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Interdisciplinary Discussion

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Gastrointestinal Stromal Tumors

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Question 1: What is your treatment policy in patients being diagnosed with intraluminal bleeding (upper gastrointestinal bleeding) in a gastric gastrointestinal stromal tumor (GIST) larger than 10 cm? Would you decide on immediate resection or would you deem treatment with tyrosine kinase inhibitors (TKIs) (imatinib) appropriate if the tumor is sensitive to the drug?

Hohenberger: We would always try to also treat a primary stomach GIST, which becomes symptomatic with an upper gastrointestinal bleeding by a neoadjuvant therapy with imatinib. The immediate suspension of tumor proliferation and the rapid reduction of tumor perfusion (detectable in perfusion magnetic resonance imaging, contrast-enhanced computed tomography, and positron emission tomography (PET)) is almost always expected to stop the bleeding. The prerequisite is that an imatinib-sensitive mutation is present. Since it often takes a few days before the mutational findings are available, we would also immediately start therapy with imatinib if we were to detect a spindle cell tumor that otherwise has the characteristic signs of GIST. The rate of side effects is low, while the response probability is high. We have seen only one or two patients out of more than 90 patients treated with neoadjuvant intent in whom the strategy did not work – the patient was finally diagnosed with a PEComa (perivascular epithelioid cell neoplasm).

Montemurro: If the bleeding is serious or if a potential response to TKIs would not change the extent of surgery, we regularly decide on immediate resection. Imaging identifies both risk factors (large areas of necrosis etc.) and potential for tumor embolization. If the bleeding is not life-threatening or if a reduction of the GIST size would allow for a later resection with better functional outcomes, we decide to start TKI treatment and often keep the patient hospitalized for a few days. This is a multidisciplinary decision which should be taken together with the patient. In doubt we regularly decide on immediate resection.

Raut: I assume that these patients have imatinib-sensitive mutations.

There are at least three different scenarios involving intraluminal bleeding:

In the first scenario, there are patients with an incidental finding of a bleeding submucosal mass (found on upper endoscopy indicated for other reasons) or those with anemia undergoing endoscopic evaluation for the source. In these various presentations, the bleeding is not usually symptomatic. In such patients, I would almost always recommend neoadjuvant imatinib for a 10-cm primary GIST. The goal of therapy would be sufficient shrinkage to attempt a laparoscopic resection.

In the second scenario, there are patients in the other extreme – life-threatening bleeding. For such patients, for whom the risk of re-bleeding is great, I proceed immediately to surgery.

In between, we have the third scenario – patients with relatively brisk, often symptomatic bleeding who are found to have such a mass on endoscopy, and the bleeding can be controlled. In this subset of patients, I do consider neoadjuvant imatinib. However, given our concern about re-bleeding, we follow such patients very closely, with frequent hematocrit checks. I find that imatinib can have such an outstanding treatment effect that bleeding can stop from progressive hyalinization of the tumor.

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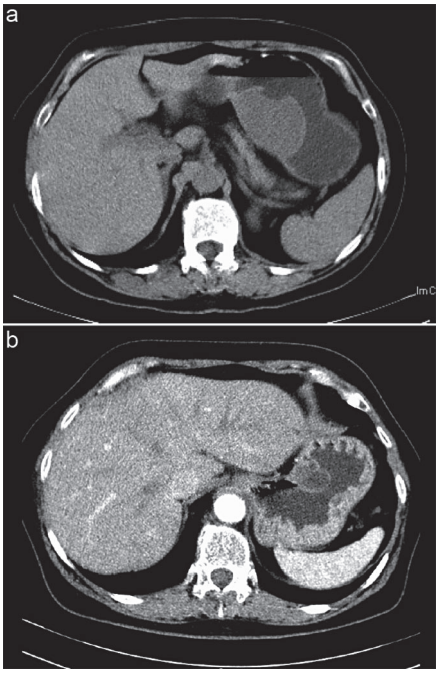

Fig. 1. Computed tomography images demonstrating response of locally advanced gastric gastrointestinal stromal tumors detected due to gastrointestinal bleeding with significant shrinkage of tumor allowing for complete tumor removal via wedge resection. **a** Before and **b** after treatment with imatinib (400 mg daily).

If the patient has an imatinib-insensitive mutation, such as *PDGFRA* D842V, then I would not recommend neoadjuvant imatinib under any circumstance.

