Received: 31 March 2019 | Revised: 22 June 2019 | Accepted: 4 July 2019

DOI: 10.1111/bcp.14061

ORIGINAL ARTICLE

The effect of gastrectomy on regorafenib exposure and progression-free survival in patients with advanced gastrointestinal stromal tumours

Floor J.E. Lubberman[1] | Winette T.A. van der Graaf[2] | Lei Xu[3] | Adriaan Cleton[4] | George D. Demetri[5] | Hans Gelderblom[6] | Nielka P. van Erp[1]

[1] Department of pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands

[2] Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

[3] Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA

[4] Bayer AG, Berlin, Germany

[5] Dana-Farber Cancer Institute, Harvard Medical School, Department of Oncology, Boston, MA, USA

[6] Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Nielka van Erp, Radboud University Medical Center, Department of Pharmacy (864) PO box 9101, 6500 HB Nijmegen.
Email: nielka.vanerp@radboudumc.nl

Aims: We investigated whether major gastrectomy influences the plasma exposure of regorafenib and treatment outcome.

Methods: Efficacy and pharmacokinetic data from 133 gastrointestinal stromal tumour patients included in a phase III trial were analysed. Patients were subdivided into 2 groups according to the extent of the gastrectomy (no/nonsignificant gastrectomy and major gastrectomy). Progression-free survival (PFS) on regorafenib was measured and regorafenib and its pharmacological active metabolites plasma exposure were measured.

Results: A total of 133 patient were included, of whom 27 underwent major gastrectomy. In patients with no/nonsignificant gastrectomy the median PFS was 145 (interquartile range 43–281) days. The PFS in patients with a major gastrectomy was 172 (interquartile range 57–280) days. Regorafenib pharmacokinetic samples were collected in 80 patients of which 19 patients with a major gastrectomy and 61 patients with no/nonsignificant gastric surgery. The average ± standard deviation total concentration of regorafenib including the metabolites M-2 and M-5 was 6.9 ± 1.53 μmol/L and 6.7 ± 1.56 μmol/L in patient with major gastrectomy and no/nonsignificant gastrectomy respectively.

Conclusion: Our study shows that major gastrectomy did not influence plasma exposure of regorafenib and metabolites. In addition, no difference in PFS between the subgroups was seen.

KEYWORDS

gastrectomy, gastrointestinal stromal tumour, pharmacokinetics, regorafenib

PI of the substudy is Nielka P. van Erp. The PI of the GRID study was George D. Demetri, who had direct clinical responsibility for the patients.

1 | INTRODUCTION

Gastrointestinal stromal tumour (GIST) is 1 of the most common soft tissue sarcoma subtypes.[1] GIST is primarily located in the stomach (56%) followed by the small intestine (32%).[2] Imatinib is the first-line treatment in patients with unresectable or metastatic GIST followed by sunitinib and thereafter regorafenib as third-line treatment.[3]

Regorafenib is an oral multikinase inhibitor (TKI) that blocks the activity of multiple protein kinases, including those involved in the regulation of oncogenesis (**KIT**, **RET**, **RAF-1**, **BRAF** and BRAFV600E), tumour microenvironment (**PDGFRs** and **FGFRs**) and tumour angiogenesis (**VEGFR 1–3** and **TIE2**).[4] Regorafenib is taken once daily with a low-fat meal for 3 weeks out of a 4 week cycle.[5] Regorafenib is classified as a Biopharmaceutics Classification System (BCS) type II drug due to its high permeability and poor solubility independent of medium.[6] To improve the solubility of regorafenib, an amorphous solid dispersion tablet of regorafenib was developed resulting in a mean relative bioavailability of 69–83%.[6] At doses above 60 mg regorafenib exposure increases less than dose proportional, suggesting saturated absorption.[7] After regorafenib administration, 3 peaks in plasma concentrations were observed at t = 4, 8 and 24 hours indicating that regorafenib might undergo entrohepatic cycling.[7] The 2 main metabolites of regorafenib, M-2 and M-5, show equipotent antitumour efficacy and therefore contribute to the pharmacological activity of regorafenib.[8]

