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Preoperative tyrosine kinase inhibitors risks bowel anastomotic healing in patients with advanced primary and recurrent/metastatic gastrointestinal stromal tumors— A rose has its thorns☆

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ABSTRACT

Background: The combination of tyrosine kinase inhibitors (TKIs) and surgery has created a paradigm shift for advanced primary and metastatic gastrointestinal stromal tumors (GISTs). However, the associated surgical morbidity rate is reportedly high, which we hypothesized is attributable to the adverse effects of the previous use of TKIs on bowel anastomosis healing.
Methods: A total of 613 GIST patients with (n = 108) and without (n = 505) preoperative TKI treatment were enrolled. Propensity score matching compared the surgical morbidities and mortalities between the two cohorts. An animal model was used to elucidate the relevant mechanism.
Results: After propensity score matching, the incidence and severity of surgical complications were higher in patients with preoperative TKIs than in those without (34% vs 10%, $p < 0.0001$; grades 3–5, 16% vs 2%, $p < 0.0001$). Specifically, the incidence of bowel anastomosis leakage was increased in those with versus those without preoperative TKI (18% vs 6%, $p = 0.032$). A constellation of mucosal shedding, shortening of villus height and crypt depth, and disarrayed epithelial lining of the bowel was observed with preoperative TKI treatment. The animal model showed that bowel anastomosis healing was weakened by imatinib through the downregulation of *Col1A1*, *Col3A1*, and *MMPs*.
Conclusions: Impaired bowel anastomosis healing was responsible for the extraordinarily high surgical morbidity rate of patients with GIST after TKI treatment. The mechanism involved altered tissue microarchitecture and dysregulated *Col1A1*, *Col3A1*, and *MMP* expressions.

Introduction

Despite their rarity, gastrointestinal (GI) stromal tumors (GISTs) are the most common mesenchymal neoplasms (i.e., sarcoma) arising from the interstitial cells of Cajal of the GI tract [1]. GISTs can occur anywhere along the GI tract, but most cases arise in the stomach (65%), small intestine (25%), colon and rectum (5–10%), or esophagus (5%) [1]. As a milestone, Hirota et al., in 1991, demonstrated that GISTs harbor gain-of-function mutations in the tyrosine kinase receptor encoded by the proto-oncogene *KIT* [2], which led to the first-ever case of metastatic GIST that was successfully treated with a tyrosine kinase inhibitor (TKI) [3]. Since then, several outstanding clinical trials have demonstrated spectacular disease control by targeting the mutant KIT oncoprotein in cases of metastatic GISTs with imatinib mesylate (Gleevec; Novartis, Switzerland) [4–7]. Imatinib, a 2-phenylaminopyrimidine derivative, is a competitor of adenosine triphosphate that inhibits specific tyrosine kinases, including Brc-Abl, c-Kit, and platelet-derived growth factor (PDGF) receptors (PDGFR) [4]. Thereafter, sunitinib malate (Sutent; Pfizer, US) and regorafenib (Stivarga; Bayer, Germany) were approved as second- and third-line tyrosine kinase inhibitors (TKIs) for metastatic GISTs, respectively [8,9]. Durable responses to TKIs are, however, inevitably limited by drug resistance, with time to progress of 24 months for imatinib, 6.8 months for sunitinib, and 4.8 months for regorafenib. To remedy this deficit, cytoreductive surgery has been proposed as a strategy

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to salvage patients with metastatic GISTs, particularly those with responsive, stable, or limited disease progression who are receiving TKI therapy [10–13]. This strategy was recently expanded to act as a neoadjuvant therapy for locally advanced primary GISTs with the advantages of tumor shrinkage, a reduced need for multiorgan resection, and a diminished risk of intraoperative tumor rupture [14–16]. Collectively, the emergence of TKIs for the treatment of GISTs, either in the (neo)adjuvant or metastatic setting, combined with surgical intervention in well-selected cases and optimal timing, is a paradigm shift for the treatment of GISTs. However, this survival gain is partially traded off by a disproportionally increased risk of surgical morbidity. Previous studies reported postoperative complication rates of 10%–61% [5,11,14–17]. Most recently, two leading centers altogether yielded a 28% morbidity rate after cytoreductive surgery for metastatic GISTs treated with TKIs, with major complications (grade $\geq$ 3 based on Clavien-Dindo classification) occurring in up to 18% of cases [18]. In our experience, bowel anastomosis insufficiency was most accountable for the major morbidities in such a scenario [12,13,19]. Accordingly, in the present study, we highlighted for the first time that the bowel anastomosis healing of patients with GISTs was adversely affected by TKI administration in the neoadjuvant or recurrent/metastatic setting and elucidated the associated mechanism.

