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Efficacy evaluation of imatinib in the treatment of patients with gastrointestinal stromal tumors

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Background/aims: *Published data on the dose of imatinib to treat gastrointestinal stromal tumors seemed inconclusive. To derive a more precise estimation of dose of imatinib to treat gastrointestinal stromal tumors, a meta-analysis was performed.* ***Material and Methods:*** *Studies have been identified by searching PubMed and Embase. Inclusion criteria were patients with incurable or advanced gastrointestinal stromal tumors, received chemotherapy of imatinib of 400 mg once a day (low-dose group) or 300 mg/400 mg twice a day (high-dose group) for controlled trial, and efficacy evaluation were cumulative response based on SWOG criteria, including complete response and partial response. The safety evaluation of imatinib included toxic effect and dose reduction. The odds ratio for cumulative response, toxic effect and dose reduction in patients with low-dose of imatinib over those with high-dose of imatinib with 95% confidence interval was calculated for each study as an estimation of the better effect of imatinib.* ***Results:*** *A total of 3 studies including 1,787 patients were involved in this meta-analysis. The overall odds ratio for cumulative response, toxic effect and dose reduction were 0.91 (95% confidence interval, 0.75–1.09; p=0.31, Pheterogeneity=0.80), 0.55 (95% confidence interval, 0.42–0.72; p<0.0001, Pheterogeneity=0.01), respectively.* ***Conclusion:*** *The meta-analysis indicated that cumulative response for patients with low-dose imatinib showed no significant difference compared with that with high-dose imatinib. However, high-dose imatinib brought patients more toxic effect and more dosage adjustment for down regulation was made for these patients with severe toxic effect. With long follow-up of the patients, result of neither progression-free survival nor overall survival reached statistical significance between low-dose arm and high-dose arm.*

Key words: Gastrointestinal stromal tumors, imatinib, efficacy, meta-analysis.

Gastrointestinal stromal tümörü olan hastalarda imatinib'in etkinliğinin değerlendirilmesi

Amaç: *Gastrointestinal stromal tümörü olan hastalarda kullanılan imatinibin dozu hakkındaki yayınların sonuçları yetersizdir. Gastrointestinal stromal tümör tedavisi için kullanılan imatinibin dozunun tespit edilmesi için meta-analiz gerçekleştirilmiştir.* ***Yöntem:*** *Çalışmalar PubMed ve Embase taranarak tespit edildi. Dahil edilme kriterleri olarak kür şansı olmayan veya ileri evre gastrointestinal stromal tümörü olan hastaların alındığı, imatinib 400 mg/gün (düşük doz grubu), 300/400 mg BID (yüksek doz grubu) kullanılan kontrollü çalışmalar incelendi ve tedavilerin etkinlik değerlendirmesi SWOG kriterlerine göre tam veya parsiyel yanıtın da dikkate alındığı kümülatif yanıt olarak yapıldı. Imatinib'in güvenilirliğinin değerlendirilmesi için toksik etkileri ve doz azaltımı verileri kullanıldı. Kümülatif yanıt, toksik etkileri ve doz azaltımı için düşük doz tedavi alanlar yüksek doz tedavi ile karşılaştırılarak odds oranları her çalışma için güvenlik aralığının %95'i kullanılarak hesaplandı.* ***Bulgular:*** *1787 hastayı kapsayan 3 çalışma meta-analize dahil edildi. Genel odds oranları, kümülatif yanıt, toksik etkileri ve doz azaltımı sırasıyla 0,91 (95% CI, 0.75–1.09; p=0.31, Pheterogeneity=0.80), 0.55 (95% CI, 0.42–0.72; p<0.0001, Pheterogeneity=0.01) olarak bulundu.* ***Sonuç:*** *Bu meta-analizin sonuçlarına göre düşük doz imatinib alan hastaların toplam tedavi yanıtı yüksek doz alanlarınkinden farklı değildir. Ancak, yüksek doz imatinib tedavisi, hastaları daha fazla toksik etkiye maruz bırakmakta ve doz azaltımına neden olmaktadır. Uzun dönem takipte, düşük doz ve yüksek doz tedaviler karşılaştırıldığında progresyonsuz sağ kalım ve genel sağ kalım arasındaki farklar istatistiksel olarak anlamlı değildir.*

