VIA MEDICA

REVIEW ARTICLE

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Avapritinib in the treatment of gastrointestinal stromal tumors (GIST)

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Oncology in Clinical Practice
DOI: 10.5603/OCP.2023.0036

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Avapritinib is a highly selective inhibitor of mutated KIT and PDGFRA kinases, approved in 2020 for the treatment of patients with gastrointestinal stromal tumors (GIST). It has particular activity against GIST with the *PDGFRA D842V* mutation associated with imatinib resistance. The safety and efficacy of avapritinib have been evaluated in two clinical trials, NAVIGATOR and VOYAGER, which showed particularly favorable results in patients with the *PDGFRA D842V* mutation. In the NAVIGATOR study, the objective response rate (ORR) in patients with the mutation was 91%. In the VOYAGER study, the ORR was 17.1% in all patients receiving avapritinib and 42.9% in the group of patients with the *PDGFRA D842V* mutation. While the efficacy in the subgroup of patients with the mutation was significantly superior to regorafenib, this benefit was not demonstrated for the overall population. In both studies, adverse events were reported in more than 90% of patients, with more than 50% of patients experiencing Grade 3 or higher reactions. The most commonly reported treatment-related adverse events were nausea, fatigue, anemia, diarrhea, periorbital edema, and cognitive impairment. Based on the preliminary study results, avapritinib was approved in the United States and the European Union for treating patients with metastatic or unresectable GIST with the *PDGRA D842V* mutation. It is the first inhibitor showing activity against this mutation. In this review, we summarize the current data on the efficacy and safety of avapritinib and present its place in the diagnostic and therapeutic guidelines.

Keywords: avapritinib, GIST, *PDGFRA,* tyrosine kinase inhibitor

Oncol Clin Pract 2023; 19, 5: 371–376

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the digestive system. The incidence of GIST is estimated at 10 to 15 cases per million people. It occurs with similar frequency in men and women, and the average age of diagnosis is 65–70 years. GIST originates from interstitial cells of Cajal and can be located in any segment of the gastrointestinal tract, with the most common locations being the stomach (55%) and small intestine (30%) [1].

In most GIST cases, mutations in the *KIT* (75–80%) or *PDGFRA* (10%) genes are found. The region associated with the most frequent mutations in the *KIT* gene is exon 11 (65% of all GISTs), especially codons 557 and 558. In 8–10% of cases, mutations occur in *KIT* exon 9. Primary mutations in other exons of the *KIT* gene, i.e., 13, 17, or 18, are relatively rare [2]. *PDGFRA* mutations are the cause of 10% of all GISTs, with the *D842V* mutation within exon 18 being the most common among them [3]. Other less common *PDGRFA* mutations may be found in exon 12 or 14 [4]. Gastrointestinal stromal tumor with *PDGFRA* mutations is mainly found in the stomach [4].

Received: 30.05.2023 Accepted: 05.06.2023 Early publication date: 06.07.2023

The remaining 10–15% of GISTs may be associated with mutations in genes from the *RAS* family (e.g., *BRAF* mutations), *NF1* mutations, or succinate dehydrogenase (SDHA/B/C/D) deficiency. Some GISTs are associated with *NRTK* translocations [2].

Determining the GIST molecular subtype is very important because this information influences further therapeutic decisions. The choice of GIST treatment method depends on the stage and molecular profile of the tumor [5]. GISTs are generally resistant to conventional chemotherapy. The prognosis of GIST has improved since 2002 when the US Food and Drug Administration (FDA) approved imatinib for this indication [6].

The most effective method in the treatment of primary localized GISTs is surgical treatment [7, 8]. In the case of unresectable or metastatic disease, treatment with tyrosine kinase inhibitors (TKIs) is the standard of care. The gold standard in the first line of treatment is imatinib. Sunitinib is used in the second line of treatment, while regorafenib and ripretinib are subsequent-line options [9]. Treatment with imatinib gives the best results in GISTs with mutations in *KIT* exon 11, and it is less effective in *KIT* exon 9 mutations and in some *PDGFRA* mutations [10]. All TKIs used so far are ineffective in the treatment of tumors with the *PDGRFA D842V* mutation [4]. For this reason, this group of patients has a notably poor prognosis.

