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Original Research

Personalization of regorafenib treatment in metastatic gastrointestinal stromal tumours in real-life clinical practice

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Abstract

Background: Regorafenib (REG) has now been approved as the standard third-line therapy in metastatic gastrointestinal stromal tumour (GIST) patients at the recommended dose and schedule of 160 mg once daily for the first 3 weeks of each 4-week cycle. However, it has a relevant toxicity profile that mainly occurs within the first cycles of therapy, and dose and schedule adjustments are often required to reduce the frequency or severity of adverse events and to avoid early treatment discontinuation. To date, large amounts of data on the use of REG in metastatic GIST patients in daily clinical practice are not available, and we lack information about how this treatment personalization really affects the quality of life (QoL) of patients. The aim of the present retrospective study is to build a comprehensive picture of all alternative REG strategies adopted in daily clinical practice for use in metastatic GIST patients.
Methods: Metastatic GIST patients treated with dose adjustment or alternative schedules of REG at seven reference Italian centres were retrospectively included.
Results: For a total of 62 metastatic GIST patients, we confirmed that REG treatment adjustment is common in clinical practice and that it is very heterogeneous, with approximately 20 different strategies being adopted. Independent of which strategy is chosen, treatment personalization has led to a clinical benefit defined as complete or partial resolution of side effects in almost all patients, affecting the duration of REG treatment.
Conclusions: The personalization of REG, even if it is heterogeneous, seems to be crucial to maximize the overall treatment duration.

Keywords: GIST, personalized treatment, quality of life, referral centres, regorafenib, tyrosine kinase inhibitors

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Introduction

After the identification of KIT or PDGFRA mutations, gastrointestinal stromal tumours (GIST), the most common mesenchymal tumours of the gastrointestinal (GI) tract, soon became a model for targeted therapies.[1–4] The advent of imatinib (IM) and, a few years later, sunitinib (SU), regorafenib (REG), and all oral tyrosine kinase inhibitors (TKIs), has dramatically changed the natural history of this chemoresistant disease, and

these TKIs have become the standard sequence of treatment in the advanced setting.[5–8]

REG is an oral multi-kinase inhibitor that blocks the activity of multiple protein kinases, including those involved in the regulation of tumour angiogenesis (VEGFR-1, VEGFR-2, VEGFR-3, and TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, and BRAF V600E), and the tumour microenvironment (PDGFR and FGFR).[9] REG has now

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been approved as the standard third-line option with a significant improvement in progression-free survival compared with placebo in GIST patients after failure of IM and SU.[8] The recommended dose and schedule of REG is 160 mg once daily for the first 3 weeks of each 4-week cycle. However, drug-related adverse events of grade 3 or higher were reported in more than half of the patients (61.4%), leading to a dose modification in 72% of patients.[8] In particular, the majority of adverse events occurred in the first months of treatment, and there were significantly lower rates of adverse events in subsequent months.[10]

Similar to the experience with other TKIs, treatment personalization is extremely important in everyday clinical practice to reduce the frequency or severity of adverse events and to avoid early treatment discontinuation.[11–13]

However, in the real-life setting, the personalization of REG treatment is not uniform and standardized. In addition to the recommended dose reduction, a wide spectrum of alternative schedules has been adopted, combining dose reduction with different intermittent administrations.

To date, large amounts of data on the use of REG in daily clinical practice in metastatic GIST patients are not available. Therefore, we lack information about how this treatment personalization really affects the quality of life (QoL) and outcomes of patients.

The aim of the present retrospective study is, for the first time, to build a comprehensive picture of all alternative REG strategies adopted in practice, focusing on the impact of the strategies on patient safety and outcomes, to optimize the use of this effective but challenging drug.

Patients and methods

Patients
Metastatic GIST patients treated with dose adjustment or alternative schedules of REG at seven referring Italian institutions (Bologna GIST STUDY GROUP- Sant'Orsola-Malpighi Hospital, Istituto Nazionale Tumori, Milan; University Campus Bio-Medico, Rome; Policlinico P. Giaccone, Palermo; Candiolo Cancer Institute; Università Politecnica delle Marche, Ancona; Azienda Ospedaliero-Universitaria Careggi, Florence) were included in

the present retrospective analysis. This study was approved by the local ethic committee of Sant'Orsola-Malpighi Hospital, Bologna, Italy (N° 164/2017/O/Oss). All patients provided written informed consent for the use of their clinical data in the present study.