One of the possible mechanisms that could majorly affect orally administered TKI exposure is alteration of the pH of the gastrointestinal tract.[9,10] Due to the location of the GIST, patients commonly undergo gastric surgery to remove the primary tumour. In patients with gastrectomy, the local pH increases due to resection of acid producing cells in the stomach, which could affect the dissolution of drugs that require an acid environment for solubility.[11,12] Since only dissolved drug can be absorbed, decreased solubility will lead to decreased drug exposure, which might affect treatment outcome.[13] The solubility of regorafenib is claimed to be independent of pH.[6] Therefore, it is not expected that gastrectomy, resulting in altered gastric pH, would influence regorafenib solubility. This was confirmed by de Man et al. who showed that no change in regorafenib exposure was observed when it was taken with or without esomeprazole, proving no effect of gastric acid elevating agents.[14]

However, not only the acid producing cells are removed by gastrectomy. It is suggested that transporters such as ABCC4, which are mainly localized in the stomach, could facilitate drug absorption and that in patients with major gastrectomy, are also removed.[15,16] This effect was seen in patient using imatinib who underwent gastrectomy and showed a reduced imatinib exposure of 30% compared to patients without gastric surgery.[17] Imatinib solubility is, like regorafenib, not pH dependent and not affected by gastric acid elevating agents.[18] Furthermore, in a study where patients with gastrectomy were given imatinib together with Coca-Cola to decrease the pH, no effect on drug exposure was seen.[16] This indicates that mechanisms other than pH alteration play an important role in oral TKI uptake.

What is already known about this subject

- Patients with gastric gastrointestinal stromal tumour commonly undergo gastric surgery to remove the primary tumour.
- The solubility of regorafenib is independent of Ph.
- It is suggested that transporters such as ABCC4 could facilitate drug absorption. In patients with major gastrectomy these transporters are removed.

What this study adds

- This study demonstrates that neither the response to regorafenib nor the exposure to regorafenib and its metabolites changed in patient who underwent gastrectomy.
- The results of this study confirm that dose alterations are unnecessary when patients with a gastrectomy are treated with regorafenib.

Since the effect of gastrectomy on regorafenib absorption is unknown and since regorafenib exposure might have consequences for treatment outcome, we wanted to investigate the effect of major gastrectomy on regorafenib exposure and progression-free survival (PFS) in patients with GIST.

2 | METHODS

2.1 | Study design

In this retrospective analysis, data from the GRID trial were used.[19] The GRID trial was a multicentre randomised placebo-controlled phase III trial in which 57 hospitals from 17 countries participated. In the GRID trial 133 participants were randomized to receive an initial regorafenib dose of 160 mg once daily 3 weeks every 4 weeks. Regorafenib administration was continued until disease progression, occurrence of unacceptable toxic effects or withdrawal from the study. Patients were followed up in the study for a maximum of 18 months.

2.2 | Study subjects

Eligible patients had histological confirmed, metastatic or unresectable GIST, with failure on at least imatinib and sunitinib. Additional inclusion criteria included: an Eastern Cooperative Oncology Group performance status of 0 or 1 and an adequate haematological, hepatic, cardiac, and renal function. The study was performed in accordance with Good Clinical Practice and under the ethical principles established by the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Board of each participating institution and informed consent was obtained from each patient. The GRID trial was registered at Clinical trial.gov, number NCT01271712. The subanalysis on the existing dataset of Bayer was

requested by the non-Bayer affiliated authors of this manuscript and was reviewed and granted by Bayer.