Rutkowski: Locally advanced GIST are defined as those tumors that can potentially benefit from neoadjuvant treatment with imatinib through a decrease in size and vulnerability. Very large tumors can also be potential candidates for preoperative therapy, because they tend to be extremely fragile and hypervascular, with a substantial risk of intraoperative rupture and/or bleeding. My personal approach to neoadjuvant imatinib in gastric GIST depends on whether the downstaging would limit the extent of resection or improve the conditions of surgery, and, obviously, whether mutational status indicates sensitivity to imatinib.

The neoadjuvant cytoreductive treatment in localized GIST aims to facilitate resection with microscopically clear margins, to decrease the extent and morbidity of the surgical procedure, and to minimize tumor micrometastases. Neoadjuvant therapy can reduce the need for extensive, multiorgan resections and diminish the intraoperative risk of rupture of devitalized tumor as well as spill of active tumor cells into the peritoneal cavity (which is closely related to the risk of disease dissemination). Furthermore, it decreases the necessity of blood transfusions as a consequence of intraoperative tumor bleeding [1–5]. Figure 1 illustrates a locally advanced gastric exon 11 *KIT*-mutant GIST, detected due to gastrointestinal bleeding, which responded to imatinib 400 mg daily, resulting in a significant shrinkage of tumor; the bleeding stopped within 1 week of therapy. In my opinion, this enabled a complete tumor removal via wedge resection.

When used as a neoadjuvant treatment, imatinib is administered until maximal response is achieved. Usually, after 6–9 months, when two consecutive imaging procedures (mostly computed tomography) show no further tumor regression (plateau), this is considered the point of maximal response.

The proper candidates for preoperative imatinib are those patients who may benefit from tumor downstaging before operation, i.e. patients in whom preoperative therapy with imatinib enables an organ-sparing resection with negative margins, avoiding mutilating surgery, intraoperative tumor rupture, and/or extensive blood loss. Obviously, this neoadjuvant strategy is especially attractive in surgically demanding tumor sites, so it is not commonly used by me in gastric GIST. In some selected cases downstaging of the primary tumor may sometimes even allow laparoscopic surgery instead of open surgery through an extensive midline laparotomy. Naturally, these patients must be carefully selected by multidisciplinary assessment to optimize clinical outcomes. Based on the assessment of size, location, and mitotic index, the majority of primary GIST treated with preoperative imatinib are considered high- or intermediate-risk tumors. This makes them candidates for adjuvant treatment with imatinib. According to current guidelines, imatinib should be administered postoperatively for up to 36 months.

Question 2: What is your strategy in GIST of the rectum? When do you consider neoadjuvant drug therapy? What is your approach to tumor resection – transabdominal (laparoscopic) low anterior resection (LAR) or transanal resection?

Hohenberger: GIST of the rectum are only an indication for primary resection if they can be covered on all sides with soft tissue and can be removed without compromising the anal sphincter function when totally excised. This applies to tumors with a maximum size of 2–3 cm, on the dorsal or lateral side of the rectum. It is important to carry out a full rectal wall resection including the retrorectal or pararectal fatty tissue covering the tumor and not a pure resection of the rectum and enucleation towards the retrorectal space. All rectum GIST that develop anteriorly (in men towards the prostate and in women at the rectovaginal septum) benefit from a downstaging with imatinib. It should be noted in particular that rectum GIST are either low-grade or high-grade; there are hardly any tumors that can be assigned to the intermediate-risk classes. In case of doubt, we would always favor a neoadjuvant therapy.

Montemurro: Good functional outcome is of high relevance for rectal GIST. Thus, if a primary resection does not seem possible, our standard procedure is neoadjuvant treatment [6, 7]. To identify any non-responder, we closely monitor the evolution clinically and radiologically, sometimes including PET, particularly for low-

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seated lesions. Our dedicated rectal surgeons decide which technique to use, based on size, location, expected margin, and response to neoadjuvant therapy [8]. Continuing imatinib, maybe radiotherapy, and even second surgery are postoperative options for marginal resections or local progression/relapse [9].

Raut: I generally perform an open or minimally invasive LAR for GISTs in the upper two-thirds of the rectum and a transanal resection for a lower third rectal GIST. I consider neoadjuvant imatinib for lower third rectal GISTs if I think that tumor shrinkage will facilitate easy exposure for a transanal resection and minimize the possibility of needing to perform an abdominoperineal resection. If the patient has a more proximal rectal GIST requiring a LAR, I can accept a larger size for a laparoscopic resection than I can for a distal third GIST for transanal resection.