Anahtar kelimeler: Gastrointestinal stromal tümor, imatinib, etkinlik, meta-analiz

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a rare tumor of the GI tract, but the most common mesenchymal malignancy of the GI tract (1). GIST expresses the tyrosine kinase receptor KIT, which is the protein product of the KIT protooncogene. GIST is generally characterized by gain-of-function mutations of KIT (2). These mutations result in the constitutive activation of KIT signaling and are the likely causal molecular events of GIST (3,4). No effective systemic treatment is available. Imatinib (STI571) inhibits a similar tyrosine kinase, BCR-ABL, leading to responses in chronic myeloid leukemia, and has also been shown to inhibit KIT. Imatinib, a tyrosine kinase inhibitor active against KIT and platelet-derived growth factor receptor, has been shown to be highly effective in the treatment of advanced GIST. A clinical benefit was demonstrated in more than 80% of patients, resulting in a substantial improvement in the two-year survival rate, from 26% to 76% (5,6). Imatinib has, therefore, become the standard of care in patients with advanced GIST. However, imatinib is not curative, and secondary resistance to imatinib often occurs within the first or second year of treatment (7). In these patients, clinicians increase the dose of imatinib despite disease progression and, in addition, consider surgical resection or radiofrequency ablation in patients with focal imatinib resistance (8). However, the role of local treatment in this setting has not been proven yet, and additional research examining the phenomenon of focal progression is warranted. A European Organization for Research and Treatment of Cancer (EORTC) trial in GIST identified the maximum tolerated dose of imatinib for treatment of GIST as 400 mg twice daily. Several studies have been designed to test whether high-dose imatinib (400 mg twice a day or 300 mg twice a day) might elicit a higher initial response rate or a better progression-free survival (PFS) or a better overall survival (OS) than low-dose imatinib (400 mg once a day). Therefore, we conducted a meta-analysis of response to imatinib at different dose levels to identify the better choice for the treatment of patients with GIST.

MATERIALS AND METHODS

Publication Search

Two electronic databases (PubMed and Embase) were searched (the last search was updated on 1 July 2010, using the search terms: 'gastrointestinal stromal tumor' and 'imatinib'). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full-text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion Criteria

The inclusion criteria were as follows: (a) assessing imatinib at two dose levels in patients with GIST, (b) randomized controlled trial (RCT) studies, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data Extraction

Each of the publications found was independently assessed by two of the authors (PC, LZ). Information was carefully extracted from all eligible studies. The following data were collected from each study: first author's surname, publication date, treatment protocols, patient numbers, length of follow-up, main results, and conclusions. The efficacy parameter of the core study was the best overall tumor response based on Southwest Oncology Group (SWOG) criteria (9). Methods and timing of response assessment were previously published (5). The safety parameters analyzed for imatinib were toxic effect (TE) and dose reduction (DR). Thus, the appraisal parameters, i.e., cumulative response (CR), TE and DR, were extracted from the main results of the inclusion articles. We did not define any minimum number limit of patients for inclusion of a study in our meta-analysis. Meta-analyses were carried out for all available parameters whenever feasible, i.e., when at least two RCTs analyzed the same specific parameter and provided adequate data for statistical analysis.

Statistical Methods

The quality of the included RCTs was evaluated using the Cochrane Collaboration's tool for assessing risk of bias. For each RCT, the risk of bias table was completed independently by two authors (PC, LZ). The summary assessments of risk of bias were evaluated not only for each RCT across outcomes, but also, as suggested for meta-analysis in particular, for each outcome across RCTs. RCTs with unclear or even high risk of bias were not excluded from the meta-analyses. However, meta-

analyses including such RCTs with unclear or high risk of bias were explicitly indicated. As mentioned above, nonrandomized prospective trials and nonrandomized retrospective analyses were excluded from the analysis. All meta-analyses were carried out on RCTs comparing the efficacy between the low-dose group and high-dose group with respect to a dichotomous end point (e.g., CR or TE or DR). The statistical analysis was carried out using the Review Manager (RevMan) software, version 4.2 (The Cochrane Collaboration, Oxford, England). Comparisons of binary outcome measurements were provided by pooled estimates of ORs with 95% CI using the fixed-effects model (the Mantel–Haenszel method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used (10). Statistical heterogeneity was assessed using the inconsistency statistic (11). The significance of the pooled OR was determined by the Z-test, and $p<0.05$ was considered as statistically significant. Sensitivity analyses were carried out to check if modification of the inclusion criteria of this meta-analysis affected the final results.