2.3 | Sampling and bio analysis

Blood samples for pharmacokinetic (PK) assessment of regorafenib and its active metabolites M-2 and M-5 were collected at t = 24 h after regorafenib intake on day 15 of the first and the second treatment cycle after reaching steady-state PK. The PK assessment visit was scheduled after at least 14 days of uninterrupted stable dosing of study drug. Regorafenib and M-2 and M-5, after repeated dosing, have very *flat* concentration–time profiles, peak/trough ratio of 1.3, 1.6 and 1.5, respectively.[20] Given the low peak–trough fluctuation at steady state due to the long half-life of regorafenib and its active metabolites, the average concentration is an adequate parameter to describe the extend of exposure to regorafenib and its pharmacological active metabolites. The average concentration was calculated based on the actual dosing of the individual patient and AUC divided by dosing interval.[21]

Regorafenib, M-2 and M-5 together represent 92.4% of the total exposure in plasma and at steady state, regorafenib together with its active metabolites are responsible for the total efficacy. Therefore, the sum of the regorafenib including M-2 and M-5 was used to determine the effect of gastrectomy on regorafenib efficacy. A validated liquid chromatography–tandem mass spectrometry method was used to analyse regorafenib and metabolites M-2 and M-5.[22]

2.4 | Statistical analysis

The gastric surgery status was specified for patients participating in the study and therefore all patients could be included for the efficacy analysis. Patients were subdivided into 2 subgroups according to their previous GI surgery: major gastrectomy and no/nonsignificant gastrectomy (defined by physicians' judgement). PFS was measured from the date of randomization until the date of radiological progression or death. Subjects without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment. Only a subset of patient PK data were available. These patients were included in the PK analysis. The statistical analysis on the existing dataset was done using SAS version 9.2.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[23] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[24]

3 | RESULTS

3.1 | Patient characteristics

A total of 133 patients with metastatic GIST were randomized to receive regorafenib in the GRID trial, of whom 27 previously underwent a major gastrectomy for their primary tumour. The other 106 patients served as controls and had no/nonsignificant gastric surgery. Regorafenib PK samples were taken in 80 of the 133 patients, 19

TABLE 1 Patient characteristics

	Major gastrectomy No.	%	No or nonsignificant gastrectomy No.	%
Number of patients	27		106	
Age (y)				
Median (range)	57 (18–76)		60 (26–82)	
Sex				
Female	12	44.4	36	34.0
Male	15	55.6	70	66.0
Race				
Caucasian	20	74.1	70	66.0
Asian	5	18.5	29	27.4
Unknown	2	7.4	7	6.6
ECOG				
0	17	63.0	56	52.8
1	10	37.0	50	47.2
Extent of disease at initial diagnose				
Localized	17	63.0	56	52.8
Advanced	2	7.4	5	4.7
Metastatic	8	29.6	44	41.5
Unknown	0	0	1	0.9
Median dose, mg	122.4		146[a]	

[a]Out of the 106 subjects, 105 subjects received regorafenib.

ECOG, Eastern Cooperative Oncology Group

TABLE 2 Drug related adverse events > grade 2

	Major gastrectomy No.	%	No or nonsignificant gastrectomy No.	%
Any event	14	73.7	49	80.3
Hypertension	6	31.6	24	39.3
Hand–foot syndrome	6	31.6	12	19.7
Diarrhoea	2	10.5	9	14.8
Fatigue	1	5.3	5	8.2
Anorexia	0	0	1	1.6
Rash, macropapullar	1	5.3	2	3.3
Nausea	0	0	1	1.6
Constipation	0	0	1	1.6
ALAT increase	1	5.3	4	6.6
ASAT increase	1	5.3	3	4.9
AP increase	1	5.3	0	0