Data collection
A database including details on demographic data, pathological and molecular data, treatments and last follow-up data of the patients was shared among the selected centres, and the data were retrospectively collected.

Detailed information on REG treatment for each patient has been recorded, focusing on number of treatment adjustments received, type of treatment adjustments adopted, reasons that have led to treatment personalization and impact of treatment personalization on safety. Adverse events were reported according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAEs) version 4.0. The patients were followed up monthly in each centre, but the frequency of the visits may have been personalized according to clinical needs.

Statistical analysis
A descriptive analysis was conducted using median values and ranges. The time between the beginning of treatment and first treatment adjustment was calculated as the period from the start of treatment to the date of the first modification. The time between the first and second treatment adjustment was calculated as the period from the date of the first modification to the date of the second one. The duration of REG treatment was calculated as the period from the start of treatment to the end of treatment or to the last follow up and, in the case of patients still in treatment, at the time of the analysis. The 95% confidence interval (CI) was calculated assuming the t-student distribution with $n - 1$ degrees of freedom (where n = sample size) and adopting the sample standard deviation.

Results

Patient population features
A total of 62 metastatic GIST patients were included. The patients' characteristics are listed in Table 1. The median age of the patients was 56

Table 1. Patients characteristics.

Number of patients	Total 62
Sex	
Male	33 (53%)
Female	29 (47%)
Age	
Median	56 years
Range	32–75 years
Primary tumour site	
Stomach	16 (26%)
Duodenum	5 (8%)
Digiunum	6 (10%)
Ileum	27 (43%)
Colon	1 (2%)
Rectum	4 (6%)
Extra-GIST	3 (5%)
Risk	
Low	4 (10%)
Intermediate	8 (20%)
High	28 (70%)
Mutational status KIT exon 9	13 (21%)
KIT exon 11	40 (64%)
KIT exon 17	1 (2%)
KIT/PDGFRA WT	3 (5%)
NA	5 (8%)
Disease status at diagnosis	
Localized	40 (64%)
Metastatic	22 (36%)
Adjuvant treatment	
Yes	13 (32%)
No	27 (68%)
Site of metastases	
Liver	16 (26%)
Peritoneum	12 (20%)
Liver and peritoneum	27 (43%)
Multivisceral	7 (11%)

GIST, gastrointestinal stromal tumour; NA, not available; WT, wildtype.

years (range: 32–75 years). A total of 33 patients (53%) were male, and 29 patients (47%) were female. The primary tumour site was the ileum in 27 patients (43%), stomach in 16 patients (26%), digiunum in 6 patients (10%), duodenum in 5 patients (8%), rectum in 4 patients (6%), colon in 1 patient (2%), and extra-GIST in 3 patients (5%). At the time of diagnosis, 40 patients (64%) had a localized disease, while 22 patients (36%) had a metastatic disease. From the mutational analysis, which was available in 92% of the cases, 40 patients (64%) had KIT exon 11 mutations, 13 patients (21%) had KIT exon 9 mutations, 3 patients (5%) were KIT/PDGFRA wild type (WT), and 1 patient (2%) harboured a KIT exon 17 primary mutation. In all patients REG treatment was started in 2011.

REG treatment personalization data

A total of 55 patients (89%) received REG at the standard dose and a schedule of 160 mg once daily for the first 3 weeks of each 4-week cycle, while 7 patients (11%) had received personalized treatment since the beginning for clinical reasons. All 55 patients initially treated with the standard dose and schedule of REG received at least one treatment adjustment due to intolerance. Among them, 23 patients (42%) received a second treatment adjustment, again for intolerance. Only in two cases was the standard dose and schedule of REG resumed due to disease progression.

Among the remaining seven patients for whom the treatment was personalized since the beginning, three patients also received a treatment adjustment due to intolerance, two patients maintained the same personalized treatment during all therapy courses, and two patients had a dose of REG that was increased again due to disease progression.

The median time between the beginning of treatment and first treatment adjustment was 2.5 months (range 0.2–20.3 months; 95% CI, 1.654–3.356). The median time between the first and second treatment adjustments was 6.9 months (range 0.9–45.8 months; 95% CI, 2.970–13.681).