Materials and methods

Patients

From March 1991 to June 2017, 616 patients underwent surgical treatment for GISTs at Chang-Gung Memorial Hospital, Taiwan. The diagnosis of GIST was confirmed histologically and by immunohistochemical staining for CD117 ± discovered on GIST-1 (DOG-1). To elucidate the impact of TKIs on bowel wound healing, we categorized the patients with GISTs into two groups: pre-op TKI (−) and pre-op TKI (+). The preop-TKI (−) group included those who underwent GIST-relevant operations primarily without a history of TKI use, whereas the preop-TKI (+) group included those who underwent GIST-relevant operations after TKI administration, including a planned neoadjuvant setting (n = 33) and cytoreductive surgery for recurrent (n = 55) or metastatic (n = 20) diseases. The last TKIs used included imatinib (n = 92), sunitinib (n = 12), and regorafenib (n = 4). The durations of TKI use were as follows: imatinib, 704 ± 697 days (median, 397 days); sunitinib, 279 ± 264 days (median, 189 days); and regorafenib, 314 ± 272 days (median, 267 days). In the preop-TKI (+) group, the TKI therapy was discontinued 2–7 days preoperatively depending on TKI type and/or surgeon preference. Medical morbidities were recorded as Charlson comorbidity indexes (CCIs) [20]. Surgical complications were graded in accordance with Clavien-Dindo classification [21]. GI tract anastomosis leaks were specifically documented by the discharge in the intraoperatively placed drainage tubes, computed tomography-guided drainage, and clinical findings.

Histological examinations of surgical specimens

We randomly selected formalin-fixed paraffin-embedded (FFPE) blocks of 10 preop-TKI (+) and 10 preop-TKI (−) cases subjected to the histological examination of the non-tumor parts of the bowel that were resected by our senior pathologist. The FFPE slides were stained with hematoxylin and eosin for microscopic examination.

Animal experiments

All experiments were conducted with approval from the Ethics Review Committee for Animal Experimentation of Chang Gung Memorial Hospital. Male Sprague-Dawley rats (300–350 g) were used and housed under a 12-h light/dark cycle. The experimental rats were divided into four groups as follows: saline-control for 3 weeks followed by bowel anastomosis (BA); imatinib for 3 weeks followed by BA; imatinib for 3 weeks and imatinib withdrawal for 1 week followed by BA; and imatinib for 3 weeks followed by sham operation (n = 6 or more in each group). Imatinib 100 mg/kg was administered orally for 5 consecutive days per week for 3 consecutive weeks. A 1-cm-long bowel side-to-side anastomosis was performed using Prolene 6-0 interrupted sutures. The animals were killed on day 7 after the operation.

Wound healing of the anastomosed bowel in rats

The evaluation of wound healing of the anastomosed bowel in the experimental rats was performed with Masson's trichrome staining. The Masson's trichrome–stained areas of 5 consecutive slides of each animal were examined, and their intensities were measured using a computer-assisted image analysis system with ImageJ 1.47V software (JAVA 1.6.0_20, 64-bit; National Institutes of Health, USA) as described previously [22]. The values of the 5 examinations for each rat are presented as mean ± SD.

Quantitative real-time polymerase chain reactions of Col1A1, Col3A1, MMP2, MMP8, MMP9, and MMP12

The frozen tissues of anastomosed bowel retrieved from the rats were prepared. Two micrograms of total RNA were treated with DNAse 1 (Introgen) to remove DNA contamination. The RNA was reverse-transcribed using Moloney Murine Leukemia Virus reverse transcriptase (Invitrogen) in a 50-μL reaction mixture. Taqman primers and probes for the quantitative detection of *MMP2*, *MMP8*, *MMP9*, *MMP12*, *Col1A1*, and *Col3A1* were designed with Primer Express (ABI-Perkin-Elmer) using the GenBank accession number. All polymerase chain reactions and analyses were performed using an ABI PRISM 7700 sequence Detection System (Applied Biosystems). All samples were run in triplicate.