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; AP: alkaline phosphatase

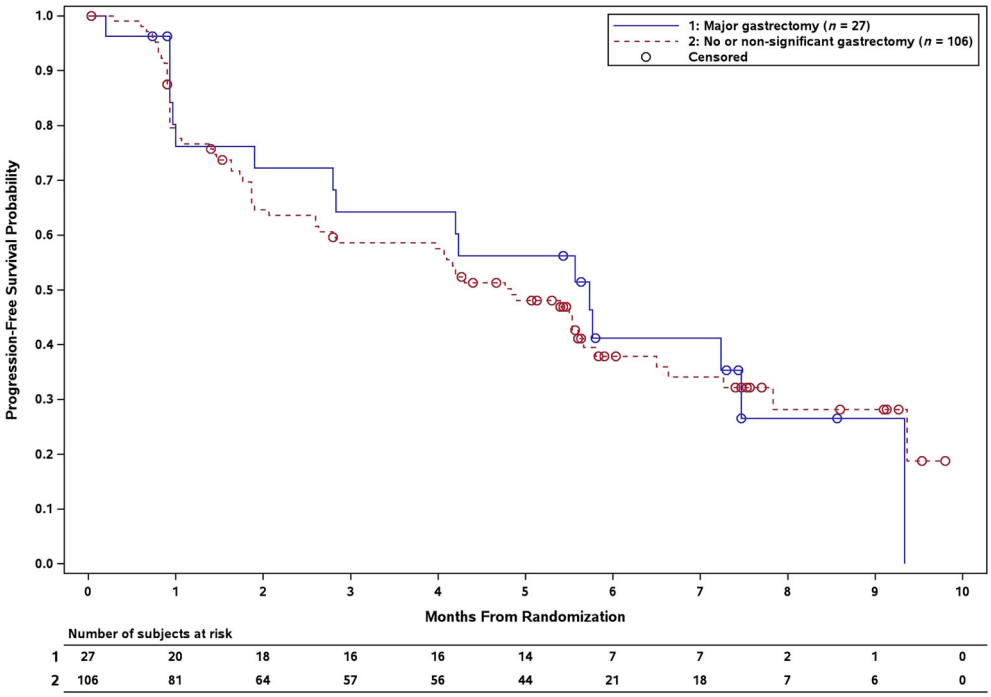

FIGURE 1 Kaplan–Meier progression free survival analysis after gastric surgery

with major gastrectomy and 61 with no/nonsignificant gastric surgery. Baseline characteristics including age, sex and extent of disease are shown in Table 1. Regarding regorafenib related adverse events, hypertension and hand–foot syndrome were the most present followed by diarrhoea. All except hand–foot syndrome were equally present in both groups (Table 2).

3.2 | Effect on PFS

In patients with no/nonsignificant gastrectomy 64 (60%) of the 106 patients experienced progression/death (event) under regorafenib therapy during study follow up. Of the 27 patients who underwent a major gastrectomy 17 (63%) patients experienced progression/death during the study. Patient with no/nonsignificant gastric surgery had a median PFS of 145 days (interquartile range 43–281) compared to a median PFS of 172 days (interquartile range 57–280) in patients with major gastrectomy (Figure 1).

3.3 | Effect on regorafenib plasma exposure

In patients with PK samples available, the geometric mean (including standard deviation [SD] and range) of the average total concentration of regorafenib, M-2 and M-5 was 6.9 ± SD 1.53 μmol/L (3.73–19.81; CV% 44.5) and 6.7 ± SD 1.56 μmol/L (2.28–18.48; CV% 46.5) in patient with major gastrectomy(n = 19) and no/nonsignificant gastrectomy (n = 61), respectively. In a subanalysis, major gastrectomy was divided into total gastrectomy and partial gastrectomy. Six patients had a total gastrectomy and had a geometric mean of the average total concentration of 5.3 ± SD 1.35 μmol/L (3.73–8.81; CV% 30.6). Thirteen patients had a partial gastrectomy and had a geometric mean of the average total concentration of 7.8 ± SD 1.53 μmol/L (3.81–19.8; CV% 44.9).

4 | DISCUSSION

This study demonstrates that neither the PFS of regorafenib treatment nor the exposure to regorafenib and its pharmacologically active metabolites changed in patients who underwent gastrectomy. The results of this study assent that there is no need for dose adjustments in patients who underwent gastrectomy and are treated with regorafenib.

To our knowledge, this is the first study to investigate the effect of gastrectomy on regorafenib exposure and clinical outcome. The predicted impact of gastric surgery on drug exposure is considered to be compound specific.[25] Therefore, results from other studies exploring the effect of gastrectomy on drug exposure cannot be extrapolated to results found in our study. Recently, a study has been published investigating the effect of an acid reducing agent on regorafenib absorption. They showed that alterations in gastric pH did not affect regorafenib exposure.[14] However, as seen with imatinib, the potential influence of gastric transporters, could not be ruled out by the study of de Man et al.[14] In our study, we showed that neither regorafenib exposure nor PFS was altered in patients who underwent gastrectomy. We therefore conclude that stomach transporters play no clinically relevant role in the uptake of regorafenib in the third line GIST population.