Types of treatment adjustments

Among the 55 patients initially treated with the standard dose and schedule of REG, the first treatment adjustment was a dose reduction in 36 patients (65%) and a schedule modification maintaining the full dose in 7 patients (13%), while in 12 patients (22%), dose reduction and different intermittent schedules were combined.
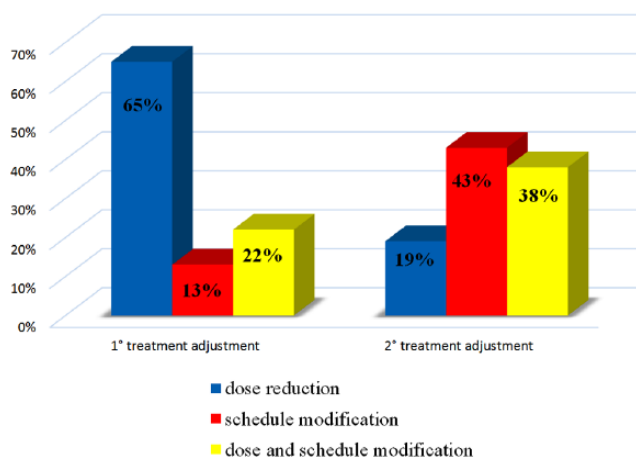
Figure 1. Frequencies of the types of personalization treatment in clinical practice in relation to the first and second adjustments.

Among the 21 patients who required a second treatment adjustment due to intolerance, 4 patients (19%) received a dose reduction and 9 patients (43%) received a schedule modification, while in 8 patients (8%), both the dose and schedule were modified (Figure 1).

All types of treatment adjustments recorded are listed in Supplementary Table 1.

Despite the wide heterogeneity observed, the most frequent strategy of personalization for the first treatment adjustment was 120 mg/day d1–21 e28, which was adopted in 60% of patients (35/58), while for the second treatment adjustment, the variability was higher, with a prevalence for the following three strategies: 80 mg/day d1–21 e28 (5 pts/21 = 24%), 120 mg/day d1–14 e21 (3 pts/21 = 14%), and 80 mg/day d1–14 e21 (3 pts/21 = 14%) [Figure 2(a) and (b)].

Impact of treatment personalization on safety profile
In the subgroup of 55 patients initially treated with the standard dose and schedule of REG, the main reported side effects leading to the first treatment adjustment were the following: Hand–foot skin reaction (HFSR) (43.6%), GI symptoms (36.4%), fatigue (34.5%), hypertension (16.3%), anorexia (13%), and oral mucositis (11%). In the subgroup of 21 patients who underwent a second treatment adjustment, the main reported side effects were the following: HFSR (52%), fatigue (33.4%), and GI symptoms (19%) (Table 2).

According to the strategy adopted for the first treatment adjustment (dose reduction, schedule modification, and dose and schedule modification), a complete resolution of side effects was reached in 17% of patients who underwent dose reduction, 0% of patients who underwent schedule modification and 17% of patients who underwent dose and schedule modification. A partial resolution of side effects was reached in 64%, 57% and 83%, while no benefit was observed in 19%, 43% and 0% of patients who underwent dose reduction, schedule modification and dose and schedule modification, respectively [Figure 3(a)].

According to the strategy adopted for the second treatment adjustment, a complete resolution of side effects was reached in 25% of patients who underwent dose reduction, 33% of patients who underwent schedule modification and 37.5% of patients who underwent dose and schedule modification. A partial resolution of side effects was reached in 75%, 67% and 50% of patients who underwent dose reduction, schedule modification and dose and schedule modification, respectively. Interestingly, none of the subgroups showed a lack of improvement in safety [Figure 3(b)].

The impact of first and second treatment adjustments on the side effects of REG are fully reported in Supplementary Table 2 and Supplementary Table 3.

