Cardiac safety and toxicity minimization of regorafenib treatment

Zoltan Szucs¹ & Robin L Jones^{*1}

“Regorafenib has been approved by the US FDA and the EMA in the treatment of metastatic gastrointestinal stromal tumors and colorectal cancer.”

First draft submitted: 14 October 2015; Accepted for publication: 27 October 2015; Published online: 4 February 2016

Regorafenib

Regorafenib is a small molecule inhibitor of a number of protein kinases, including those involved in tumor angiogenesis (VEGFR-1, -2 and -3, TIE2), oncogenesis (*KIT*, *RET*, *RAF1*, *BRAF*, *BRAFV600E*) and maintenance of the tumor microenvironment (PDGFR, FGFR) [1].

Regorafenib has been approved by the US FDA and the EMA in the treatment of metastatic gastrointestinal stromal tumors (GIST) and colorectal cancer. Based on the results of the GRID Phase III clinical trial, regorafenib has established itself as the standard third-line option in the treatment of advanced GIST patients failing imatinib and sunitinib [2]. In the CORRECT Phase III trial, single-agent regorafenib also showed activity in the treatment of heavily pretreated metastatic colorectal cancer patients, with a statistically significant overall survival benefit of 1.4 months [3].

Currently there are no further licensed alternative treatment options available for advanced colorectal and GIST patients

progressing on regorafenib [4,5]. Full awareness of the side-effect profile of this agent and familiarity with treatment toxicity optimization techniques is vital in maintaining treatment efficacy and ensuring maintained quality of life in heavily pretreated patients.

Cardiac toxicity of antiangiogenic tyrosine kinase inhibitors

Multitargeted VEGFR tyrosine kinase inhibitors (TKIs) have got well-recognized cardiac side effects. QT prolongation has been reported in patients exposed to a variety of TKIs, some of which have been associated with ventricular arrhythmia and sudden death [6].

QT intervals are corrected for heart rate variability using the historical methods of Fridericia (QTcF) and Bazett (QTcB) [7]. A QTc interval of >450 ms for men and 460 ms for women is generally accepted as upper limit of normal [7]. The risk of developing ventricular arrhythmias, particularly torsades de pointes, correlates with a QTc interval of >500 ms [8].

Colorectal Cancer

KEYWORDS

- cardiac safety • colorectal cancer
- gastrointestinal stromal tumor
- regorafenib

“Full awareness of the side-effect profile of this agent and familiarity with treatment toxicity optimization techniques is vital in maintaining treatment efficacy and ensuring maintained quality of life in heavily pretreated patients.”

¹Sarcoma Unit, Royal Marsden Hospital, London, SW3 6JJ, UK

^{*}Author for correspondence: Tel.: +44 020 7808 2137; Fax: +44 207 808 2113; robin.jones@rmh.nhs.uk

“The quality of life of advanced heavily pretreated gastrointestinal stromal tumors and colorectal cancer patients is of pivotal importance.”

In a very recent trial-level meta-analysis of randomized Phase II and III trials reported an all-grade QTc prolongation in 165 of 3737 (4.41%) patients receiving the VEGFR TKIs sunitinib, pazopanib, axitinib and vandetanib. The QTc prolongation was mostly asymptomatic with rare arrhythmias and death. Notably, regorafenib was not included in this large analysis because QTc prolongation was not listed as an adverse event in any of the published clinical trials at the time of the meta-analysis [9].

While early phase and licensing Phase III studies were not specifically designed to evaluate the cardiovascular safety of regorafenib, significant cardiotoxicity was not reported in these trials [2,10,11].

In order to formally assess the cardiovascular safety of regorafenib, a Phase I trial of 53 advanced cancer patients evaluated the effects of multiple doses of regorafenib on cardiac function, specifically the QT/QTc interval and left ventricular ejection fraction (LVEF). Patients received regorafenib 160 mg/day for 21 days followed by a 7-day break.

The primary end point was the change from baseline in QTcF at the regorafenib tmax (day 21, cycle one or two) and changes in LVEF from baseline on cycle 2, day 21. Less than half (25/53; 47.1%) of the patients were able to take regorafenib for 21 days without a dose reduction. No patient experienced a change from baseline in QTcF >60 ms and no patient had a QTcF or QTcB >480 ms. LVEF compromise was minimal, with only four patients experiencing a LVEF decrease between 10 and 20%. The authors concluded that the effects of regorafenib on the QT/QTc interval and LVEF were modest and unlikely to be of clinical significance in the setting of advanced cancer therapy [12].

