Rectal perforation after two years of treatment with sunitinib for metastatic kidney cancer

Perforation rectale après deux ans de traitement par sunitinib pour un cancer du rein métastatique

Case report

A 63-year-old man was admitted to our hospital at the beginning of November 2012. This patient is affected by a renal-cell carcinoma, clear-cell type, metastatic with thoracic lymph nodes and parenchymal pulmonary metastasis from mid-2010. The diagnosis of kidney cancer dated back to 2008 when he underwent a radical nephrectomy. The medical treatment was begun in October 2010 with sunitinib at the classical 50 mg/day on a 4-weeks-on/2-weeks-off schedule. The tolerance was good. At the beginning of October 2012, the patient was seen after the 17th cycle of sunitinib. He told us at that time that he suffered mid-September 2012 from febrile diarrhoea with rectal syndrome; this event was finishing at that time. We prescribed an antibiotherapy with ciprofloxacin and metronidazole and postponed the beginning of the 18th sunitinib cycle by one week, which thus began on the 15th of October. The patient was admitted on the 8th of November for acute urinary retention. He had fever and biological acute-phase inflammation. The computed tomography (CT) scan revealed a pneumo-retroperitoneum (figure 1). Antibiotherapy with piperacilline/tazobactam and metronidazole was begun. Coelioscopic surgery was performed on the 11th of November with first a diverting loop colostomy and secondly a rectal exploration which discovered a small perforation at the recto-sigmoid junction, permitting insertion of a drain. The postoperative course was uneventful and the patient was discharged to home. The colostomy reversal was performed in March 2013. We began from the end of December 2012 a new medical treatment with everolimus but tolerance was particularly poor and we stopped all treatment in March 2013. In fact, there were no more tumoral targets on CT-scans from the spring of 2012. The patient is currently (December 2013) well without any evidence of progression of the malignancy.

Discussion

Sunitinib is a multitargeted and antiangiogenic tyrosine kinase inhibitor (TKI) well established in the treatment of metastatic renal-cell carcinoma (MRCC) and gastro-intestinal stromal tumours (GIST). Bowel perforation is a very rare adverse event related to this drug with so far barely six case reports in the English-language literature (data summarized in table I) [1–4]. No cases of bowel perforation have been reported in the pivotal study establishing sunitinib for the treatment of MRCC [5]. Four cases of bowel perforation are also reported with sorafenib, another antiangiogenic TKI with very similar issues [3,5,6]. All these cases apart from one [1] are described in patients affected by MRCC. Bowel perforation is much more known with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor. Two different kinds of bowel perforations related to sunitinib can be described: by antitumoral efficacy against tumoral localisations in the gastro-intestinal wall (for instance in case of a gastro-intestinal stromal tumor treated by sunitinib [1], or even in a case of gastro-intestinal metastasis of renal-cell carcinoma [4]); or, as in our case, by still unclear mechanisms involving microvascular toxicity and therefore mucosal fragility. Bowel perforation under antiangiogenic TKI treatment is in most cases of early occurrence, in the first months (up to five months) if not the first weeks of treatment. Late event, as in our case, has just been reported in one case (thirteen months) [2]. Our case is peculiar in that the bowel perforation has been preceded by febrile diarrhoea, probably infectious, may be acting as a first
hit on the mucosae paving the way to the subsequent perforation. Risk factors of bowel perforation under antiangiogenic TKI treatments are not known. However, in three cases linked with radiotherapy, all three with sorafenib, a possible radiosensitization is underlined [6,7]. At last, our case illustrates the issue of long-lasting antiangiogenic TKI treatments and the risk of late toxicity. It also illustrates the need of having guidelines concerning this small but existing subset of patients with MRCC in complete response under TKI treatments; a French group has already given clues: the interruption of TKI is possible with more than 60% of patients remaining in complete response with a median follow-up of about nine months [8].

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References

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Received 26 January 2014
Accepted 17 March 2014

http://dx.doi.org/10.1016/j.lpm.2014.03.021
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Table I
Summarized data of patients with bowel perforation during sunitinib treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender</th>
<th>Age</th>
<th>Tumour</th>
<th>Time to perforation</th>
<th>Perforation location</th>
<th>Surgical treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hur et al. [1]</td>
<td>Female</td>
<td>70</td>
<td>GIST</td>
<td>6 weeks</td>
<td>Transverse colon</td>
<td>Percutaneous drainage</td>
<td>Favourable</td>
</tr>
<tr>
<td>Flaig et al. [2]</td>
<td>Female</td>
<td>Unknown</td>
<td>MRCC</td>
<td>13 months</td>
<td>Right colon</td>
<td>Right hemicolectomy</td>
<td>Unknown</td>
</tr>
<tr>
<td>Flaig et al. [2]</td>
<td>Female</td>
<td>Unknown</td>
<td>MRCC</td>
<td>5 months</td>
<td>Right colon</td>
<td>None</td>
<td>Favourable</td>
</tr>
<tr>
<td>Walraven et al. [3]</td>
<td>Female</td>
<td>62</td>
<td>MRCC</td>
<td>Second cycle</td>
<td>Anal</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>Hoshino et al. [4]</td>
<td>Male</td>
<td>50</td>
<td>MRCC</td>
<td>6 months (four cycles)</td>
<td>Right colon</td>
<td>Right hemicolectomy</td>
<td>Favourable</td>
</tr>
<tr>
<td>Hoshino et al. [4]</td>
<td>Female</td>
<td>60</td>
<td>MRCC</td>
<td>11 days</td>
<td>Jejunum</td>
<td>Jejunostomy</td>
<td>Death</td>
</tr>
<tr>
<td>Our case</td>
<td>Male</td>
<td>63</td>
<td>MRCC</td>
<td>24 months 18 cycles</td>
<td>Recto-sigmoid junction</td>
<td>Diverting loop colostomy, drainage</td>
<td>Favourable</td>
</tr>
</tbody>
</table>

GIST: gastro-intestinal stromal tumours; MRCC: metastatic renal-cell carcinoma.