Treatment duration and follow-up data
The mean duration of REG treatment was 13.8 months (median 9.9 months; range: 1.5–53.6
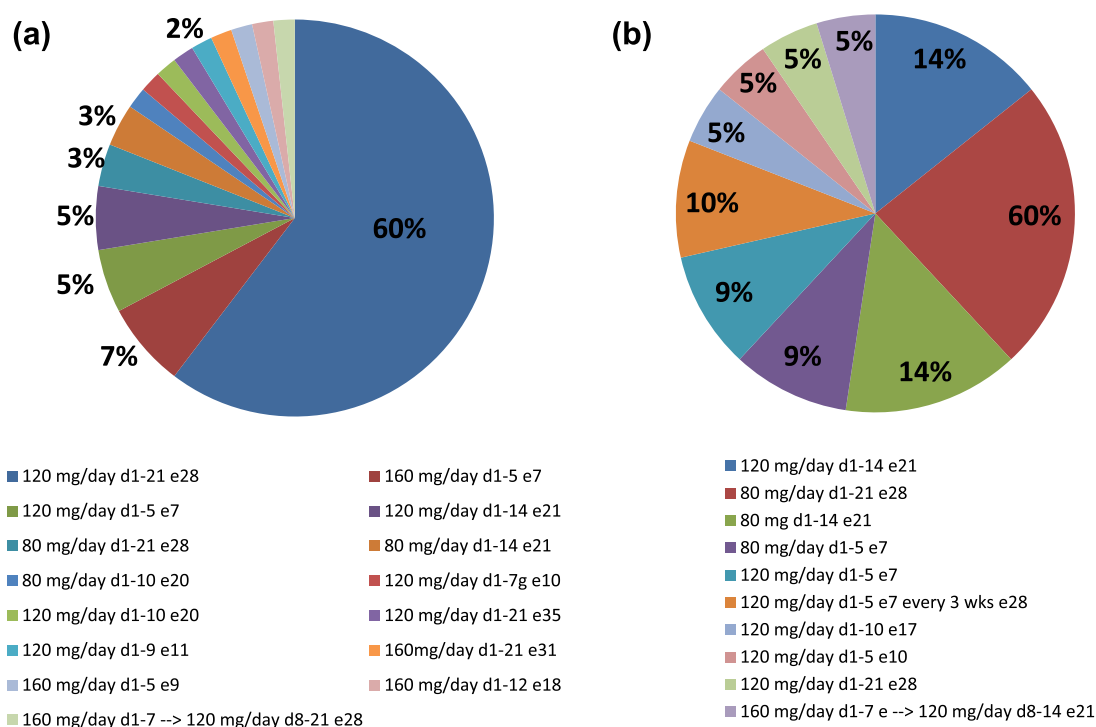
(a)

- 120 mg/day d1-21 e28
- 120 mg/day d1-5 e7
- 80 mg/day d1-21 e28
- 80 mg/day d1-10 e20
- 120 mg/day d1-10 e20
- 120 mg/day d1-9 e11
- 160 mg/day d1-5 e9
- 160 mg/day d1-7 --> 120 mg/day d8-21 e28
- 160 mg/day d1-5 e7
- 120 mg/day d1-14 e21
- 80 mg/day d1-14 e21
- 120 mg/day d1-7g e10
- 120 mg/day d1-21 e35
- 160mg/day d1-21 e31
- 160 mg/day d1-12 e18

(b)

- 120 mg/day d1-14 e21
- 80 mg/day d1-21 e28
- 80 mg d1-14 e21
- 80 mg/day d1-5 e7
- 120 mg/day d1-5 e7
- 120 mg/day d1-5 e7 every 3 wks e28
- 120 mg/day d1-10 e17
- 120 mg/day d1-5 e10
- 120 mg/day d1-21 e28
- 160 mg/day d1-7 e --> 120 mg/day d8-14 e21

Figure 2. (a) Types of strategies adopted in clinical practice for the first treatment adjustment. (b) Types of strategies adopted in clinical practice for the second treatment adjustment.

Table 2. Main side effects that led to the first and second treatment adjustment.

Main side effects that led to the first treatment adjustment (55 pts)	
Hand–foot skin reaction	43.6%
Gastrointestinal symptoms	36.4%
Fatigue	34.5%
Hypertension	16.3%
Anorexia	13%
Oral mucositis	11%
Main side effects that led to the second treatment adjustment (21 pts)	
Hand–foot skin reaction	52%
Fatigue	33.4%
Gastrointestinal symptoms	19%

months; 95% CI 11.143–17.301), which included 12 patients still in treatment at the time of the analysis. For 14 patients (23%), the duration of treatment was >20 months, and they had a mean of 32.14 months (range 20.50–53.67; 95% CI, 27.672–39.487); 4 of them underwent only one treatment adjustment, whereas the remaining 10 patients underwent two consecutive treatment adjustments (Table 3).