Statistical analyses

Continuous variables are expressed as mean ± SD or median (range), while categorical variables are shown as percentages. Student's *t*-test or the Mann-Whitney *U* test was used for intergroup comparisons of continuous variables, whereas the chi-square test or Fisher's exact test was used to compare categorical variables. We also conducted a propensity score matching analysis to compensate for the differences in some baseline characteristics between preop-TKI (−) and preop-TKI (+) in the assessment of surgical outcomes. First, we compared the clinicopathological parameters of preop-TKI (−) and preop-TKI (+)using Student's *t*-test or the chi-square test. Next, a propensity score was calculated using a logistic regression with the variables. Finally, all of the patients in the preop-TKI (+) group were matched 1:1 according to propensity scores of the patients in the preop-TKI (−) group, which led to an even distribution of potential confounding factors between the treatment groups. P values < 0.05 were considered statistically significant.

Results

Clinicopathological characteristics

The baseline characteristics of the patients in the preop-TKI (+) and preop-TKI (−) groups are summarized in Table 1. Preop-TKI (+) was associated with a higher male prevalence (66% vs 50%,

Table 1
Clinicopathological analysis of GISTs with and without preoperative TKI use before and after propensity score matching.

Factors	Before matching			After matching		
	Preop-TKI		p Value	Preop-TKI		p Value
	Yes (n = 108)	No (n = 505)		Yes (n = 108)	No (n = 108)	
Age (years)						
≤60	60 (55.6)	258 (51.1)	0.399	60 (55.6)	58 (53.7)	0.785
>60	48 (44.4)	247 (48.9)		48 (44.4)	50 (46.3)	
Sex			0.002			0.662
Male	72 (66.7)	253 (50.1)		72 (66.7)	75 (69.4)	
Female	36 (33.3)	252 (49.9)		36 (33.3)	33 (30.6)	
CCI						
0	7 (6.5)	48 (9.5)	0.245	7 (6.5)	11 (10.2)	0.459
1–2	45 (41.7)	171 (33.9)		45 (41.7)	38 (35.2)	
>3	56 (51.9)	286 (56.6)		56 (51.9)	59 (54.6)	
Bowel anastomosis			<0.0001			0.561
Yes	71 (65.7)	461 (91.3)		71 (65.7)	75 (69.4)	
No	37 (34.3)	44 (8.7)		37 (34.3)	33 (30.6)	
Primary site			0.018			0.676
Stomach	44 (40.7)	269 (53.3)		44 (40.7)	41 (38.0)	
Others	64 (59.3)	236 (46.7)		64 (59.3)	67 (62.0)	
Tumor size (cm)	8.5 ± 5.1	6.6 ± 4.9	<0.001	8.5 ± 5.1	8.5 ± 5.3	0.976
Tumor risk[a]			<0.0001			0.300
None	3 (2.8)	57 (11.3)		3 (2.8)	6 (5.6)	
Very low	3 (3.2)	94 (18.6)		3 (3.2)	7 (6.5)	
Low	21 (19.8)	85 (16.8)		21 (19.8)	12 (11.1)	
Medium	19 (18.6)	83 (16.4)		19 (18.6)	19 (17.6)	
High	59 (54.6)	171 (33.9)		59 (54.6)	58 (53.7)	
Unknown	3 (2.8)	3 (3.0)		3 (2.8)	6 (5.6)	

GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; CCI, Charlson comorbidity index.
[a] Defined on the basis of the Fletcher risk factor stratification.

p = 0.002), larger tumor size (8.5 cm vs 6.6 cm, p < 0.001), and higher tumor risk potential (high-risk, 54% vs 33%, p < 0.001) than preop-TKI (−). However, the patients in the preop-TKI (−) group were more frequently associated with bowel anastomosis (91% vs 65%, p < 0.001) and the stomach as the primary tumor site (53% vs 40%, p < 0.018) than those in the preop-TKI (+) group. The above-mentioned discrepancies became insignificant among the preop-TKI (+) and preop-TKI (−) groups after propensity score matching.

