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for young doctors

Case report

NEOADJUVANT IMATINIB AND RADIOTHERAPY IN GASTROINTESTINAL STROMAL TUMOR OF THE RECTUM: A CASE REPORT

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Summary

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Rectal localization is rare. The gold standard for treatment is: surgery and tyrosine kinase inhibitors (TKIs) for metastatic or unresectable disease.

We report a case of a 62 year-old woman who underwent a gastroenterology visit for abdominal pain, tenesmus and constipation. After GIST diagnosis and staging, the patient started induction therapy with imatinib followed by concomitant radio and targeted therapy before a sphincter-saving anterior resection, with a regular postoperative course.

The rationale of neoadjuvant treatment is lesion downsizing for an easier surgery. In epithelial cancers treated through concomitant therapies, the goal is also to preserve the functional integrity of organs, lowering the risk for salvage therapies. Also in GISTs, there is a direct correlation between downsizing, downstaging and outcomes.

There are few reports about concurrent radio-therapy and TKIs, and this approach is probably underutilized. Further studies are needed.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumors arising in the gastrointestinal tract. These tumors, characterized by CD117 expression, may occur anywhere in the gastrointestinal tract, but stomach and small bowel localizations account for 80 –95% of cases, while rectal only account for 5% [1].

The gold standard for treatment of localized disease is complete surgical excisions. Tyrosine kinase inhibitors (TKIs) are the reference drugs for patients with metastatic or unresectable disease, and neoadjuvant TKI therapy has been recently used increasingly for more extended surgical resection [2].

Of all cancers arising from the rectum, only 0,1% are GISTs, and due to their rarity,

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there are no standardized surgical procedures for distal rectum, anal canal and rectovaginal space localizations.
Furthermore, given the rarity of rectal GIST localization and its histological characteristics, can not be applied colorectal screening project, as Fecal Occult Blood Tests [3].

Case report

We report a case of a 62 year-old woman, who in May 2013 underwent to a gastroenterology visit for abdominal pain, tenesmus and constipation. The patient was never subjected to pancolonoscopy screening and her comorbidities were high blood pressure and mental instability, both treated by medical therapy.
At the level of the pectineal line, the colonoscopy showed the presence of a lesion, on which a biopsy was performed (not diagnostic for neoplasm). A subsequent endoscopic ultrasonography (EUS) showed a hypoechoic ultrasound alteration with an average diameter of 5 cm, which covered the entire thickness of the bowel wall, with internal liquefaction areas, providing an initial suspicion of GIST.
Staging was performed with pelvis MRI, complete abdomen and chest CT and 18F -FDG PET-CT, all positive for rectum localization of the disease (maximum diameter: 6,5 cm). The main features highlighted were: extension to the proximal portion of the anus, no locoregional lymph nodes and the lack of certain cleavage planes.
The patient was given a temporary colostomy and a second biopsy was performed, this time diagnostic for mesenchymal spindle cell neoplasm, resulted positive for CD34 and CD117, with a morphological and immunophenotypic profile compatible with GIST.
The patient was referred to our Department and started induction therapy with oral imatinib mesylate (standard dose: 400 mg/die) for a total of four months. MRI and PET-CT were performed at this stage, showing an initial response to TKI therapy. Then, the patient was submitted to concomitant radio and targeted therapy, continuing to take the same drug dose until the end of the radiotherapy.
Radiation treatment was performed with 3-D conformal technique with the patient in the prone position (using belly board). The total dose administered to the pelvis was 45 Gy in 25 fractions, with a concomitant boost of 9 Gy (1.5 Gy/fraction) in 6 fractions on the lesion. All organs at risk for dose constraints were respected according to the QUANTEC table. During the treatment, weekly check-ups were performed, also checking general clinical conditions and evaluating blood tests results. After the first two weeks of treatment, there was an improvement of symptoms, particularly pain. Therapy was completed without major toxicity, according with CTCAE scale (v. 4.0).
After two months, both pelvic MRI and PET-CT showed a further partial response of disease (Figure 1; Figure 2) and patient underwent a rectal resection (Figure 3), with a normal post surgery course.