At the last follow up, 32 patients had died of disease, whereas 27 patients were still alive and with disease. Of them, 12 patients were still on REG, while 15 patients discontinued REG due to disease progression.
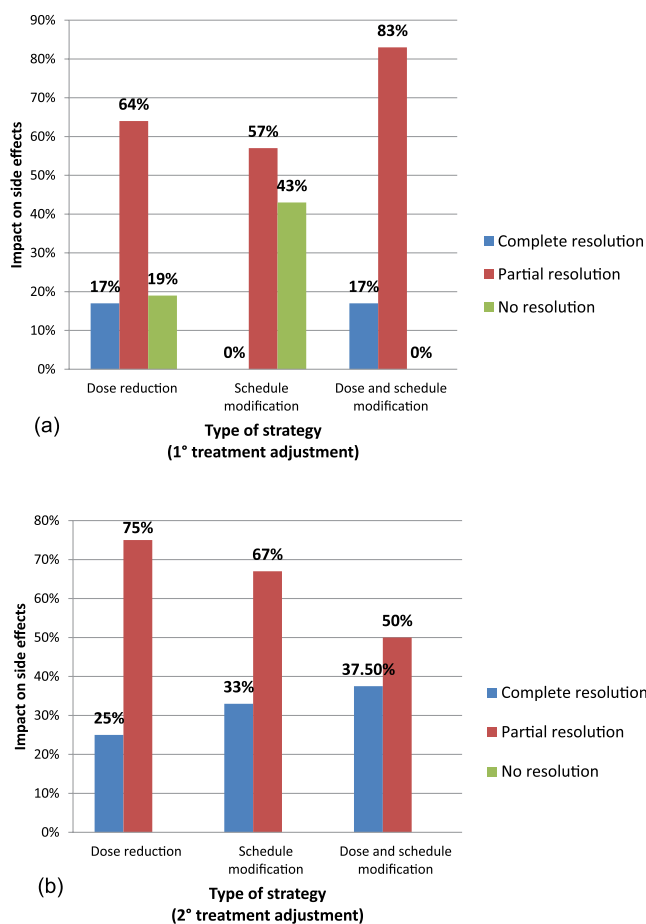
Figure 3. (a) Impact of the first treatment adjustment on the side effects of REG according to the type of strategy adopted. (b) Impact of the second treatment adjustment on the side effects of REG according to the type of strategy adopted.
REG, regorafenib.

Discussion

REG has now been approved as the standard third-line option for metastatic or advanced GIST after failure of IM and SU at the recommended dose and schedule of 160 mg once daily for the first 3 weeks of each 4-week cycle. However, REG has a relevant toxicity profile, including dermatologic and mucosal toxicities, fatigue, nausea, weight loss, hypertension and diarrhoea, which mainly occurs within the first cycles of therapy.[10] Consequently, similar to the experience with other TKIs, dose and schedule adjustments are crucial to reduce the frequency or severity of adverse events and thus to avoid early treatment discontinuation.[11–13]

However, in the real-life setting, the personalization of REG treatment is not uniform and standardized, and in addition to the recommended dose reduction, a wide spectrum of different strategies has been adopted. Thus, the efficacy of

the clinical use of REG in metastatic GIST patients is still unknown in the real-life setting. To our knowledge, this is the first retrospective analysis describing REG alternative strategies adopted in practice, focusing on their impact on the safety and outcomes of patients, to optimize and share alternative schedules derived from the real-world scenario.

Firstly, this multicentre retrospective analysis has confirmed that REG treatment adjustment is common in clinical practice, even twice for the same patient, and that it is mainly due to toxicity. As expected, the main reported side effects that led clinicians to treatment adjustments were HFSR, fatigue, anorexia, GI symptoms, hypertension, and oral mucositis. The median time between the beginning of treatment and first treatment adjustment was 2.5 months, confirming that most of the side effects of REG occur within the first cycles of therapy.[10]

Table 3. Long-treated patients with personalized REG therapy.

Pts code	Type of 1° treatment adjustment	Type of 2° treatment adjustment	Treatment duration (mo)
03*	160 mg/day d1–21 e31	120 mg/day d1–5 e7	33.17
04*	120 mg/day d1–21 e28	80 mg/day d1–21 e28	53.67
06*	80 mg/day d1–21 e28	80 mg/day d1–14 e21	40.30
07	120 mg/day d1–21 e28	120 mg/day d1–5 e7 for 3 weeks e28	24.97
47	160 mg/day d1–12 e18	–	20.50
48	120 mg/day d1–21 e28	120 mg/day d1–14 e21	20.80
50	120 mg/day d1–21 e28	160 mg/day d1–21 e28	35.40
53	160 mg/day d1–7 →120 mg/day d8–21 e28	160 mg/day d1–7 →120 mg/day d8–14 e21	26.30
31*	120 mg/day d1–21 e28	120 mg/day d1–5 e7	39.67
32	120 mg/day d1–21 e28	–	34.30
33	120 mg/day d1–21 e28	–	34.67
23	120 mg/day d1–21 e28	–	26.43
14	120 mg/day d1–21 e28	80 mg/day d1–14 e21	21
44*	120 mg/day d1–21 e28	80 mg/day d1–21 e28	38.87
			mean = 32,14
			range = 53.67–20.50