Surgical outcomes

The overall surgical complication rate in the preop-TKI (+) group was much higher than that in the preop-TKI (−) group (34% vs 6%, p < 0.001) despite the fact that the patients in the preop-TKI (+) group were less associated with medical morbidities (CCI > 3, 51% vs 56%) and bowel anastomosis than those in the preop-TKI (−) group. Furthermore, the severity of the surgical complications in the preop-TKI (+) group was higher, with up to 16% of the patients having Clavien-Dindo grade 3–5 complications compared with 1% in the preop-TKI (−) group (p < 0.001). Specifically, the incidence of bowel anastomosis leakage was increased in the preop-TKI (+) group compared with the preop-TKI (−) group (18% [13/71] vs 2% [13/461], p < 0.0001; Table 2). The surgical mortality rates in the preop-TKI (+) and preop-TKI (−) groups were 7.4% (8/108) and 0.2% (1/505), respectively (p < 0.0001).

Surgical outcomes after matching

After propensity score matching, the preop-TKI (+) and preop-TKI (−) groups became more balanced in terms of sex, frequency of bowel anastomosis, primary tumor site, tumor size, and tumor risk potential. Similar to before matching, the rates and severity of the surgical complications in the preop-TKI (+) group after adjustment remained higher than those in the preop-TKI (−) group (34% vs 10%, p < 0.0001; grades 3–5, 16% vs 2%, p < 0.0001). The bowel anastomosis insufficiency after matching remained increased in the preop-TKI (+) group compared with the preop-TKI (−) group (18% [13/71] vs 6% [5/75], p = 0.032; Table 2). The surgical mortality rates in the preop-TKI (+) and preop-TKI (−) groups were 7.4% (8/108) and 0.9% (1/108), respectively (p < 0.0001). Of utmost significance is the fact that 13 patients in the preop-TKI (+) group sustained bowel anastomosis insufficiency categorized as Clavien-Dindo grades 3–5 in 10 patients, five of whom eventually died.

Histological examination of surgical specimens

We randomly selected 10 preop-TKI (+) and 10 preop-TKI (−) cases for the histological examination of non-tumor parts of the bowel using FFPE blocks of the surgical specimens to determine the long-term effect of TKIs on the texture of the bowel in addition to its oncological effect on GIST *per se* (Fig. 1). We found that a constellation of mucosal shedding, shortening of villus height and crypt depth, interstitial edema, disarrayed epithelial lining, and decreased cell polarity were remarkably detected in 8 of the 10 patients in the preop-TKI (+) group but was not detected in the preop-TKI (−) group.

Animal experiments

To evaluate the phenotypes and molecular mechanism by which imatinib affects bowel anastomosis healing, we conducted an animal experiment. Grossly, the bowel of imatinib-treated rats appeared relatively thinner and transparent and were microscopically associated with mucosal shedding and disarrayed architecture compared with the saline-control rats. Imatinib withdrawal for 1 week attenuated the bowel damage, but not completely. The imatinib-treated rats showed decreased bowel wound healing compared to the saline-controlled rats, whereas the imatinib-withdrawal rats showed intermediate bowel wound healing to a degree between those of the saline-control and imatinib-

Table 2
Surgical complications of GISTs with and without preoperative TKIs before and after propensity score matching.

Factors	Before matching			After matching		
	Preop TKI		p Value	Preop-TKI		p Value
	Yes (n = 108)	No (n = 505)		Yes (n = 108)	No (n = 108)	
Surgical complications			<0.0001			<0.0001
Yes	37 (34.3)	35 (6.9)		37 (34.3)	11 (10.2)	
No	71 (65.7)	470 (93.1)		71 (65.7)	97 (89.8)	
Grade of surgical complications[a]			<0.0001			<0.0001
0	71 (65.7)	473 (93.1)		71 (65.7)	97 (89.8)	
1 and 2	19 (17.6)	27 (5.3)		19 (17.6)	8 (7.4)	
3–5	18 (16.7)	8 (1.6)		18 (16.7)	3 (2.8)	
Bowel anastomosis-related complications			<0.0001			0.032
Yes	13 (18.3)	13 (2.8)		13 (18.3)	5 (6.7)	
No	58 (81.7)	448 (97.2)		58 (81.7)	70 (93.3)	

In parentheses are percentages, unless otherwise stated.
[a] Graded according to the Clavien-Dindo classification.