Rutkowski: If it is not possible to remove it locally (2–3 cm GIST), I always consider neoadjuvant therapy, especially because the majority of these GIST harbor *KIT* mutations and because they are very sensitive to imatinib. The neoadjuvant strategy is especially attractive in surgically demanding tumor sites, such as the distal rectum, gastroesophageal junction, duodenum, or esophagus, where preservation of vital functions is pivotal. Resection of advanced primary tumors at these sites may be related to significant morbidity and functional defects. I prefer transanal resection [4].

Question 3: In patients with tumor rupture but subsequent complete macroscopic tumor resection, do you consider those patients for adjuvant treatment if there is a drug-sensitive mutation? How long would you treat those patients?

Hohenberger: In patients with a real tumor rupture into the peritoneal cavity, in which a macroscopic R0 resection was performed, it must always be assumed that a contamination of the peritoneal cavity exists (like in perforated gastric cancer). This applies to primary surgical tumor rupture as well as to intraoperative tumor disruption. Such patients are considered peritoneally metastasized. They do not qualify for an adjuvant therapy but need a permanent, actually lifelong, therapy with a drug against the tumoral mutation detected. In contrast, tumor erosion towards the stomach or intestinal lumen cannot be regarded as tumor rupture.

Montemurro: We consider tumor rupture as a major risk factor for tumor recurrence [10]. All patients with tumor rupture receive postoperative imatinib for at least 3 years. Admittedly, this policy might need cautious review: Tumor rupture should be more precisely characterized into major and minor [11].

Raut: I consider tumor rupture (intraperitoneal rather than intraluminal) as tantamount to metastatic disease. I would absolutely recommend imatinib (if a drug-sensitive mutation). Even if I can remove all of the disease, I would still stress to the patient that lifelong TKI therapy is required.

Rutkowski: Tumor rupture is a very negative prognostic factor and can change definition; according to recommendation, lifelong imatinib should be considered but it also depends on the extent of tumor rupture (Norwegian group).

In Poland I can use adjuvant therapy for 3 years.

Tumor rupture – spontaneous or iatrogenic – may change GIST from low-risk to high-risk or micrometastatic. All available data indicate unequivocally that an important, negative factor influencing the recurrences is tumor perforation or intraperitoneal bleeding [8, 11–14]. In the study performed by our group [12], the estimated 5-year relapse-free survival rate was only 17% in a group of patients with ruptured tumor as compared to 55% in the rest of the patients, and it was a statistically significant independent prognostic factor. The postoperative course of patients with tumor rupture preoperatively or during resection was similar to that of patients with macroscopic incomplete R2 resection. In the study by McCarter et al. [8], the risk of recurrence within the R1 group appeared to be driven largely by the presence of tumor rupture or intraperitoneal bleeding. Hølmebakk et al. [11] tried to further define the clinical significance of tumor perforation and reported that recurrence rates after primary tumor resection were increased after major tumor ruptures defined as tumor spillage, tumor fracture or piecemeal resection, bowel perforation at the tumor site, blood-tinged ascites, microscopic tumor infiltration into an adjacent organ, and open surgical biopsy, but not after minor tumor perforations (peritoneal tumor penetration, iatrogenic peritoneal laceration, and microscopically involved margins). Moreover, according to an analysis of databases of two adjuvant trials, i.e. SSG XVIII and ACOSOG Z9001, tumor rupture maintains significance for unfavorable recurrence-free survival in a population of GIST patients treated with adjuvant imatinib [14].

To summarize, I always consider patients with tumor rupture for adjuvant therapy (if there is imatinib-sensitive mutation); the extent of tumor rupture should be included in the decision-making tree (as it was described by a Norwegian group). In Poland, I can use adjuvant therapy for 3 years, although existing recommendations suggest that lifelong imatinib should be considered [3].

Question 4: What is your indication for mutational testing of primary tumors? Is there a threshold regarding size? Do you indicate testing of the primary tumor or would you wait until tumor progression?

Hohenberger: From a scientific point of view, we perform mutational testing on all our patients/tumors. Under practical conditions, mutational testing is indicated for all patients requiring drug therapy. This naturally also applies to neoadjuvant treatment concepts. Again and again we find that patients were treated with imatinib only due to the size and mitotic rate of the tumor, and later it turns out that they have a D842V, N822K mutation or show

no detectable mutation at all. In view of a rate of approximately 15–20% of patients with tumors that are not sensitive to imatinib, there is a significant potential for unnecessary toxicity and financial burden. We also initiate a mutational analysis in patients with high-risk GIST even if no metastases are detectable yet. In case of later detection of metastases, we do not have to wait for the results if unusual mutations are present.

