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Efficacy of regorafenib in gastrointestinal stromal tumours (GISTs) — case report

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ABSTRACT

The systemic treatment of gastrointestinal stromal tumours (GIST) is based on targeted therapies such as imatinib, sunitinib, sorafenib, or regorafenib. One of the most important treatment options is the recruitment of patients into clinical trials, especially in the late stage of the disease.

Herein we present a case of a 62-year-old woman with metastatic GIST. In 2008, after a gastrectomy, she was recruited to the EORTC 62024 clinical trial. She was randomly assigned to the observational arm of the study. In 2009 due to non-resectable recurrence of the disease, imatinib therapy was started, and continued until 2014. Then, due to another progression of the disease, the dose of imatinib was doubled and finally replaced by sunitinib. The tolerance of imatinib was satisfactory whereas the sunitinib therapy required dose modification due to a grade CTC3 toxicity. In 2015, due to a further progression, she received sorafenib for 12 months, and subsequently re-treatment with imatinib combined with chemotherapy based on the doxorubicin and dacarbazine schedule (the response to therapy lasted four months). Considering the patient's good performance status, regardless of the fifth line of treatment, she was started on regorafenib. After the first course, the patient reported a definite improvement of the general condition and good tolerance to the therapy. The main complications were hand-foot syndrome and diarrhoea (grade CTC2). On regorafenib treatment, the patient achieved a partial response. In case of further progression the patient will be offered participation in a clinical trial.

In GIST patients, regorafenib monotherapy after previous progression on imatinib, sunitinib, and sorafenib is an effective and well-tolerated treatment leading to clinical and radiological response.

Key words: GIST, regorafenib, metastatic, management

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Introduction

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. GISTs probably derive from the progenitors of the myenteric ('pacemaker') interstitial cells of Cajal, which are responsible for the generation of the peristaltic wave of the intestines [1, 2]. The overexpression of the membrane KIT receptor may be detected by immunohistochemical methods (CD117) on the histopathological sections of the tumour. This method is the most important criterion in the microscopic diagnostics of GIST [3]. The molecular tests performed in patients with GIST show the presence of

mutations of *KIT* and *PDGFRA* genes, which encode the membrane receptors possessing tyrosine kinase activity [4, 5]. The majority of *KIT* gene mutations are placed in exon 11 (about 70%) and less frequently in exon 9 (6–8%). Mutations may also occur in exons 13 and 17 of this gene. In the majority of GIST without any mutations of the *KIT* gene some mutations are detected in the *PDGFRA* gene. These mutations are located in two exons of the *PDGFRA* gene (mostly in 18 and more rarely in 11). The *KIT* and *PDGFRA* gene mutations are mutually exclusive (i.e. they do not occur simultaneously in both genes) [6–8]. The clinical

presentation of GIST is variable. GIST may present as a small tumour, randomly detected by the endoscopic tests (in this case the clinical course is usually relatively benign), or as an important neoplastic mass or a metastatic tumour — located mostly in the abdominal cavity [9]. Surgical-resection is a first-line treatment for primary GIST. In patients with high-risk GISTs adjuvant use of a small molecule tyrosine kinase inhibitor — imatinib — decreases the risk of relapse of the disease. Adjuvant therapy should be continued for three years from the date of the radical surgery. In case of the unresectable relapse or dissemination of the disease, the first-line treatment consists of imatinib administration and consecutive lines of sunitinib, regorafenib, or sorafenib [10]. GIST patients should be diagnosed (with use of molecular methods) and receive a treatment plan in a reference centre.

Case report

We present a case of a 62-year-old woman with GIST in her stomach, who underwent a radical partial gastrectomy in 2008. At the time of diagnosis, no mutations in the *KIT* and *PDGFRA* gene were detected. Because the factors of a high risk of relapse were present [11], the patient was enrolled into the clinical study: EORTC 62024 — ‘Imatinib Mesylate or Observation Only in Treating Patients Who Have Undergone Surgery for Localised Gastrointestinal Stromal Tumour’. She was randomised to the observational arm. Non-resectable disease relapse with metastases to the liver and retroperitoneal space was diagnosed in 2009. Prospective clinical studies of the use of imatinib in patients with non-resectable or metastatic GIST showed that a complete response is achieved in 5–7% of patients, a partial response in 40% of patients, and stable disease in 36% of threatened subjects. [12, 13]. Moreover, the resection rate of the residual changes increases during therapy with imatinib [14, 15]. Therefore, the patient was started on imatinib 400 mg per day, which resulted in partial remission with subsequent long-lasting stabilisation of the disease and very good tolerance to the therapy. Due to the important decrease of the neoplastic masses, the patient was qualified for a pancreatoduodenectomy. She did not give her consent for surgery. That is why the imatinib therapy was continued at the recommended dose until the occurrence of another progression of the disease in 2014. The estimated rate of the disease progression during the 2–3 years of the imatinib therapy reaches 40–50% [16, 17]. In this clinical situation, according to the recommendations of the Polish Association of Clinical Oncology and of the European Society of Medical Oncology, imatinib should be continued at the escalated dose of 800 mg

