Gastrointestinal Stromal Tumors

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Exactly 20 years have passed since the publication on the gain-of-function mutation in the *KIT* proto-oncogene by Seiichi Hirota in *Science* in 1998 [1], establishing the diagnosis of a gastrointestinal stromal tumor (GIST) as a defined disease. As a result, tumors would no longer be mixed with leiomyosarcoma, aggressive leiomyoma, or leiomyblastoma. Based on Hirota's report, the first patient was treated with imatinib (STI571) by Heikki Joensuu in the summer of 2000, and the first randomized phase III studies to establish imatinib as the major therapeutic agent started immediately thereafter at the EORTC (trials 62001 and 62005) and US (trial B2222) level.

Nowadays, the standards of treatment are clearly stated and focus on primary tumors, the indication for adjuvant treatment has been established and approved, and a sequence of the lines of treatment (imatinib, sunitinib, regorafenib) is generally accepted in the metastatic stage. The European Society for Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (NCCN) guidelines are regularly updated but do not differ much between versions. One might almost think that everything is clear regarding the treatment of GIST.

However, this is by far not the case. Sarcomas belong to the family of rare cancers, and GIST is the most common subtype accounting for 20–25% of all cases. To a significant extent, treatment is started at the non-expert level. The initial decision-making how to treat a biopsy-proven or suspected GIST may often be challenged later, and collaboration between gastroenterologists and visceral surgeons could be improved:

- The diagnostic accuracy in the differential diagnosis of submucosal tumors of the stomach is not sufficiently good. Pancreatic heterotopias, inflammatory fibroid polyps, desmoids, and neurofibromas are still not sufficiently diagnosed preoperatively. Many of the resections do not remove a GIST and could have been avoided.

- For the presentation of GIST in an emergency situation, there are few meaningful studies as to whether a primary antiproliferative therapy might be preferable over immediate surgery.
- The proportion of patients undergoing major resection for large primary tumors, e.g. a gastrectomy, without considering neoadjuvant therapy is still high.
- This is unfavorable for later adjuvant therapy, since plasma imatinib levels are significantly lower in gastrectomy patients than in those with stressful segmental resection of the stomach.
- In the follow-up of patients with high-risk GIST or those with systemic metastasis under antiproliferative therapy, it is still unclear whether a computed tomography (CT) scan with contrast agent or a dual-energy CT [2] or ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography is the best procedure to detect tumor progression [3].
- Magnetic resonance imaging was favored from the point of view of radiation protection, which is now being critically discussed by patients who often do not wish to have contrast media applied.

VISCERAL MEDICINE is an interdisciplinary journal covering the principles of both gastroenterological diagnostics and therapy as well as visceral surgery aspects of tumor treatment. Therefore, in this issue, we address *several* of the crucial points mentioned above.

In their contribution, Menge et al. [4] analyse the clinical symptomatology of primary GIST. They nicely show that there is a significant difference in the emergency presentation rates between the different tumor locations. The authors also report that patients presenting with metastases at initial diagnosis still have a 10-year survival rate of 36%. However, those patients develop metastases at unusual sites in the later course of their disease.

Raut [5] thoroughly discusses the different tumor biological aspects between mesenchymal and epithelial tumors of the gastroin-

testinal tract. It is quite clear that gastroenterologists have to address cancers and diseases of the epithelial layer much more often than those of the submucosal areas. He also answers the question why we should treat margins differently in carcinomas versus sarcomas for gastric and rectal tumors.

Rutkowski et al. [6] address the question of surgical margins in resections for GIST, particularly taking into account the fact that the tumors are sometimes very fragile, are well-perfused, and might easily shed tumor cells to the peritoneal cavity. They also discuss the question on whether R1 resections require a second surgical procedure to achieve negative margins, as in the case for extremity sarcomas.

Tu and Cao [7] provide insights into different treatment approaches to GIST in China. Drug treatment is much more in the hands of surgeons, and Chinese patients show a different toxicity profile to imatinib compared to European patients. On the other hand, laparoscopic techniques are not available everywhere. However, our Chinese colleagues provide highly interesting data on molecular prognosticators.

Jakob and Hohenberger [8] report the data of the few studies published on the use of imatinib in a neoadjuvant setting of large GIST of the upper gastrointestinal tract and the rectum. They emphasize that the spectrum of KIT mutations is very similar to the overall distribution; thus, almost 80% of the patients could be successfully treated preoperatively in order to downstage large GIST.

Ronellenfitch and Hohenberger [9] review the current status of

laparoscopic resection of GIST in comparison to open surgical procedures. Given the high detection rate of asymptomatic submucosal tumors in the stomach, this is a relevant question. Endoscopic enucleation techniques, which cannot be classified as oncological procedures, are often highlighted.

A discussion forum on four unsolved questions concludes this issue [10]. The handling of patients being diagnosed with intraluminal bleeding in a gastric or duodenal GIST is clearly not well addressed by the available data. Furthermore, the strategy when treating GIST of the rectum is of interest for endoscopists and surgeons. Mutational testing of the tumor tissue is a must in the neoadjuvant setting, but does the status of KIT or PDGFRA mutations of every GIST need to be analyzed? Finally, the therapy of GIST patients with intraoperative tumor rupture poses an issue, particularly concerning the aspect of how long they should be medically treated.

We hope that you will find fruitful information in this issue devoted to a rare cancer entity.

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