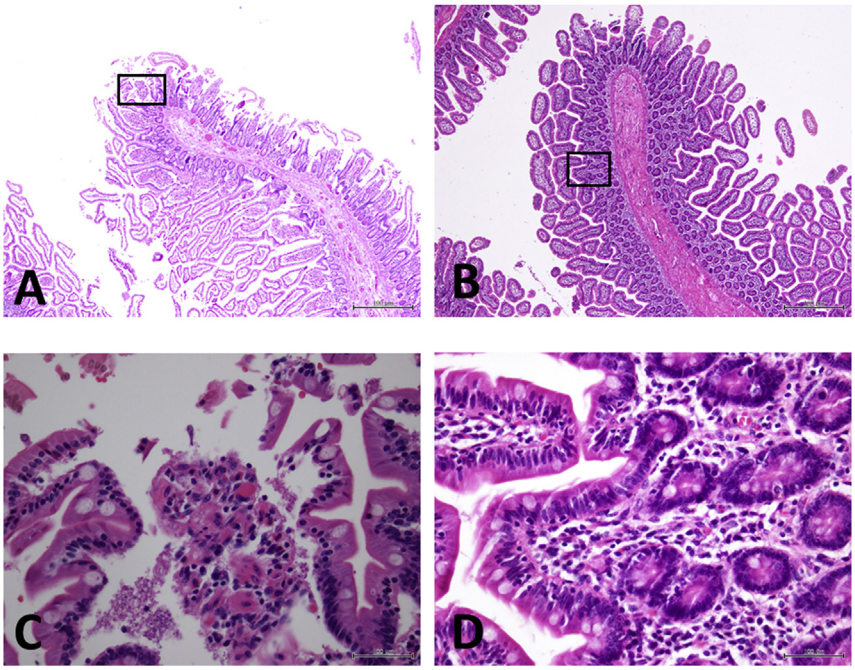

Fig. 1. A constellation of mucosal shedding, shortening of villus height and crypt depth, interstitial edema, disarrayed epithelial lining, and decreased cell polarity was evident in the preop-TKI (+) group (A) but not in the preop-TKI (−) group (B). Higher magnification of the black box labelled in A (C). Higher magnification of the black box labelled in B (D). Hematoxylin-eosin staining. Original magnification: A, B, × 40 and C, D, × 400.

withdrawal rats (intensity, 7.03 ± 2.4 vs 2.53 ± 0.89 vs 4.06 ± 1.33, $p < 0.001$, analysis of variance; Fig. 2). The expressions of *Col1A1*, *Col3A1*, *MMP2*, *MMP8*, *MMP9*, and *MMP12* mRNA in the anastomosed bowel of the rats according to different treatment protocols were determined using quantitative polymerase chain reaction (Fig. 3). The expression levels of all of the mRNAs except that of *MMP8* in the imatinib-treated rats were significantly lower than those of the saline-treated rats (all $p < 0.01$), whereas those in the imatinib-withdrawal rats were between those of the saline-control and imatinib-treated rats.

Discussion

The approved TKIs were variously labelled to cause a broad spectrum of adverse effects that are directly relevant in surgery, such as impaired wound healing, venous thromboembolism, hemorrhage, gastric perforation, and fistulas [23]. These TKI-related complications were sporadically documented in registered clinical trials, while the adverse effect of TKIs on less-selected patients in daily practice who are subjected to oncological surgery is supposed to be greater. To the best of our knowledge, ours is the first team to specifically scrutinize the impact of preoperative TKIs on the bowel anastomosis healing of patients with GISTs. A great proportion of our patients were fragile as evidenced by more than half of our patients in the preop TKI (+) and preop-TKI (−) groups being graded with CCIs of ≥3 and faced recovery from visceral surgeries but not without adverse events. A constellation of mucosal shedding, shortening of villus height and crypt depth, interstitial edema, and disarrayed epithelial lining of the bowel was distinct in the preop-TKI (+) group but not in the preop-TKI (−) group, indicating that the texture of the bowel had already been disturbed, even with the routine withdrawal of TKIs before elective surgery. As a result, the incidence of high-grade surgical complications was much higher in the preop-TKI (+) group than in the preop-TKI (−) group. The high-grade complication rate (16%) in the preop-TKI (+) group was equivalent to that reported recently by