RESULTS

Study Characteristics

A total of three publications met the inclusion criteria. The study by van Oosterom et al. (18) was excluded due to dose levels that were divided into 400 mg once a day, 300 mg twice a day, 400 mg twice a day, and 500 mg twice a day. Likewise, the study by Dematteo et al. (6) was excluded because the study was designed as a randomized, double-blind, placebo-controlled trial, which was only used to prove that imatinib was effective to treat GIST. Hence, a total of three studies including 1,787 patients were used in the pooled analysis. Table 1 lists the studies identified and their main characteristics. Of the three studies, sample sizes ranged from 147 to 946. Almost all of the patients with GIST were confirmed by histology and immunohistochemistry. No significant differences were found in the age and sex distributions between the cases of 400 mg once a day and the cases of 300 mg/400 mg twice a day.

Meta-Analysis Results

Overall meta-analysis indicated that CR of low-dose imatinib was not significantly different compared with that of high-dose imatinib (OR 0.91 [95% CI, 0.75–1.09]; p=0.31 $P_{heterogeneity}$=0.80), which was estimated (as shown in Figure 1a). The overall OR for TE revealed that high-dose imatinib was accompanied by a higher rate of side effects than low-dose imatinib (OR 0.55 [95% CI, 0.42–0.72]; $p<0.0001$, $P_{heterogeneity}$=0.01) (Figure 1b). The test of heterogeneity by simply comparing these three combined samples suggested a significant heterogeneity among them ($p<0.10$). In the analysis of dose adjustment of imatinib, we found that DR was arranged for these patients with significant side effects, and high-dose imatinib was more likely to have a DR (OR 0.14 [95% CI, 0.11–0.17]; $p<0.00001$ $P_{heterogeneity}$=0.70) (Figure 1c).

Publication Bias

Begg's funnel plot was performed to access the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 2a, b and c).

DISCUSSION

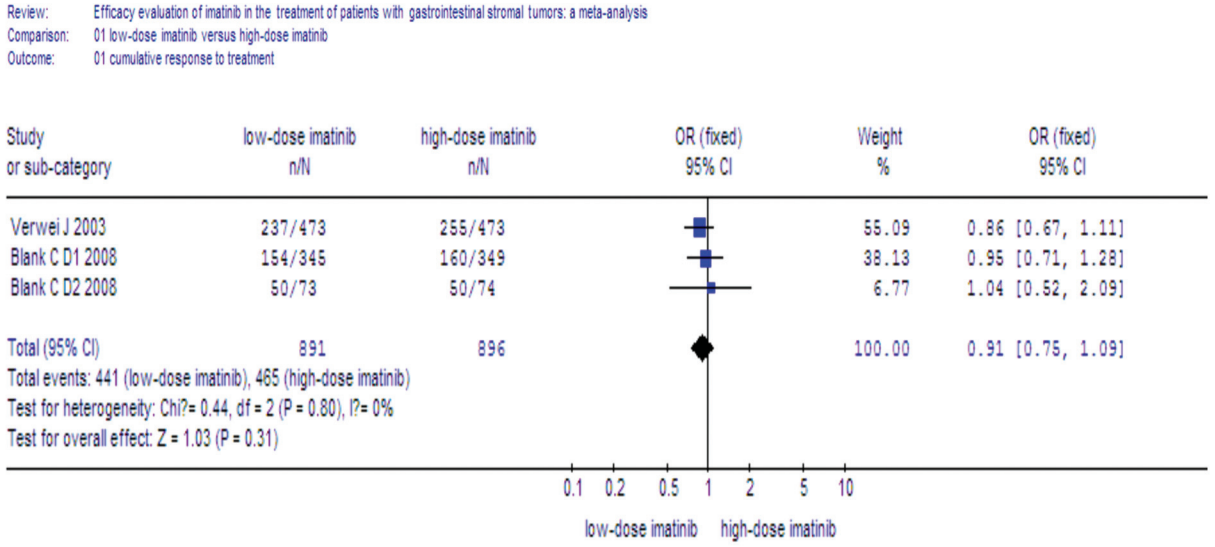
Before the introduction of imatinib mesylate (formerly known as STI571), poor responses to radiation and chemotherapy made surgery the only realistic treatment to cure GIST (15-17). Imatinib mesylate has quickly become the most active targeted, small-molecule therapy in patients with solid tumors. Molecularly targeted therapy with imatinib can inhibit the etiologic aberrant cell-signaling mechanisms in GIST, leading to major objective responses and prolonged disease control. Patients experienced a dramatic response, supporting the rational use of imatinib in this disease. Prior studies have noted that imatinib can be effectively and safely administered across a broad dose range (5,18,19). An EORTC trial in GIST identified the maximum tolerated dose of imatinib