Due to the resistance to imatinib in GIST patients with the *PDGFRA D842V* mutation, studies on new tyrosine kinase inhibitors are ongoing to find new molecules that could be effective against this mutation. As a result of these studies, avapritinib, a highly selective inhibitor of mutant KIT and PDGFRA kinases, belonging to the type I inhibitors that bind to the KIT and PDGRA proteins in their active conformation, was developed. For GIST with the *PDGFRA D842V* mutation, *in vitro* studies have shown that half of the maximum inhibitory concentration (IC50) of avapritinib is about 3000 times lower than that of imatinib [11]. In addition, avapritinib was selected for its specificity for KIT and PDGFRA activation loop mutations. In 2015, the first clinical trials evaluating the effectiveness and safety of avapritinib were initiated. Based on the preliminary results of the phase I NAVIGATOR study, on January 9, 2020, the FDA approved avapritinib as a first-line drug in patients with metastatic or unresectable GIST with the *PDGRFA* mutation in exon 18, including D842V mutations [12]. This was followed by registration by the European Medicines Agency and the European Commission, which was narrowed down to the treatment of patients with metastatic or unresectable GIST with the *PDGRA D842V* mutation [13].

Pharmacodynamic and pharmacokinetic properties of avapritinib

Avapritinib is a type 1 kinase inhibitor with *in vitro* enzymatic activity against products of mutated *PDGFRA D842V* and *KIT D816V* with IC50 values of 0.24 nM and 0.27 nM. Both of those mutations are generally considered to be resistant to imatinib, sunitinib, and regorafenib. Avapritinib also showed better activity against clinically significant mutation products in exon 11 or 17 of *KIT* than against unmutated *KIT*. Avapritinib inhibits the autophosphorylation of mutant KIT and PDGFRA proteins with IC50 values of 4 nM and 30 nM, respectively. In cell-based assays, avapritinib inhibited proliferation in *KIT*-mutant cell lines, including the mouse mast-cell line and the human mast-cell leukemia cell line. Avapritinib also inhibited the growth of murine mast-cell xenografts with *KIT* exon 17 mutations.

Following single and multiple doses of avapritinib, systemic exposure to avapritinib is dose-dependent, with time to peak concentration (C_{max}) ranging from 2 to 4 hours [13]. Steady-state is reached after approximately 15 days of once-daily dosing. High-fat meals increase C_{max} in healthy subjects compared to C_{max} after overnight fasting. Avapritinib is nearly 99% bound to human plasma proteins, and the estimated mean volume of distribution is 1200 liters. *In vitro*, studies have shown that avapritinib oxidative metabolism is mediated primarily by CYP3A4 and CYP3AP and, to a lesser extent, by CYP2C9. The mean plasma half-life in GIST patients ranges from 32 to 57 hours. Avapritinib is excreted mainly in feces (80%) and, to a lesser extent, in urine (20%) [13].

Efficacy of avapritinib in clinical trials

The safety and efficacy of avapritinib were evaluated in 2 clinical trials: NAVIGATOR (NCT02508532) and VOYAGER (NCT03465722) (Tab. 1).

The NAVIGATOR study was an open-label, non-randomized phase I study in patients with unresectable or metastatic GIST. Two hundred fifty patients were enrolled, 56 of whom had GIST with the *PDGRFRRA D842V* mutation (20 patients in part 1 with dose escalation and 36 patients in part 2). In the first part, the primary endpoints were the maximum tolerated dose, the recommended dose for phase II, and the safety profile of avapritinib. The maximum tolerated dose of avapritinib has been established at 400 mg/day, and the recommended phase II dose at 300 mg/day. In the second part of the study, the primary endpoints were objective response rate (ORR) based on central radiological review by RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) and safety profile.

Table 1. Summary of NAVIGATOR and VOYAGER clinical trial results

Endpoint	NAVIGATOR trial	VOYAGER trial			
	Patients with *PDGFRA D842V* mutation n = 56	All patients receiving avapritinib n = 240	All patients receiving regorafenib n = 236	Patients with *PDGFRA D842V* mutation receiving avapritinib n = 7	Patients with *PDGFRA D842V* mutation receiving regorafenib n = 6
Median PFS	34 months	4.2 months	5.6 months	NR	4.5 months
12-month OS	93%	68.2%	67.4%	–	–
Treatment response according to RECIST 1.1					
ORR	91%	17.1%	7.2%	42.9%	0%
CR	13%	0%	0%	0%	0%
PR	79%	17.1%	7.2%	42.9%	0%
SD	9%	47.1%	67.4%	57.1%	50%

