, and sleep disorder. [e]Taste effects include dysgeusia and ageusia. [f]Mood disorders includes agitation, anxiety, depression, depressed mood, dysphoria, irritability, mood altered, nervousness, personality change, and suicidal ideation. [g]Rash includes rash, rash maculo-papular, rash erythematous, rash macular, rash generalized, and rash papular.

In contrast to other common adverse events described above, unique cognitive adverse effects were also observed with avapritinib, and are of special concern. In the pooled analysis of completed navigator study and ongoing voyager study, cognitive effects (memory impairment, cognitive disorder, confusional state and encephalopathy) were reported in 35% (65/184) and 48% (24/50) of patients received avapritinib 300 mg once daily and 400 mg once daily, respectively, primarily driven by memory impairment (23% and 38% of patients in the respective groups). In the 65 patients experiencing cognitive effects in the 300 mg QD dose group, 72% (n=47) experienced grade 1 events, which did not affect activities of daily living and 22% (n=14) experienced grade 2 events, and 6% (n=4) experienced grade 3 events. There were no grade 4 cognitive effects in either the 300 mg QD or 400 mg QD group. Dose modification interventions were effective in improving grade 2 cognitive effects when compared no intervention with a median time to improvement being 12.0 days for any intervention vs 32.5 days for no intervention.[22]

CONCLUSION

In this era of targeted therapy and evolving oncology each day, the current decade has witnessed widespread interest in management of patients with GIST helping the clinicians who can now offer hope to the many individuals living with advanced or metastatic disease around the world. Till recently, treatment of metastatic GIST involved the sequential use of multi-targeted TKIs, which were associated with low response rates in patients with advanced disease and off-target effects. In addition, as a result of accumulation of secondary resistance mutations, multi-targeted TKIs eventually lose efficacy.

Avapritinib is an investigational precision therapy designed to be a highly selective and potent inhibitor of KIT and PDGFRA mutant kinases. The novel drug has received breakthrough therapy designation from the US FDA for the treatment of unresectable or metastatic GIST harbouring PDGFRA exon 18 mutation, including PDGFRA D842V mutations. The efficacy has been well established in the navigator study and the preliminary results of ongoing voyager study.

However, further studies are warranted to affirm safety of the drug with respect to neurological adverse events. In addition, the drug has shown promising evidence as 4th-line treatment for GIST and is undergoing regulatory assessment for the same. With clinical development underway in several countries to establish its role in treatment of systemic mastocytosis and late stage solid organ tumors, the future of the drug seems promising.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Pathology. 2002;10(2):81-9.
2. Kindblom LG, Remotti HE, Aldenborg F, Kindblom MJM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathology. 1998;152(5):1259.
3. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577-80.
4. Scherubl H, Faiss S, Knoefel WT, Wardelmann E. Management of early asymptomatic gastrointestinal stromal tumors of the stomach. World J Gastrointestinal Endoscopy. 2014;6(7):266.
5. Scola D, Bahoura L, Copelan A, Shirkhoda A, Sokhandon F. Getting the GIST: a pictorial review of the various patterns of presentation of gastrointestinal stromal tumors on imaging. Abdominal Radiology. 2017;42(5):1350-64.
6. Vernuccio F, Taibbi A, Picone D, Grutta LL, Midiri M, Lagalla R, et al. Imaging of gastrointestinal stromal tumors: From diagnosis to evaluation of therapeutic response. Anti-cancer Res. 2016;36(6):2639-48.
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Archives Pathology Laboratory Med. 2006;130(10):1466-78.
8. Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Molecular cancer. 2018;17(1):58.
9. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: soft tissue sarcoma (version4.2019).2019. Available at https://www.nccn.org/patients/guidelines/content/PDF/sarcoma-patient.pdf. Accessed on 15 April 2020.
10. Evans EK, Gardino AK, Kim JL, Hodous BL, Shutes A, Davis A, et al. A precision therapy against cancers driven by KIT/PDGFRA mutations. Science Translational Med. 2017;9(414):1690.
11. Gebreyohannes YK, Wozniak A, Zhai ME, Wellens J, Cornillie J, Vanleeuw U, et al. Robust activity of avapritinib, potent and highly selective inhibitor of mutated KIT, in patient-derived xenograft models of gastrointestinal stromal tumors. Clin Cancer Res. 2019;25(2):609-18.
12. Blueprint Medicines Corporation. Ayvakit (avapritinib): US prescribing information; 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212608s000lbl.pdf. Accessed on 15 April 2020.
13. US Food and Drug Administration. FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation; 2020. Available at https://www.fda.gov/news-events/press-announc-ements/fda-approves-first-targeted-therapy-treat-rare-mutation-patients-gastrointestinal-stromal-tumors. Accessed on 15 April 2020.
14. Blueprint Medicines. Blueprint Medicines announces FDA approval of AYVAKIT™ (avapritinib) for the treatment of adults with unresectable or metastatic PDGFRA Exon 18 mutant gastrointestinal stromal tumor; 2020. Available at http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-fda-approval-ayvakittm-avapritinib. Accessed on 15 April 2020.
15. United States Securities and Exchange Commission. Form 8-K; 2020. Available at http://ir.blueprintmedicines.com/static-files/760ac82a-c1ad-4d52-bcba-b3bd3bdb6310. Accessed on 15 April 2020.
16. Dhillon S. Avapritinib: First Approval. Drugs. 2020;25:1-7.
17. Wu CP, Lusvarghi S, Wang JC, Hsiao SH, Huang YH, Hung TH, et al. Avapritinib: A Selective Inhibitor of KIT and PDGFRα that Reverses ABCB1 and ABCG2-Mediated Multidrug Resistance in Cancer Cell Lines. Molecular Pharmaceutics. 2019;16(7):3040-52.
18. Blueprint Medicines Corporation. Ayvakit (avapritinib): US prescribing information; 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212608s000lbl.pdf. Accessed on 15 April 2020.
19. Heinrich M, Jones R, Mehren VM. Clinical response to avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST) (oral presentation). In: Connective Tissue Oncology Society annual meeting; 2019. Available at https://www.blueprintmedicines.com/wp-content/uploads/2019/11/Blueprint-Medicines-CTOS-2019-Avapritinib-GIST-Clinical-Response-RECIST-Choi-Criteria-Presentation.pdf. Accessed on 15 April 2020.
20. Heinrich MC, Jones RL, Mehren VM, Bauer S, Kang YK, Schoffski P, et al. Clinical activity of avapritinib in≥ fourth-line (4L+) and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). (abstract no. 11022 and poster). J Clin Oncol Conf. 2019;37(15).
21. Bauer S, George S, Kang YK, Tap WD, Zhou T, Picazio N, et al. Voyager: an open-label, randomized, phase III study of avapritinib vs regorafenib in patients (pts) with locally advanced (adv) metastatic or unresectable gastrointestinal stromal tumour (GIST). Annals Oncology. 2018;29:595.
22. Joseph CP, Abaricia SN, Angelis MA, George S, Jones RL, Kang YK, et al. Avapritinib for the Treatment of GIST: Analysis of Efficacy, Safety, and Patient Management Strategies at the Recommended Phase 2 Dose; 2020.

Cite this article as: Maggo S, Dubey AP, Dhull P, Singh NK. Avapritinib: novel hope for patients with metastatic gist with PDGFRA exon 18 mutation. Int J Basic Clin Pharmacol 2020;9:1175-9.