Table 1. Main characteristics of all studies included in the meta-analysis

Author	Eligibility criteria	Case/ Control	Dose distribution	Time to response	Median time of follow-up	Study quality
Verweij (12)	Advanced GIST	473/473	400 mg/800 mg	107 days	760 days	RCT
Blanke (13)	Advanced GIST	345/349	400 mg/800 mg	NA	4.5 years	RCT
Blanke (14)	Advanced GIST	73/74	400 mg/600 mg	81days	63 months	RCT

RCT: Randomized controlled study

1a



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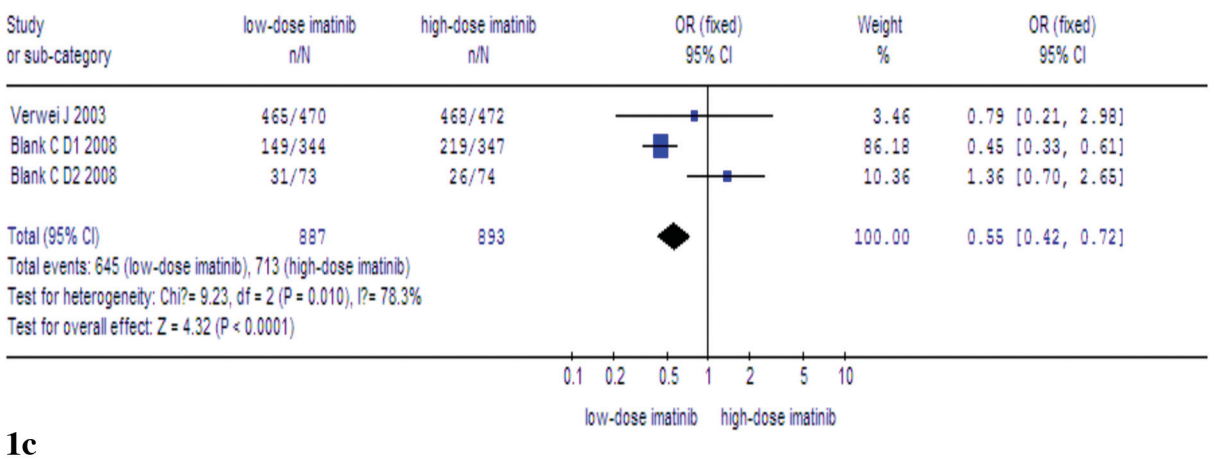