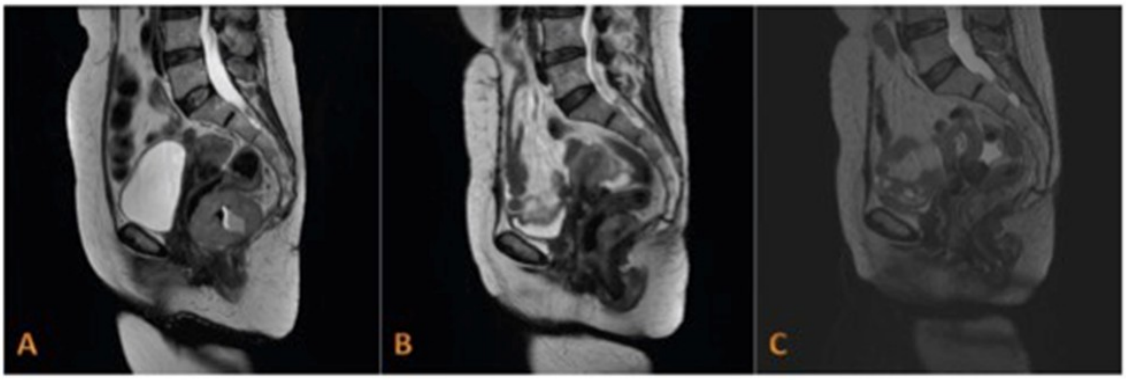

Figure 1. A) MRI at diagnosis (baseline); B) after 4 months of oral imatinib therapy; C) after radiotherapy concomitant to imatinib. Lesion downsizing is evident.

The first clinical check-up took place three months after surgery. The general clinical conditions were good, with normal blood tests and negative pelvis and abdomen CT. In June 2015, date of the last follow-up, the patient was free of disease recurrence.

Discussion

Although GISTs are rare tumors, their incidence is increasing [4]. The cornerstones for treatment are: complete surgical resection for limited resectable disease, and the use of TKIs, particularly imatinib mesylate, for patients with inoperable or metastatic disease [2].

In the pre–TKI era, GISTs treated with traditional cytotoxic chemotherapeutic agents, or conventional preoperative radio-chemotherapy, have been proven to be very poorly responsive [5].

In the literature, there are few studies available on neoadjuvant treatments with imatinib alone, or the use of radiotherapy for curative intent other than palliative care, and most of the times have a limited number of patients.

The rationale of neoadjuvant treatment is to downsize the lesion for a better surgical approach. Epithelial cancers are generally treated through preoperative concomitant therapies, which also have the goal to preserve, when possible, the functional integrity of healthy organs. Moreover, the mere function of debulking is to reduce symptoms and complications from surgery, lowering the risk for salvage therapies. Also, for these tumors there is a direct correlation between downsizing, downstaging and outcomes.

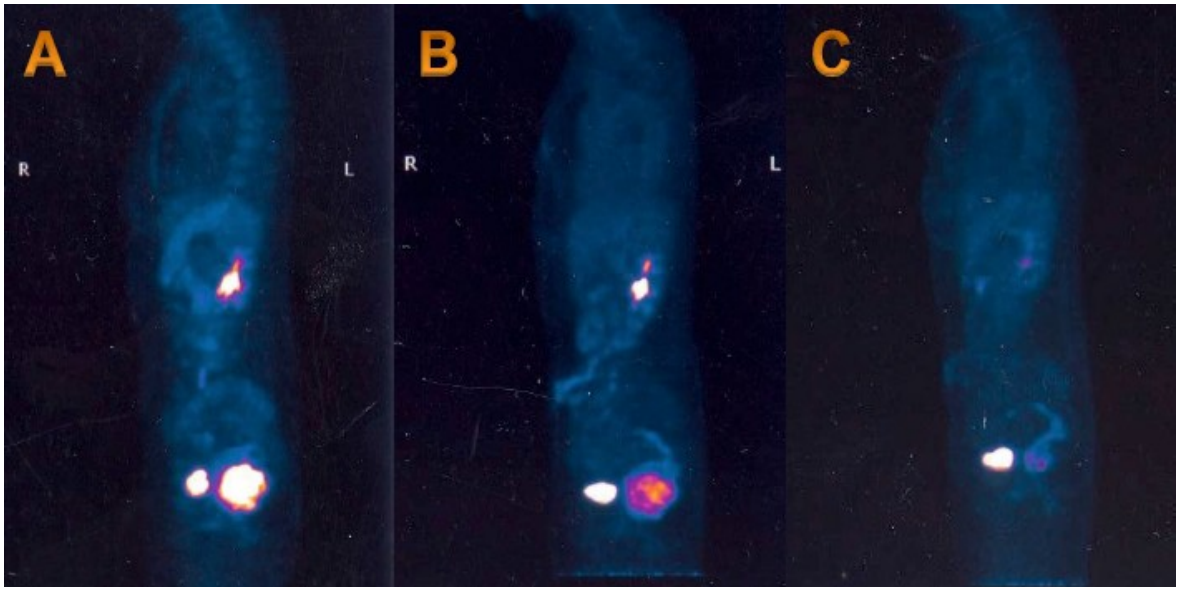

Figure 2. A) 18F-FDG PET-CT at diagnosis (baseline); B) after 4 months of oral imatinib therapy; C) after radiotherapy concomitant to imatinib. PET also shows response to neoadjuvant imatinib and radiotherapy.