Noncardiac dose-limiting toxicity of regorafenib

In the GRID and CORRECT Phase III trials, the drug-related grade 3 noncardiac toxicity affected almost two-thirds of all patients treated with the drug [2,3]. Hand–foot skin reaction, hypertension and diarrhea were most often recorded [2,3]. The hand–foot reaction (often also referred to as palmar–plantar erythrodysesthesia) involves inflammation and blister formation mainly on

the feet and can swiftly become extremely painful and debilitating, interfering with activities of daily living.

The recommended licensing dose of regorafenib is 160 mg daily for 3 weeks followed by 1 week off treatment. A series of supportive measures were recommended to optimize the long list of side effects associated with regorafenib treatment [13].

As a ‘primary prophylaxis’ measure to overcome excessive toxicities in the first cycle of treatment, the Mayo Clinic implemented an incremental dose-escalation protocol [14]. As routine clinical practice, colorectal cancer patients commencing regorafenib return weekly for follow-up visits, during cycle one. According to the dose-escalation protocol, they start treatment with a 50% dose reduction, in other words, a dose of 80 mg per day. The dose of the treatment is escalated on weekly basis, up to the recommended dose of 160 mg per day by the third week. Patients get a break off treatment in the fourth week. In the subsequent treatment cycle, dosing is based on the toxicity and tolerability of the first cycle. Quite commonly, the dosage used in the second cycle would be 120 mg daily, with some patients tolerating the higher dose of 160 mg.

Conclusion

The quality of life of advanced heavily pretreated GIST and colorectal cancer patients is of pivotal importance. Regorafenib does not hold any clinically significant cardiac risk in the treatment of advanced cancer patients. However, the management of noncardiac toxicities is of paramount importance. One approach is to commence therapy at a lower 80 mg dose, followed by dose escalation depending on tolerability and toxicity.

Financial & competing interests disclosure

RL Jones has conducted clinical trials sponsored by Bayer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- 1 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* 129, 245–255 (2011).

- 2 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* 381, 295–302 (2013).
- 3 Grothey A, Van Cutsem E, Sobrero A *et al.* CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, Phase 3 trial. *Lancet* 381(9863), 303–312 (2013).
- 4 National Comprehensive Cancer Network Colon and Rectal Cancer Guideline (2015). www.nccn.org/professionals
- 5 National Comprehensive Cancer Network Soft Tissue Sarcoma Guideline (2015). www.nccn.org/professionals
- 6 Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf.* 36(5), 295–316 (2013).
- 7 Al-Khatib SM, LaPointe NM, Kramer JM *et al.* What clinicians should know about the QT interval. *JAMA* 289(16), 2120–2127 (2003).
- 8 Bednar MM, Harrigan EP, Anziano RJ *et al.* The QT interval. *Prog. Cardiovasc. Dis.* 43(5 Suppl. 1), 1–45 (2001).
- 9 Ghatalia P, Je Y, Kaymakcalan MD, Sonpavde G *et al.* QTc interval prolongation with vascular endothelial growth factor receptor tyrosine kinase inhibitors. *Br. J. Cancer* 112, 296–305 (2014).
- Summarizes the effect of most commonly used tyrosine kinase inhibitors on QTc interval and identifies lack of information in this context as far as regorafenib is concerned.
- 10 Strumberg D, Scheulen ME, Schultheis B *et al.* Regorafenib (BAY 73-4506) in advanced colorectal cancer: a Phase I study. *Br. J. Cancer* 106, 1722–1727 (2012).
- 11 Mross K, Frost A, Steinbild S *et al.* A Phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clin. Cancer Res.* 18, 2658–2667 (2012).
- 12 Jones RL, Bendell JC, Smith DC *et al.* A Phase I open-label trial evaluating the cardiovascular safety of regorafenib in patients with advanced cancer. *Cancer Chemother. Pharmacol.* 76(4), 777–784 (2015).
- This Phase I trial provides essential unique information on the effect of regorafenib on cardiac safety, as defined by QTc prolongation and left ventricular ejection fraction changes.
- 13 Krishnamoorthy SK, Relias V, Sebastian S *et al.* Management of regorafenib-related toxicities: a review. *Therap. Adv. Gastroenterol.* 8(5), 285–297 (2015).
- Contains comprehensive information about best supportive measures for toxicity management of regorafenib.
- 14 Grothey A. Regorafenib in metastatic colorectal cancer: optimal dosing and patient selection recommendations. *Clin. Adv. Hematol. Oncol.* 13(8), 514–517 (2015).
- Contains essential information about regorafenib treatment initiation practice at an internationally recognized cancer center.