Clinical activity of sorafenib in patients with advanced gastrointestinal stromal tumor bearing PDGFRA exon 18 mutation: a case series

PDGFRA is mutated in 5%–10% of gastrointestinal stromal tumors (GISTs), the PDGFRA D842V mutation accounting for ~60% of all PDGFRA mutations known in GISTs [1]. The DIMH842–845 and the IMH843–846 deletions represent ~15% of all PDGFRA mutations. While the latter have been associated with sensitivity to imatinib, the PDGFRA D842V mutation confers primary resistance to imatinib [1–4], sunitinib [5], and nilotinib [6]. In vitro data suggested that dasatinib is a potent inhibitor of PDGFRA D842V [7]. Sorafenib also displayed some intermediate efficacy even if it was significantly lower than for PDGFRA D842V [7]. Given the rarity of metastatic GIST with PDGFRA mutation, clinical data in this setting are almost nonexistent [8]. We report here a series of five patients with metastatic GIST bearing a mutation of the exon 18 of PDGFRA and treated with sorafenib (400 mg twice daily). The results are presented in Table 1. Tolerance was acceptable. Treatment interruption was required in one patient with past medical history significant for congestive heart failure because of a symptomatic decrease of left ventricular ejection >10% from baseline (patient 1). Three patients (including one with D842V mutation) had partial response according to Choi criteria [9] (Figure 1).

Sorafenib is a multi-kinase inhibitor that blocks several tyrosine kinase receptors such as KIT, vascular endothelial growth factor receptors, and platelet-derived growth factor (PDGF) receptors, as well as serine/threonine kinases in the RAS/RAF/MEK/ERK pathway [10]. The antitumor effect of sorafenib in GIST may result from a direct inhibition of KIT and PDGFRA but also from an inhibition of Raf/ERK/MEK signaling and of the proangiogenic growth factor receptors Flk1 and PDGFRB [11]. A phase II study recently reported in abstract form included 32 patients with imatinib- and sunitinib-resistant GIST who received 400 mg sorafenib twice daily. The results showed a clinical benefit rate of 68%, a median progression-free survival of 5.2 months, and a median overall survival of about 11.6 months [12]. However, no data were provided about the efficacy of sorafenib according to the primary mutational status. Our case series represents the first clinical evidence of the potential efficacy of sorafenib in patients with exon 18 PDGFRA mutation including the D842V missense mutation and confirms the previously reported in vitro data [7]. Dasatinib has been also recently associated with promising clinical activity in patients with advanced GIST carrying exon 18 mutation of the PDGFRA gene (including the D842V mutation) [8]. Interestingly, recent in vitro data have suggested that crenolanib, a highly selective and potent inhibitor of both PDGFRA and PDGFRB, blocks phosphorylation of D842V mutant PDGFRA at clinically achievable concentrations [13]. These promising results represent the rationale for an ongoing phase II clinical study of crenolanib in patients with advanced GISTs with the D842V mutation in the PDGFRA gene (http://clinicaltrials.gov/ct2/show/NCT01243346). Further collaborative studies are still needed to define recommendations about the best management of this uncommon and heterogeneous subset of GIST.

Table 1. Clinical activity of sorafenib in GIST bearing PDGFRA exon 18 mutation

<table>
<thead>
<tr>
<th>PDGFRA mutation</th>
<th>Line setting</th>
<th>Prior progression on imatinib</th>
<th>Best RECIST response</th>
<th>Best Choi response</th>
<th>Time to progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>D842V</td>
<td>First line</td>
<td>No</td>
<td>SD</td>
<td>&gt;6 months stop for cardiac adverse events</td>
</tr>
<tr>
<td>Case 2</td>
<td>D842V</td>
<td>Third line</td>
<td>Yes</td>
<td>SD</td>
<td>4 months</td>
</tr>
<tr>
<td>Case 3</td>
<td>DIMH842–846</td>
<td>Third line</td>
<td>Yes</td>
<td>SD</td>
<td>3 months (died from intercurrent pneumonia)</td>
</tr>
<tr>
<td>Case 4</td>
<td>DIMH842–845</td>
<td>Third line</td>
<td>Yes</td>
<td>SD</td>
<td>12 months</td>
</tr>
<tr>
<td>Case 5</td>
<td>DIMH842–845</td>
<td>Third line</td>
<td>Yes</td>
<td>PR</td>
<td>&gt;21 months (treatment ongoing)</td>
</tr>
</tbody>
</table>

PR, partial response; SD, stable disease; NA, not available.
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disclosure
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references
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Figure 1. Case 1: CT scans performed prior (A) and 4 weeks (B) after treatment onset. Decreased density [A: 44 Hounsfield units (HU); B: 27 HU] and size (8%) of the target lesion.