*Patients still in treatment.
mo, months; Pts, patients; REG, regorafenib.

Interestingly, the use of REG in clinical practice has emerged as heterogeneous in referral centres in our country, in which approximately 20 different strategies of treatment personalization have been identified that can be simplified into three categories: dose reduction maintaining the standard schedule of once daily for the first 3 weeks of each 4-week cycle, schedule modification maintaining the full dose 160 mg daily, and the combination of a dose reduction with a schedule modification (Figure 4). Despite this wide heterogeneity, we observed that dose reduction only, with a prevalence for 120 mg/day d1–21 e28, represents the most frequently used strategy of personalization for the first treatment adjustment, as it was adopted in 60% of patients. In contrast, the observed variability was higher for the second treatment adjustment, which had a prevalence for more articulated strategies of personalization in favour of shorter cycles at lower doses.

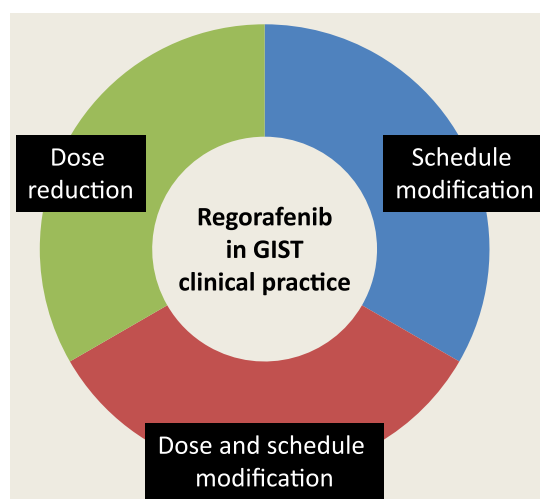Moreover, we observed that the treatment personalization of REG has also been adopted since

Figure 4. Three main strategies of personalization of REG treatment used in clinical practice.
GIST, gastrointestinal stromal tumour; REG, regorafenib.

the beginning due to clinical reasons and that even if the sample size of patients is very small,

the most common strategy used has been dose reduction only. Contrary to the 'start low and go slow' approach suggested by Tabchi and colleagues in the metastatic colorectal cancer field, which is based on incremental increases of one dose level (40 mg) every 5 days until the desired dose is reached or until the patient presents grade II or higher adverse effects,[14] in our series, the low dose was maintained until disease progression or intolerance. It is worth noting that one patient (BO05) who started REG at the lower dose of 120 mg/day d1–21 e28 is still in treatment after 53.67 months.

From a clinical point of view, treatment personalization, even when repeated, has led to a clinical benefit in almost all patients, which we simply defined as complete or partial resolution of side effects. However, given the wide heterogeneity of the strategies used together with the small case series due to the rarity of the disease, it is not possible to define which strategies have the best safety profile/disease control ratio in GIST patients. It is evident that treatment personalization, independent of which strategy is used, likely affected the duration of treatment in almost all patients. Indeed, in our retrospective real-life series, a median duration of 9.9 months was observed, which is superior to the 22.9 weeks of the GRID trial. In particular, there is a small subgroup of 14 patients (23%) who exceeded 20 months, presenting a mean duration of 32.14 months (range 20.50–53.67 months). In this subgroup of long-treated patients, the most frequently adopted strategy of personalization was that of 120 mg/day d1–21 e28. Taking all these findings together, it is likely that the standard dose of REG, even if recommended, is not suitable for several heavily treated GIST patients, and similar to the SU experience, the administration of REG at a lower dose on a continuous daily dosing schedule, without off-treatment periods, should be explored in the future as another safe and effective dosing option.[15] Certainly, given the clinical importance of treatment personalization, the role of referral centres in the management of GIST patients is increasingly relevant during the disease course, when the clinical experience can make a difference in the long-term outcome. Therefore, metastatic GIST patients treated with REG, compared with those still in treatment with IM or SU, can benefit more from this centralized management.