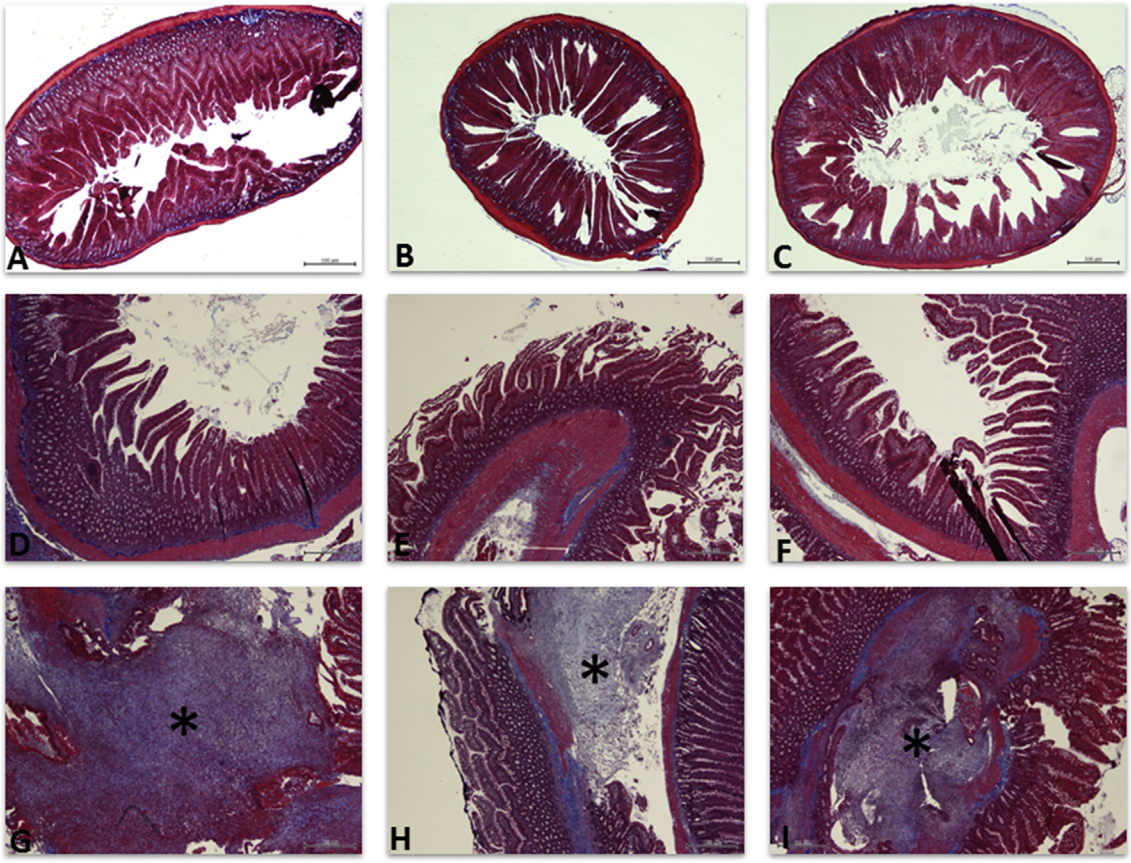

Fig. 2. The bowel of the imatinib-treated rats appeared thinner and were associated with mucosal shedding and a disarrayed microarchitecture (B, E) as compared with the saline-treated rats (A, D). The imatinib-withdrawal rats were intermediate between saline-control and imatinib-treated rats (C, F). The bowel anastomosis healing of the imatinib-treated rats (H) was less matured than that of the saline-control rats (G), whereas the bowel anastomosis healing of the imatinib-withdrawal rats (I) was intermediate between that of the saline-control and imatinib-treated rats. The Masson-trichrome-stained area (blue color) served as surrogates of anastomosis healing (see Materials and Methods section). A-I, × 40 original magnification.