The exposure–response relation in GIST patients treated with regorafenib has not been thoroughly investigated. The phase 1 dose escalation study by Mross et al.[7] demonstrated a dose dependent reduction in plasma sVEGFR-2, which might be an indirect marker for an exposure-response relationship. Additionally, the frequency of treatment-related adverse events increased with higher dose levels.[7] In a exposure–response analysis in patients with hepatocellular carcinoma a trend, although not significant, towards a shorter overall

survival in the low exposure group was seen when compared to the patients with a medium or high exposure.[26,27] In our subanalysis, the sum exposure to regorafenib and its pharmacological active metabolites in the total gastrectomy group was slightly lower compared to the no or nonsignificant gastrectomy group. On the contrary, the exposure in the partial gastrectomy group was higher than the exposure in the no or nonsignificant gastrectomy group. The results of this subanalysis are based on a very small number of patients with a wide interpatient variability and therefore do not influence our finding that the type of gastrectomy does not alter regorafenib exposure and PFS.

Hypothetically, toxicity is driven by local or systemic exposure levels and therefore less systemic toxicity and more GI toxicity would be expected in the patients with major gastrectomy. The only difference in drug-related adverse events reported is hand–foot syndrome, which is observed more frequently in the patients with major gastrectomy in whom less toxicity would be expected. The number of patients who reported >grade 2 drug-related adverse events is limited and therefore no conclusions can be derived from these data.

The number of patients who had undergone a major gastrectomy in our study is limited and, as a consequence, has limited statistical power. Furthermore, the retrospective nature of this study could have introduced different sources of bias inherent to retrospective analyses. However, the data used in our study are data from a well-documented clinical study and the gastrectomy status was recorded for all patients. In addition, PK data are not prone to be influenced by patients or physician interventions. Therefore, we believe that our study contributes to further understanding of the effect of regorafenib in patient with a gastrectomy and on the PK behaviour of regorafenib in these patients.

In conclusion, GIST patient with a gastrectomy who are treated with regorafenib have no altered regorafenib exposure and do not show a difference in PFS. Patients with gastrectomy do not need upfront adjustments of regorafenib dose.

ACKNOWLEDGEMENTS

We thank Liping Huang, for support of the statistical analysis.

The retrospective analysis of the data was provided by Bayer and was funded by the academic hospitals Radboud University Medical Center and Leiden University Medical Center.

COMPETING INTERESTS

L.X. and A.C. are employees of Bayer, WvdG received a grant from Novartis and N.P.v.E. received grants from Novartis, Astellas, AstraZeneca, Bristol-Meyers Squibb, Gilead, Ipsen, Janssen, Pfizer and Roche. The other authors have no competing interests to declare.

CONTRIBUTORS

F.J.E.L., W.T.A.v.d.G., L.X., A.C., H.G., and N.P.v.E. wrote the manuscript. F.J.E.L., N.P.v.E., H.G., and W.T.A.v.d.G. designed the research. F.J.E.L. and G.D.D. performed the research. F.J.E.L., L.X., A.C., N.P.v.E., and H.G. analysed the data. L.X, A.C. contributed to the analytical tools.

DATA AVAILABILITY STATEMENT

Research data are not shared since this is not covered in the informed consent given by patients participating in this study.

ORCID

Floor J.E. Lubberman https://orcid.org/0000-0002-5537-0784
Nielka P. van Erp https://orcid.org/0000-0003-1553-178X

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How to cite this article: Lubberman FJE, van der Graaf WTA, Xu L, et al. The effect of gastrectomy on regorafenib exposure and progression-free survival in patients with advanced gastrointestinal stromal tumours. *Br J Clin Pharmacol*. 2019;85:2399–2404. https://doi.org/10.1111/bcp.14061