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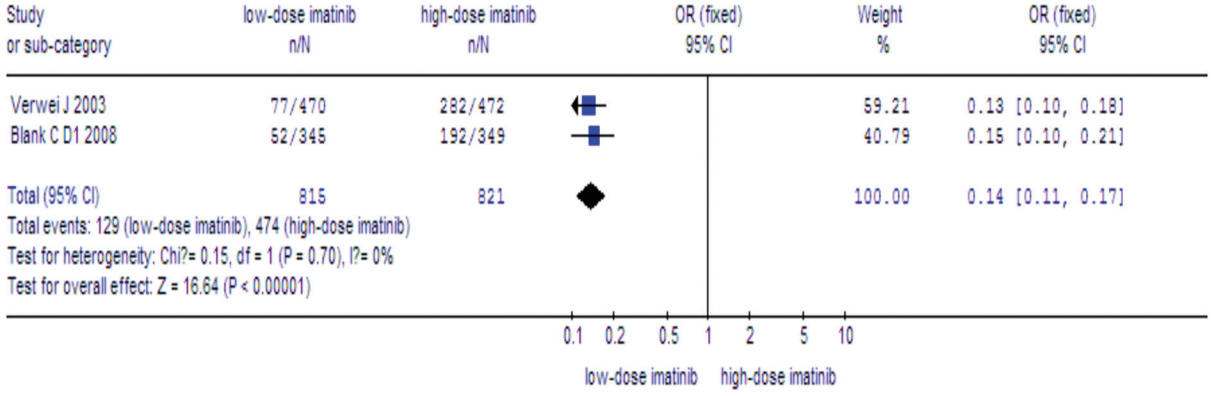

Figure 1. Meta-analysis on (a) cumulative response; (b) toxic effect; (c) dose reduction.

for treatment of GIST as 800 mg daily. Further, several studies have been designed to test whether high-dose imatinib (300 mg/400 mg twice a day) might have better benefits compared with low-dose imatinib (400 mg once a day) (Table 2). Thus, on this basis, we conducted a meta-analysis of CR to imatinib at different dose levels to identify the better starting dose for the treatment of patients with GIST. Meanwhile, the meta-analyses of TE and DR at different dose levels were also done in an effort to balance the treatment plan between effectiveness and side effects. The clinical response to imatinib was classified as CR, including complete response and partial response, stable disease (SD), progressive disease (PD), or not assessable (NA) using RECIST criteria. The results show that there was no statistical difference in CR between the two groups. However, high-dose imatinib was associated with unacceptable severe TE. Furthermore, because of the severe side effects, more DR was seen among patients receiving high-dose imatinib. Early toxicity results of the large phase III trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastro Intestinal Trials Group were reported at the ASCO 2002 annual meeting (21). The most frequent side effects were anemia (88%), edema (67%), fatigue (60%), nausea (44%), neutropenia (32%), and skin rash (24%). Most side effects were mild to moderate. However, one patient died of drug-related neutropenic sepsis. With the analysis of two aspects such as curative effect and side effect, high-dose imatinib (300 mg/400 mg twice daily) did not enhance clinical benefits compared with low-dose imatinib (400 mg daily). This trial confirmed the efficacy and safety of imatinib mesylate when used to treat patients with incurable GIST. It showed that 300 mg/400 mg twice daily, versus 400 mg daily, is a more toxic but not more effective dose. 400 mg daily remains the standard starting dose of care when imatinib is used to treat incurable GIST.

As to PFS and OS, Verwei (12) and Blanke (13) found that there was no statistical difference in the OS and PFS rates, meaning that high-dose imatinib cannot change the patients' prognosis (Table 3).

In summary, our meta-analyses found that higher-dose imatinib does not lead to any other major clinical benefits such as improved CR. On the contrary, it elicits a greater TE in patients and finally leads to an adjustment of dosage (downregulation). Importantly, neither result suggests a PFS or OS benefit from the high-dose imatinib. In two phase III trials (21,22), approximately one-fourth of patients whose dose of imatinib was increased because of disease progression showed some clinical benefit. In those trials, 88 and 133 patients, respectively, crossed over to the higher dose after progression; subsequently, 7% and 2.3%, respectively, responded, and 29% and 27.1%, respectively,