In the future, pharmacogenetic studies, as well as the determination of plasma levels of REG, may help to better identify the most effective and best tolerated personalization strategies to allow for more homogeneous and uniform decision-making in clinical practice.

Of course, the main potential limits of the present study are the small sample size analysed, which is expected for all studies on rare tumours, such as GIST, and the heterogeneity of the population studied, which does not allow for the obtained data to be statistically significant but is otherwise reliable and useful for daily clinical practice.

In conclusion, from this multicentre retrospective analysis, it has been shown that the treatment personalization of REG in metastatic GIST patients seems common in clinical practice, even if it is extremely heterogeneous within each reference centre. It is evident that, similar to the experience with other TKIs, treatment personalization is crucial to maximize the duration of these chronic therapies and to attenuate their impact on the QoL of patients.[11–13,16] Furthermore, treatment optimization can increase patient adherence to REG, leading to improvements in health status and reduced healthcare costs.[17–19]

Finally, given the extreme heterogeneity observed, it is not possible to identify the personalization strategy that has the best balance between safety and efficacy because only prospective studies that include a wider range and larger number of homogeneous cases will clarify it. As early as possible, it is crucial to identify the best strategy to modulate the drug in each individual patient in everyday clinical practice.

Conflict of interest statement
The authors declare that there is no conflict of interest.

References

1. Hirota S, Isozaki K, Moriyama Y, *et al.* Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; 279: 577–580.

2. Heinrich MC, Corless CL, Duensing A, *et al.* PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; 299: 708–710.

3. Antonescu CR. The GIST paradigm: lessons for other kinase-driven cancers. *J Pathol* 2011; 223: 251–261.

4. Biasco G, Velo D, Angriman I, *et al.* Gastrointestinal stromal tumors: report of an audit and review of the literature. *Eur J Cancer Prev* 2009; 18: 106–116.

5. Demetri GD, von Mehren M, Blanke CD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; 347: 472–480.

6. Blanke CD, Demetri GD, von Mehren M, *et al.* Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008; 26: 620–625.

7. Demetri GD, van Oosterom AT, Garrett CR, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; 368: 1329–1338.

8. Demetri GD, Reichardt P, Kang YK, *et al.* Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 295–302.

9. Wilhelm SM, Dumas J, Adnane L, *et al.* Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; 129: 245–255.

10. Demetri GD, Reichardt P, Kang Y-K, *et al.* Long-term safety of regorafenib (REG) in advanced gastrointestinal stromal tumors (GIST): updated safety data of the phase 3 GRID trial. *Ann Oncol* 2016; 27(Suppl. 6): 1415P.

11. Saponara M, Lolli C, Nannini M, *et al.* Alternative schedules or integration strategies to maximise treatment duration with sunitinib in patients with gastrointestinal stromal tumours. *Oncol Lett* 2014; 8: 1793–1799.

12. Saponara M, Gatto L, Di Nunno V, *et al.* Successful treatment with personalized dosage of imatinib in elderly patients with gastrointestinal stromal tumors. *Anticancer Drugs* 2016; 27: 353–363.

13. Grothey A, George S, van Cutsem E, *et al.* Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. *Oncologist* 2014; 19: 669–680.

14. Tabchi S and Ghosn M. Regorafenib: start low and go slow. *Target Oncol* 2015; 10: 445–447.

15. George S, Blay JY, Casali PG, *et al.* Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. *Eur J Cancer* 2009; 45: 1959–1968.

16. Ryan CW. Dosing strategies and optimization of targeted therapy in advanced renal cell carcinoma. *J Oncol Pharm Pract* 2017; 23: 43–55.

17. Del Prete S, Cennamo G, Leo L, *et al.* Adherence and safety of regorafenib for patients with metastatic colorectal cancer: observational real-life study. *Future Oncol* 2017; 13: 415–423.

18. Verbrugghe M, Duprez V, Beeckman D, *et al.* Factors influencing adherence in cancer patients taking oral tyrosine kinase inhibitors: a qualitative study. *Cancer Nurs* 2016; 39: 153–162.

19. Blay JY and Rutkowski P. Adherence to imatinib therapy in patients with gastrointestinal stromal tumors. *Cancer Treat Rev* 2014; 40: 242–247.

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