CR — complete response; NR — not reached; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; PR — partial response; RECIST — Response Evaluation Criteria in Solid Tumors; SD — stable disease

In the 56 patients with GIST with the *PDGFRA D842V* mutation, the ORR was 91%, with a complete response (CR) in 7 (13%) and a partial response (PR) in 44 (79%) patients. The median duration of response (DOR) was 27.6 months [95% CI 17.6–not reached (NR)], and median progression-free survival (PFS) was 34 months (95% CI 22.9–NR). The durable clinical benefit translated into an increase in overall survival (OS) although median OS had not been reached at the time of analysis (median follow-up of 27.5 months). The percentage of patients surviving 12, 24, and 36 months was 93%, 75%, and 61%, respectively [14–16].

The VOYAGER study was an open-label, randomized, multicenter phase III study that compared avapritinib with regorafenib in GIST patients previously treated with imatinib and one or two additional TKIs (avapritinib or regorafenib was used as a third or fourth line of treatment). In the study, 476 patients were randomized to one of two groups — 240 patients received avapritinib 300 mg once daily (continuous treatment for 4 weeks), and 236 patients received regorafenib 160 mg once daily (3 weeks of treatment and 1 week off). The primary endpoint of the study was centrally assessed PFS according to mRECIST v1.1 modified for GIST. Baseline circulating DNA (ctDNA) analysis determined the type of mutation in each group. The *PDGFRA* exon 18 mutation was found in 3.8% (18) patients, of whom 13 had the *D842V* mutation [17]. Cross-over was possible in the study, and 41.9% (99/236) of patients receiving regorafenib crossed over to avapritinib after disease progression.

The study did not meet the primary endpoint with no differences in PFS — median PFS for 4.2 months for avapritinib and 5.6 months for regorafenib (HR = 1.25; 95% CI 0.99– 1.57; p = 0.055). In the 13 patients with *PDGFRA D842V* mutated GIST, median PFS was higher for the 7 patients treated with avapritinib (median NR; 95% CI 9.7–NR) than the 6 patients treated with regorafenib (4.5 months; 95% CI 1.7– NR; p = 0.035). When these 13 patients were excluded from the overall study population, median PFS was higher with regorafenib (5.6 months) than avapritinib (3.9 months; HR = 1.34; 95% CI 1.06–1.69; p =0.012).

The OS data were immature at the time of publication, with a median follow-up of 8.5 months for avapritinib and 9.6 months for regorafenib. The OS estimates at 12 months were similar for patients receiving avapritinib and regorafenib (68.2% *vs*. 67.4%). The ORR was higher in patients treated with avapritinib compared to regorafenib — 17.1% *vs*. 7.2%, and the difference persisted even after excluding patients with the *PDGFRA D842V* mutation. In the group of 7 patients with GIST with the *PDGFRA D842V* mutation treated with avapritinib, the ORR was 42.9%, and 57.1% of patients had stable disease. None of the patients experienced disease progression at the first assessment.

Interesting data were provided by the analysis of circulating DNA (ctDNA) in patients treated in the VOYAGER study [18]. When a mutation in the ATP-binding cassette portion of the *KIT* gene was found in the ctDNA, the efficacy of avapritinib was significantly lower than that of regorafenib (median PFS 1.9 *vs*. 5.6 months). In contrast, the response to regorafenib was not dependent on the presence or absence of these alterations. In addition, in the absence of the ATP-binding cassette mutation, median PFS for avapritinib and regorafenib was 5.6 months in both groups. It should be underlined that these are exploratory analyses, and the importance of using ctDNA for inclusion in clinical trials or selection of treatment options in GIST needs to be confirmed in more extensive prospective studies.