Fairweather et al. [18]. Up to 18% of the patients in the preop-TKI (+) group sustained bowel anastomotic insufficiency compared with the 6% in the preop-TKI (−) after matching, which highly suggests that the long-term administration of TKIs might have interfered with the microarchitecture and microenvironment of the bowel before surgery and impeded ongoing bowel wound healing.

Bowel anastomosis, as frequently modeled in the skin, proceeds via an overlapping pattern of events, including coagulation, inflammation, epithelialization, granulation tissue formation, and matrix and tissue remodeling [24,25]. PDGF, one of the key players in the wound healing process, binds and activates three transmembrane tyrosine kinase receptors, which are homodimers or heterodimers of an α- and β-chain. The important role of PDGF in granulation tissue formation was supported by the findings of a gain-of-function study, where the expression of a hyperactive PDGFR-β variant in fibroblasts enhanced cellular proliferation and migration. Meanwhile, the systemic treatment of mice with the PDGFR-β inhibitor imatinib mesylate caused a long delay in wound closure and granulation tissue formation [26]. Our animal study, the findings of which echoed the histological findings of the non-tumor parts of the bowels of our patients with GISTs whose anastomotic healing were affected by TKI administration, showed altered gross and microarchitecture of the bowel influenced by imatinib. A straightforward observation is that the imatinib-treated rats, which mimicked the preop-TKI (+) group, exhibited less mature bowel healing as evidenced by the decreased Masson's trichrome staining than the saline-control rats, which mimicked the preop-TKI (−) group. Meanwhile, the imatinib-withdrawal rats, which mimicked the routine withdrawal of TKIs before elective surgery, were intermediate between the saline-control and imatinib-treated rats. At the molecular level, the expression levels of *PDGFRα* and *PDGFRβ* mRNAs of the imatinib-treated rats were decreased because imatinib is a potent PDGFR-β inhibitor, and the initiation of the bowel healing was hindered as reflected by the downregulation of *Col1A1* and *Col3A1* mRNAs. The remodeling phase, during which collagen is synthesized, degraded, and reorganized, is also informative. The degradation of fibrillary collagens is driven by serine proteases and matrix metalloproteins (MMPs), the latter of which not only degrade matrix components but also function as regulatory molecules by driving enzyme cascades and processing cytokines, matrices, and adhesion molecules to generate biologically active fragments [27]. Again, the expressions of *MMP2, MMP9,* and *MMP12* mRNAs of imatinib-treated rats were downregulated compared to those of the saline-control rats, which impeded the natural remodeling phase of the bowel wound healing, whereas the expressions of these MMPs in the imatinib-withdrawal rats were intermediate between the saline-control and imatinib-treated rats. Taken together, the results of our animal experiment highlighted that preoperative TKI impairs the bowel wound healing with regard to the microscopic findings and molecular biomarkers and that TKI withdrawal attenuated the adverse effect of TKI on bowel wound healing to a considerable extent but not completely.