Montemurro: Our population mainly consists of patients with either metastatic or large primary GIST, who often receive TKIs either neoadjuvant, adjuvant, or both. Only a minority of our patients does not need TKIs. Thus, we perform mutational testing on all patients to identify those with TKI-resistant GIST.

Raut: I now routinely order mutation testing for all GIST patients. At our institution, this can be ordered as a clinical test, and insurance usually pays for such testing. I do not use any particular size cut-off. Separate from this, we do have an ongoing research study looking at secondary mutations in patients with tumor progression who undergo surgery, in an effort to better understand the genomic landscape of primary and secondary mutations across all individual clones.

Rutkowski: All GIST cases except low- and very low-risk tumors are tested for mutational *KIT/PDGFRA* status in our center. In entire Poland it is also obligatory to genotype the tumor before initiation of adjuvant therapy, as *D842V PDGFRA*-mutant and wild-type GIST are not recommended for postoperative therapy and are not reimbursed. Personally, I always indicate testing at the time of diagnosis, thus not waiting until tumor progression to have more evidenced-based personalized decisions in each individual case [15].

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References

1 Rutkowski P, Gronchi A, Hohenberger P, et al: Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol 2013;20:2937–2943.
2 Hohenberger P, Eisenberg B: Role of surgery combined with kinase inhibition in the management of gastrointestinal stromal tumor (GIST). Ann Surg Oncol 2010;17:2585–2600.
3 Casali PG, Abecassis N, Bauer S, et al.; ESMO Guidelines Committee and EURACAN: Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;DOI: 10.1093/annonc/mdy095.
4 Rutkowski P, Hompes D: Combined therapy of gastrointestinal stromal tumors. Surg Oncol Clin N Am 2016;25:735–759.
5 Hohenberger P, Langer C, Wendtner CM, et al: Neoadjuvant treatment of locally advanced GIST: results of APOLLON, a prospective, open label phase II study in KIT- or PDGFRA-positive tumors. J Clin Oncol 2012; 30(suppl):abstr 10031.
6 Huynh TK, Meeus P, Cassier P, Bouché O, Lardière-Deguelte S, Adenis A, André T, Mancini J, Collard O, Montemurro M, Bompas E, Rios M, Isambert N, Cupissol D, Blay JY, Duffaud F: Primary localized rectal/pararectal gastrointestinal stromal tumors: results of surgical and multimodal therapy from the French Sarcoma group. BMC Cancer 2014;14:156.
7 Hawkins AT, Wells KO, Krishnamurty DM, Hunt SR, Mutch MG, Glasgow SC, Wise PE, Silviera ML: Preoperative chemotherapy and survival for large anorectal gastrointestinal stromal tumors: a national analysis of 333 cases. Ann Surg Oncol 2017;24:1195–1201.
8 McCarter MD, Antonescu CR, Ballman KV, Maki RG, Pisters PW, Demetri GD, Blanke CD, von Mehren M, Brennan MF, McCall L, Ota DM, DeMatteo RP; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant Gist Study Team: Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Coll Surg 2012;215:53–59; discussion 59–60.
9 Joensuu H, Eriksson M, Collan J, Balk MH, Leyvraz S, Montemurro M: Radiotherapy for GIST progressing during or after tyrosine kinase inhibitor therapy: a prospective study. Radiother Oncol 2015;116:233–238.
10 Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP, Rutkowski P: Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265–274.
11 Hølmebakk T, Bjerkehagen B, Boye K, Bruland Ø, Stoldt S, Sundby Hall K: Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine. Br J Surg 2016;103: 684–691.
12 Rutkowski P, Bylina E, Wozniak A, Nowecki ZI, Osuch C, Matlok M, Świtaj T, Michej W, Wroński M, Głuszek S, Kroc J, Nasierowska-Guttmejer A, Joensuu H: Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour – the impact of tumour rupture on patient outcomes. Eur J Surg Oncol 2011;37:890–896.
13 Peparini N, Chirletti P: Tumor rupture during surgery for gastrointestinal stromal tumors: pay attention! World J Gastroenterol 2013;19:2009–2010.
14 Joensuu H, Eriksson M, Hall KS, Hartmann JT, Pink D, Schütte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran S-E, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, Ballman KV, Leinonen M, DeMatteo RP, Reichardt P: Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 2014;120: 2325–2333.
15 Rutkowski P, Lugowska I: Soft tissue sarcomas in adults. Oncol Clin Pract 2017;5:181–201.