The NAVIGATOR and VOYAGER trials showed that avapritinib has anticancer activity in GIST patients with the *PDGFRA D842V* mutation (Tab. 1). The

Table 2. Comparison of the most common adverse reactions to avapritinib in the NAVIGATOR and VOYAGER studies

Adverse event	NAVIGATOR trial (n = 250)		VOYAGER trial (n = 239)	
	All grades	≥ G3	All grades	≥ G3
Total	245 (98%)	147 (72%)	221 (92.5%)	132 (55.2%)
Nausea	161 (64%)	5 (2%)	94 (39.3%)	2 (< 1%)
Fatigue	157 (63%)	15 (7%)	84 (35.1%)	9 (3.8%)
Anemia	136 (54%)	58 (28%)	96 (40.2%)	50 (20.9%)
Cognitive impairment	115 (46%)	8 (4%)	62 (25.9%)	3 (1.3%)
Diarrhea	112 (45%)	10 (5%)	50 (20.9%)	4 (1,7%)
Periorbital edema	110 (44%)	1 (< 1%)	66 (27.6%)	3 (1.3%)
Vomiting	106 (42%)	4 (2%)	44 (18.4%)	0
Decreased appetite	101 (40%)	6 (3%)	42 (17.6%)	2 (< 1%)
Increased lacrimation	88 (35%)	0	42 (17.6%)	0
Memory impairment	81 (32%)	1 (< 1%)	28 (11.7%)	3 (1.3%)
Peripheral edema	80 (32%)	2 (< 1%)	46 (18.8%)	1 (< 1%)
Abdominal pain	64 (26%)	11 (5%)	ND	ND
Constipation	64 (26%)	3 (1%)	ND	ND
Hair discoloration	62 (25%)	1 (1%)	ND	ND
Vertigo	59 (24%)	1 (< 1%)	ND	ND
Face edema	57 (23%)	1 (< 1%)	65 (27.2%)	6 (2.5%)
Increased bilirubin level	54 (22%)	9 (4%)	66 (27.6%)	12 (5%)
Hypokalemia	48 (19%)	6 (3%)	ND	ND
Headache	48 (19%)	1 (< 1%)	ND	ND
Dysgeusia	47 (19%)	0	ND	ND
Body weight loss	46 (18%)	2 (< 1%)	13 (5.4%)	–
Cough	39 (16%)	0	ND	ND
Neutropenia	29 (12%)	4 (2%)	ND	ND
Leukopenia	ND	ND	38 (15.9%)	10 (4.2%)
Treatment discontinuation due to adverse event	54 (22%)	–	20 (8.3%)	–
Death related to adverse evenest	1 (< 1%)	–	0	–

G — grade; ND — no data

VOYAGER study showed that avapritinib was not superior to regorafenib in patients with unresectable or metastatic GIST in the third or later lines of treatment. Patients with various *KIT* and *PDGFRA* exon 18 mutations were included in the study population, and the type of mutation in patients was not determined in some patients. Therefore, the assessment of the effectiveness of these drugs against a specific mutation is not precise, and ctDNA data should be interpreted with caution. Analyzing a small subgroup of patients with the *PDGFRA D842V* mutation (n = 13), it can be concluded that avapritinib is a more effective drug against this mutation than regorafenib.

Avapritinib toxicity

The incidence of adverse events in the phase I NAVIGATOR (NCT02508532) trial in patients with and without the *PDGFRA D842V* mutation was similar and reported by over 99% of patients [16]. Similarly, in the VOYAGER study, in 239 patients treated with avapritinib, at least one adverse event was observed in 92.5%, of which more than 50% were grade 3 or higher (Tab. 2) [17].

Gastrointestinal toxicity — nausea (39–68%), diarrhea (21–66%), and vomiting (18–42%) were common adverse reactions. Fatigue was observed in up to two-thirds of patients, and edema, including periorbital or facial edema, in 20–40% of patients [16, 17]. Cognitive impairment (memory impairment, confusion, encephalopathy) may be an essential issue with avapritinib, reported in 46–57% of patients, of whom approximately 3% had grade 3 or higher. These disorders depend mainly on the drug dose used, as the phase I study demonstrated. Intracranial bleeding occurred in 3–5% of patients [16, 17].

An increased risk of QT prolongation has been observed in clinical trials in patients treated with avapritinib. This has been associated with the risk of ventricular arrhythmias, including *torsade de pointes*. In all grades, the incidence of QT interval prolongation was 2%, while in grade ≥ 3, it was 0.2% [13].

Of the patients treated with avapritinib in the NAVIGATOR study, 22% discontinued treatment due to adverse events, compared to 8.3% in the VOYAGER study [16, 17]. Adverse events leading to treatment discontinuation in NAVIGATOR included: nervous system disorders (14%), psychiatric disorders (7%), and gastrointestinal disorders (2%). Dose modification was required in 73% of patients, and temporary discontinuation of treatment in 89% [16].

