Editorial Commentary

Avapritinib—a therapeutic breakthrough for PDGFRA D842V mutated gastrointestinal stromal tumors

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Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and represent approximately 1–2% of primary GI cancers. GIST tumors express a broad spectrum of mutations but the majority (85%) is driven by activating mutations in the genes encoding for KIT or platelet-derived growth factor receptor A (PDGFRA) (1). Targeting these genes with tyrosine kinase inhibitors (TKIs) dramatically improved the outcome of these patients. However, 5–6% of GIST harbor activating mutations of PDGFRA involving a substitution of an aspartic acid (D) with a valine (V) at position 842, also known as D842V. This mutation stabilizes the PDGFRA activation loop in the active conformation and prevents binding of type II TKIs, providing primary resistance to all previously approved TKIs (2).

In preclinical models, the type I TKI, avapritinib, already demonstrated antitumor activity in KIT and PDGFRA mutated GIST (3,4). These results prompted the initiation of the multicenter phase I NAVIGATOR trial which assesses the safety and antitumor activity of avapritinib in GIST. This study by Heinrich *et al.* (5) included 3 groups: patients without a PDGFRA D842V mutation who progressed following imatinib plus ≥2 other approved TKIs, patients with PDGFRA D842V mutated GIST regardless of previous therapy and patients without a PDGFRA D842V mutation that only received previous imatinib.

In this report of the subgroup with PDGFRA D842V mutated GIST by Jones *et al.* (6), avapritinib demonstrated an objective response rate of 95% in patients with PDGFRA D842V mutated GIST receiving a 300/400 mg starting dose, regardless of previous therapy. Median time to response in this group was 60 days. Based on the results of this trial, the VOYAGER trial, comparing avapritinib versus regorafenib as ≥ 3rd line treatment in molecularly unselected GIST patients, was initiated (7). Avapritinib did not meet the primary endpoint of superior progression free survival (PFS) compared with regorafenib. However, the subgroup of 7 patients with PDGFRA D842V mutated GIST receiving avapritinib showed an overall response rate (ORR) of 42.9% [95% confidence interval (CI) 9.9–81.6; all partial respons (PR)].

Other TKIs assessed in PDGFRA D842V mutated GIST only showed low potency. Crenolanib blocked phosphorylation of PDGFRA D842V mutated cell lines, suggesting a possible activity in PDGFRA D842V mutated GIST patients (8). In a phase II trial, crenolanib showed a 31% clinical benefit rate with a partial response in 2/16 patients and stable disease in 3/16 patients (9). Inclusion in the phase III trial (CRENOGIST) is ongoing. In preclinical studies ripretinib, a type II switch-pocket kinase inhibitor, demonstrated activity in PDGFRA D842V mutated GIST. However, avapritinib is 10-fold more potent than ripretinib as shown in an enzymatic assay (10). In another preclinical trial, a PDGFRA D842V mutated GIST cell line was highly resistant to ripretinib (11).

The most frequently reported adverse events (AEs) of avapritinib, such as fatigue, gastro-intestinal complains, edema and anemia commonly also occur with other TKIs. However, cognitive side effects are of special interest in patients treated with avapritinib. Any grade cognitive effects were reported in

104/250 (41.6%) patients receiving any dose of avapritinib. In the NAVIGATOR trial, among patients treated with a 300 mg starting dose the majority (92.5%) of patients experienced grade 1 or 2 cognitive effects and no patients experienced grade 4 or 5 cognitive effects. Also, cognitive effects occur more frequently in elderly patients (≥65 years) than in younger patients [38/65 (58.5%) *vs.* 40/102 (39.2%); P=0.018]. After dose interruption 53.3% of patients with grade ≥2 cognitive effects showed improvement of the AE. Post hoc analysis of the NAVIGATOR trial showed a lower rate of cognitive effects with 300 mg (67/167, 40.1%) compared with 400 mg avapritinib (25/50, 50.0%) (12). Association between the avapritinib dose and the rate of cognitive effects was also seen in the combined VOYAGER and NAVIGATOR analysis, with 23% and 38% of patients reporting any grade cognitive effects in respectively the 300 and 400 mg dosing group (13). Pharmacokinetic (PK) data from both studies suggest a trend for a higher rate of grade 3 or 4 AEs in patients with higher concentrations of avapritinib, regardless of the prescribed dose. Given a high interpatient variability it is important to realize drug exposure is stronger related to these AEs than drug dose. Hence one could consider measuring avapritinib drug concentrations to guide treatment.

Avapritinib is the first drug that shows a prominent and durable response in patients with PDGFRA D842V mutated GIST. Response rates were similar between TKI-pretreated and TKI-naive patients. Treatment related adverse events, including cognitive effects, were generally well tolerated and manageable with dose modifications. Based on these results, in January 2020, avapritinib received FDA approval for the treatment of adults with unresectable or metastatic PDGFRA D842V mutated GIST. This registration is remarkable in different ways. First of all, due to the rarity of this subgroup of GIST the size of the combined cohort of PDGFRA D842V mutated GIST patients was limited to 45 patients receiving a starting dose of 300/400 mg and there was no control group. Also, registration was approved even before long term efficacy and safety data were obtained. However, treatment options are minimal and therefore the observed antitumor effect supports the use of avapritinib as first line therapy for PDGFRA D842V mutated GIST. Even though the fate of this subgroup of patients has changed with the introduction of avapritinib, treatment options are still limited when secondary resistance develops and further research is needed to overcome the development of resistance.

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