The interval between the last TKI dose and surgery is typically

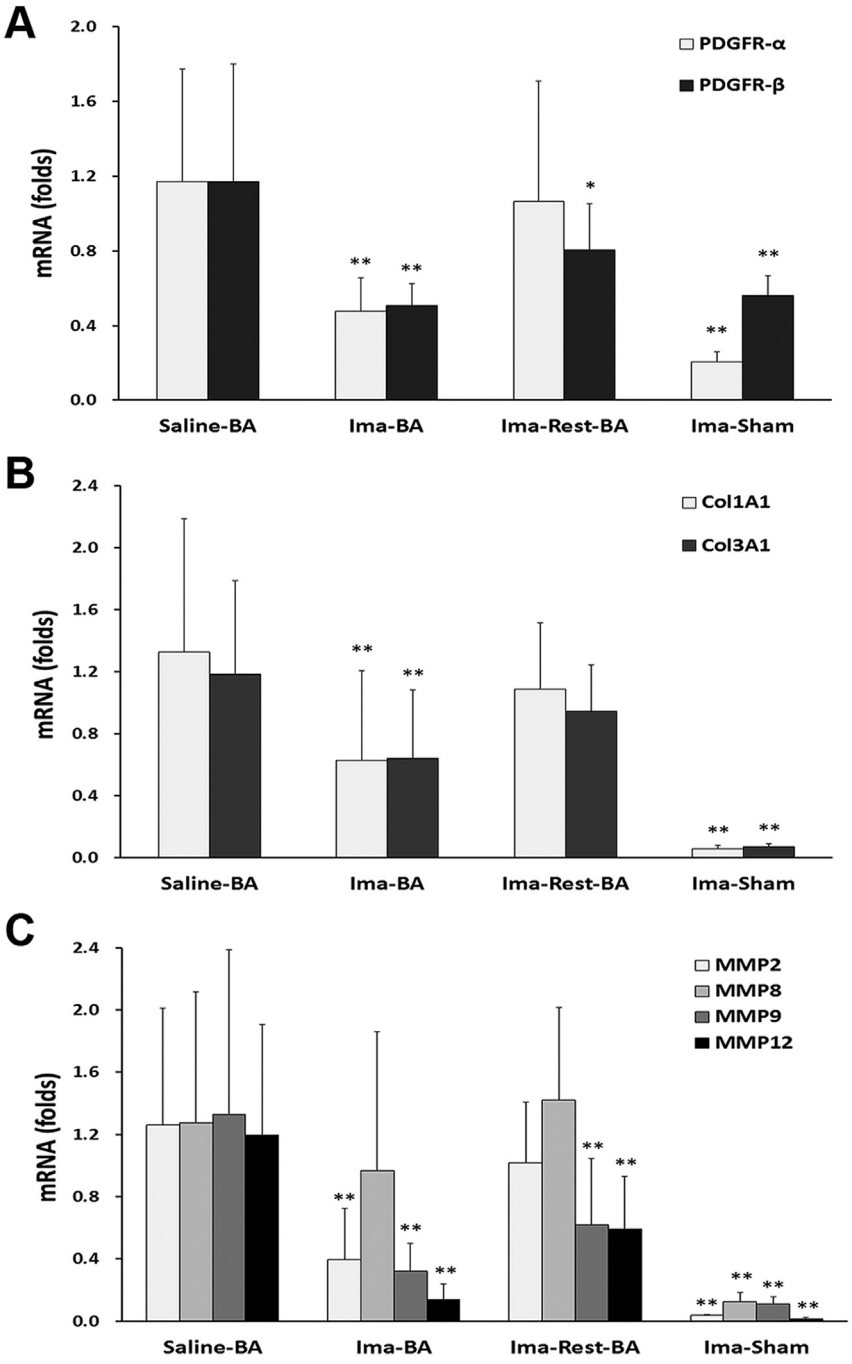

Fig. 3. Expressions of *Col1A1*, *Col3A1*, *MMP2*, *MMP8*, *MMP9*, and *MMP12* mRNA of the anastomosed bowel of the rats detected using quantitative real-time PCR. *$p < 0.05$, versus saline-control; **$p < 0.01$, versus saline-control.

determined by the half-life of the TKI used. An interval equivalent to five half-lives is generally adequate for almost complete elimination of the drug from the body. The half-lives of parent imatinib, sunitinib, and regorafenib are 19, 40–60, and 28 h, respectively, while those of their main metabolites are even longer at 40, 80–110, and 25–51 h, respectively [23]. Accordingly, a theoretical 4, 12, and 6 days are needed to withdraw from imatinib, sunitinib, and regorafenib, respectively, to schedule an elective surgery. However, many investigators concern the rebounding phenomenon of GIST from TKI withdrawal. Therefore, a 3–7-day period for TKI withdrawal for an elective abdominal surgery might be an acceptable option.

On the other hand, in emergency surgeries, scenarios such as tumor rupture and/or bleeding during TKI treatment are not unusual since the discontinuation of TKIs is insufficient for them to be eliminated from the body; thus, the surgical risk is even higher.

In conclusion, along with the increasingly accepted concept that the integration of surgery and molecular therapy is a paradigm shift for advanced primary and recurrent/metastatic GISTs, impaired bowel anastomosis caused by preoperative TKIs emerges as a nonnegligible issue. The associated mechanisms are multifaceted, including the dysregulation of *Col1A1*, *Col3A1*, and *MMP*s and an altered microarchitecture of the tissue despite TKI withdrawal days before the operation.

Conflicts of interest

We do not have “conflict of interest”toclaimand this statement has been addressed in the manuscript.

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