Avapritinib in Polish and international guidelines

The 2022 National Comprehensive Cancer Network (NCCN) guidelines recommend using avapritinib therapy in the first line of treatment (recommendation level 2A — an uniform NCCN consensus that the intervention is appropriate) in patients with unresectable or metastatic GIST with the *PDGFRA D842V* mutation. Dasatinib is recommended as a second-line option (2A). Under certain circumstances, for patients with GIST harboring the *PDGFRA D842V* mutation and showing progression despite treatment with avapritinib and dasatinib, ripretinib at a dose of 150 mg daily can be used (2A). Also, the European Society of Clinical Oncology (ESMO) guidelines indicate avapritinib as the basis for treating advanced GISTs with the *PDGFRA D842V* mutation (III, A: ESMO-MCBS v1.1. score: 3; ESCAT score: I–B) [19]. These recommendations are also reflected in the recommendations of the Polish Society of Clinical Oncology (PTOK) [20].

In the case of localized GISTs with the *PDGRA D842V* mutation, adjuvant imatinib therapy should not be used (IV, D). If radical surgery is unfeasible or is associated with severe consequences and the tumor contains the *PDGFRA D842V* mutation, neoadjuvant therapy with avapritinib may be considered (III, A: ESMO-MCBS v1.1 score: 3; ESCAT score: I–B) although reports on preoperative treatment are very scarce [19].

Practical information

When treating patients with GIST, the recommended starting dose of avapritinib is 300 mg. The tablet is administered orally daily on an empty stomach [13]. Treatment is continued until disease progresses or severe side effects occur. It is not recommended to use avapritinib concomitantly with moderate or potent CYP3A inhibitors (these include some macrolides: erythromycin, clarithromycin, telithromycin, antifungals — itraconazole, ketoconazole, voriconazole, drugs used to treat HIV/AIDS — cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, conivaptan used to treat hyponatremia, and boceprevir used to treat hepatitis, and grapefruit juice). If discontinuation of the CYP3A inhibitor is not possible, the daily dose of avapritinib should be reduced from 300 mg to 100 mg [13].

No dose adjustment of avapritinib is required in patients 65 years of age and older. No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin < upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin 1–1.5 × ULN and any AST level], moderate impairment (total bilirubin 1.5–3.0 × ULN and any AST level), and mild-to-moderate renal impairment (creatinine clearance 30–59 mL/min). Avapritinib has not been studied in patients with severe hepatic (Child-Pugh class C) and renal (creatinine clearance 15–29 mL/min) impairment or end-stage renal disease and, therefore, is not recommended in these groups of patients [13].

Avapritinib may increase the risk of bleeding, and complete blood counts (including platelet counts) and coagulation parameters should be monitored during treatment. Monitoring is particularly important in patients with conditions predisposing to bleeding and in patients receiving anticoagulant therapy. Another important complication of avapritinib is intracranial bleeding. If the patient develops neurological symptoms of intracranial bleeding (vision problems, severe headache, drowsiness, or weakness), treatment should be discontinued immediately, and diagnostics should be performed through magnetic resonance imaging or computed tomography. If the diagnosis of intracranial hemorrhage is confirmed, treatment should be permanently discontinued [13].

Article Information and Declarations

Author contributions

B.K.: literature review, preparation of the original version of the manuscript, preparation of figures; N.W.: literature review, preparation of the original version of the manuscript, preparation of figures; P.S.: preparation of the work concept, literature review; preparation of the final version of the manuscript, supervision of the team; P.R.: preparation of the final version of the manuscript, supervision of the team.

All authors approved the final version of the manuscript.

Funding

None.

Conflict of interest

B.K., N.W.: declare no conflict of interest.

P.S.: received conference grants from BMS, MSD, Novartis; honoraria for lecture from Sandoz, BMS, Gilead, honoraria for Advisory Board fees from Sandoz; is the holder of Celon Pharma shares.

P.R.: received honoraria for lectures from Astra Zeneca, Merck, MSD, BMS, Novartis, Pierre Fabre, Sanofi; remuneration for participation in the Advisory Board Blueprint Medicines, BMS, Merck, MSD, Philogen, Pierre Fabre, Sanofi; research funding from BMS and Pfizer.

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