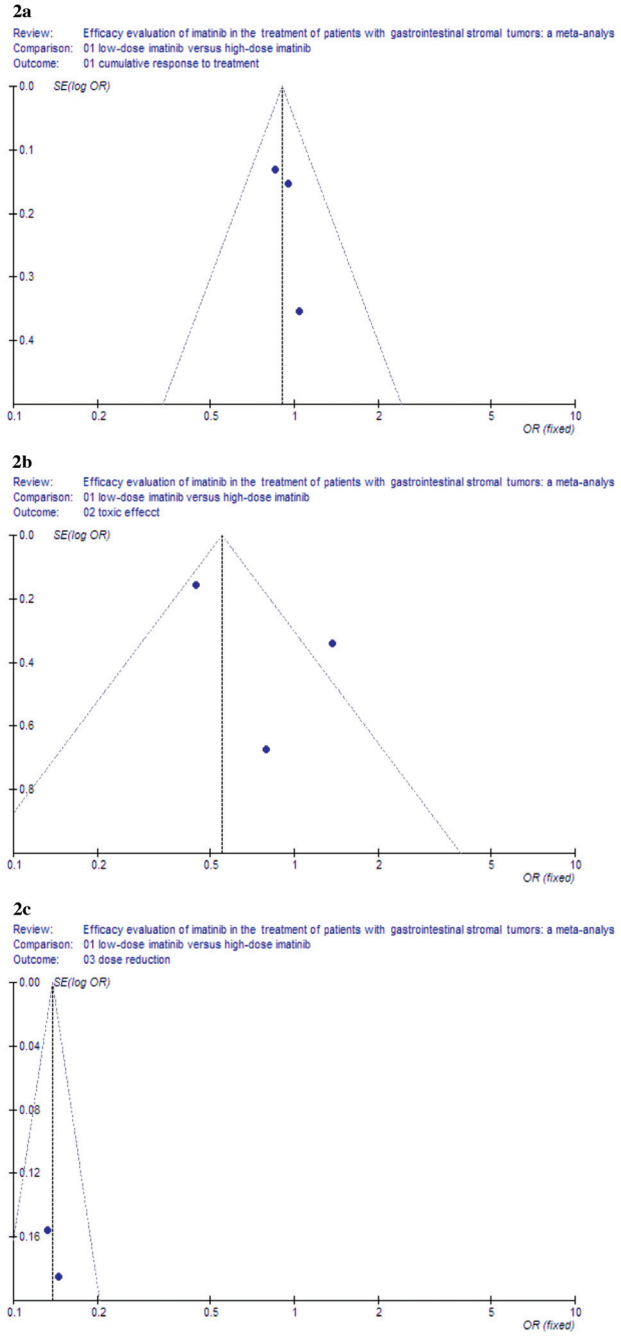

Figure 2. Begg's funnel plot for publication bias test: (a) cumulative response; (b) toxic effect; (c) dose reduction.

Table 2. Treatment of imatinib for tumor response, toxic effect and dose reduction

	Cumulative Response			Toxic Effect			Dose Reduction		
	Rate	OR	95% CI	Rate	OR	95% CI	Rate	OR	95% CI
Verweij (12)		0.86	0.67-1.11		0.79	0.21-2.98		0.13	0.10-0.18
Low-dose	50%			99%			16%		
High-dose	54%			99%			60%		
Blanke (13)		0.95	0.71-1.28		0.45	0.33-0.61		0.15	0.10-0.21
Low-dose	45%			43%			16%		
High-dose	45%			63%			58%		
Blanke (14)		1.04	0.52-2.09		1.36	0.70-2.25		-	-
Low-dose	69%			42%			NA		
High-dose	68%			35%			NA		

Table 3. Treatment effects for OS and PFS

	Overall Survival	Progression-Free Survival
Verweij (12)		
Low-dose	69% (2 yr)	44% (2 yr)
High-dose	74% (2 yr)	52% (2 yr)
Blanke (13)		
Low-dose	78% (2 yr)	50% (2 yr)
High-dose	73% (2 yr)	53% (2 yr)
Blanke (14)		
Low-dose	NA	NA
High-dose	NA	NA

exhibited stability. Thus, patients whose dose escalates after taking 400 mg daily also appear to tolerate higher doses better. The benefit from dose escalation makes it even more reasonable for patients with advanced GIST to start treatment with 400 mg per day and to escalate to 600 mg/800 mg if progression occurs. For future study, it is possible that the mutation site on the KIT gene determines the kinetics of KIT inhibition by imatinib mesylate. It may be that not only the dose, but also the drug applied, will depend on the mutation found. As a result, it can be assumed that the treatment of GIST, in terms of which agent and which dose, will be guided by the mutation found in the near future.

Competing Interests

The authors declare that they have no competing interests.

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