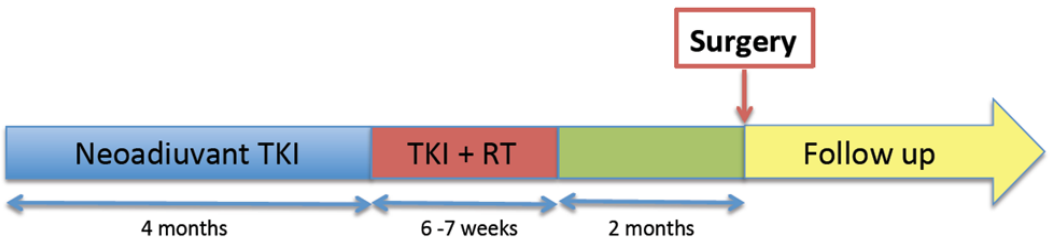

Figure 3. Treatment schedule

This observation is confirmed by a Radiation Therapy Oncology Group (RTOG) phase II trial of neoadjuvant/adjuvant imatinib for GIST, which clearly describes that complete resection of gross and microscopic disease (R0) had an impact on time to progression, with no mention to radiation or concomitant treatments [6]. The importance of surgical R0 resection is also described in other well-respected studies [1,7,8].

Xiao et al. analyzed clinicopathological characteristics and prognostic factors of twenty-one patients with rectal GISTs who underwent curative resection between 1986 and 2010. They demonstrated that only high NIH risk category (p = 0.040) and hematochezia symptoms (p = 0.019) were predictors for less DFS patients. The other factors studied such as age, gender, obstruction, family history of cancer, etc. had no correlation with DFS and OS, including use of imatinib [9].

In the past, radiation therapy has never been considered effective in the treatment of GIST, even if it could have various roles. Preop-erative RT could be considered for tumors at high risk of local recurrence or R1 resection, and for particular surgically inaccessible sites, such as duodenum and esophagus, radiotherapy may be a local treatment option. Finally, RT can be used also for palliative care [10].

Probably, the most important role of radiation is given by the potential effect of resistance to targeted therapy, an emerging common clinical problem with relatively few therapeutic solutions.

In the case we reported, radiation treatment combined with target therapy was not burdened by particular toxicity. Ciresa et al. reported a similar experience in which a patient developed hematological and lower intestinal toxicities, stopping treatment on total dose of 37.8 Gy. Although the planned dose of 50.4 Gy was not reached, the achieved response led to surgery [11].

There are few case reports about concurrent radio-therapy and TKIs, and this approach is probably underutilized for GISTs. Further studies are needed to establish the best treatment for managing this disease.

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virch Arch 2001;438:1–12.

2. Casali PG, Blay JY, ESMO/ CONTICANET/EUROBONET Consensus Panel of Experts (2010) Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 5:98–102

3. Costantino C, Calamusa G, Cusimano R, Firenze A, Romano N, Trecca A, Vitale F. A proposal for an evidence-based model of the screening for the colorectal carcinoma in an Italian setting. J Prev Med Hyg. 2011 Dec;52(4):191-5.

4. Demetri GD, Von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, et al: NCCN Task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010, 8 (Suppl 2):S1 S41. quiz S42-44.

5. Cuaron JJ, Goodman KA, Lee N, Wu AJ. External beam radiation therapy for locally advanced and metastatic gastrointestinal stromal tumors. Radiat Oncol. 2013 Nov 23;8:274. doi: 10.1186/1748-717X-8-274.

6. Wang D, Zhang Q, Blanke CD, Demetri GD, Heinrich MC, Watson JC, Hoffman JP, Okuno S, Kane JM, von Mehren M, Eisenberg BL. Phase II trial of neoadjuvant/ adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol. 2012 Apr;19(4):1074-80. doi: 10.1245/s10434-011-2190-5.Epub 2011 Dec 28.

7. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39:1411–9.

8. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after re-

section of primary gastrointestinal stromal tumor (GIST). Cancer. 2008; 112:608–15.
9. Xiao CC, Zhang S, Wang MH, Huang LY, Wu P, Xu Y, Zhu XL, Sheng WQ, Du CY, Shi YQ, Guan ZQ, Cai SJ, Cai GX. Clinicopathological features and prognostic factors of rectal gastrointestinal stromal tumors. J Gastrointest Surg. 2013 Apr;17(4):793-8. doi: 10.1007/s11605-012-2086-0. Epub 2013 Jan 4.
10. Corbin KS, Kindler HL, Liauw SL. Considering the role of radiation therapy for gastrointestinal stromal tumor. Onco Targets Ther. 2014 May 12;7:713-8. doi: 10.2147/OTT.S36873. eCollection 2014.
11. Ciresa M, D'Angelillo RM, Ramella S, Cellini F, Gaudino D, Stimato G, Fiore M, Greco C, Nudo R, Trodella L. Molecularly targeted therapy and radiotherapy in the management of localized gastrointestinal stromal tumor (GIST) of the rectum: a case report. Tumori. 2009 Mar-Apr;95 (2):236-9.