per day [18, 19]. The double dose of imatinib resulted in this patient in a three-month-long clinical response. Subsequently, further progression was observed and the patient was switched to sunitinib. In 2014 (as well as nowadays) sunitinib malonate — a small molecule tyrosine kinase inhibitor — was the only drug registered for the second-line treatment of GIST patients, resistant or intolerant (very rare) to imatinib. Sunitinib targets multiple tyrosine kinases receptors (e.g. *KIT*, *PDGFR*), vascular-endothelial growth factor receptor (*VEGFR*), and *FLT-3* receptor. Data from the literature show that a median time to progression in GIST patients treated with sunitinib equals 6–8 months [20, 21]. According to the product characteristics, therapy with sunitinib should be started from the dose of 50 mg per day according to the following schedule: four weeks of therapy followed by two weeks of no treatment. The tolerance of sunitinib therapy is usually worse than that of imatinib. That is why the patients had intermitted symptoms of toxicity in grade CTC2 and CTC3, such as: arterial hypertension, palmar-plantar erythrodysesthesia, diarrhoea, or hypothyroidism, requiring modification of the sunitinib dose. Finally, the sunitinib dose was reduced from 50 mg to 25 mg per day. Tiredness, neutropaenia, thrombocytopaenia, diarrhoea, nausea, mucositis, and some other, rarely occurring side effects may be observed during therapy with sunitinib. A clinical study proved that the occurrence of arterial hypertension is a predictive factor of the response to sunitinib [22]. An alternative schedule of a continuous dosing, i.e. 37.5 mg per day without any pause, becomes generally accepted and seems to be more justified due to better tolerance of treatment [23].

In July 2015, due to further progression of the disease, the patient was qualified to receive sorafenib. In studies involving small groups of patients resistant to previous therapy with imatinib and sunitinib or intolerant to these drugs, use of sorafenib resulted in reaching a median PFS (progression-free survival) of 6.4 months (95% CI, 4.6–8.0) and a median OS (overall survival) of 13.5 months (95% CI, 10.0–21.0) [24, 25]. Therapy with sorafenib was well tolerated by our patient. There was no need to modify the dose of the drug. The patient continued therapy with sorafenib at dose of 800 mg per day until subsequent progression of the disease in June 2016.

Because there was no accessible clinical trial and the patient remained in a good performance status, therapy with imatinib was restarted in combination with chemotherapy as per schedule ADIC (doxorubicin and dacarbazine). The disease stabilisation lasted for four months.

Further progression of the disease in September 2016 resulted in the use of regorafenib — the most recent oral drug registered in the treatment of

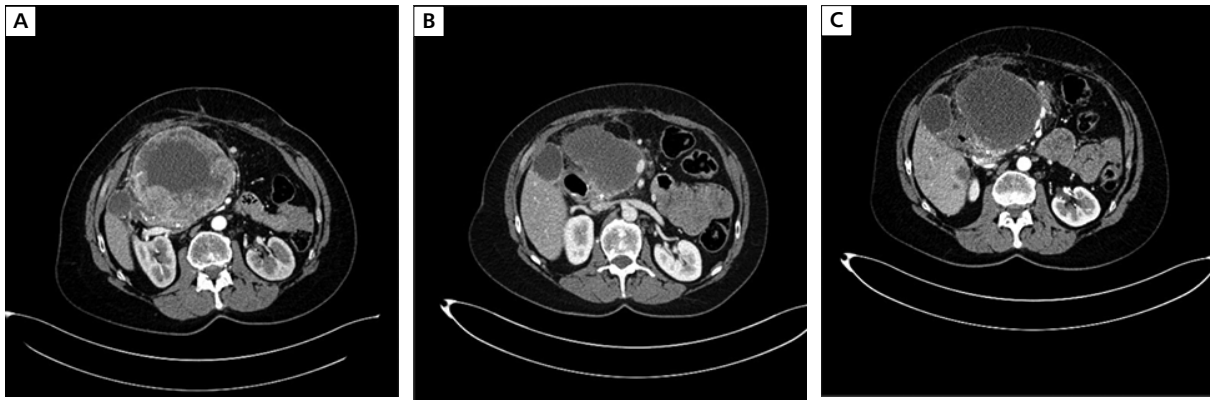


Figure 1. Radiologic evaluation: A — initial imaging; B — after 6 months of therapy; C — after 9 months of therapy

patients with GIST, who have failed to respond to therapy with imatinib and sunitinib. Regorafenib is a multi-kinase inhibitor that inhibits the activity of, among others, KIT, RET, RAF1, BRAF, and TIE2, receptors responsible for the regulation of the neoplastic angiogenesis (VEGFR1-3, TEK) or neoplastic stroma (PDGFR and FGFR). In the GIRD clinical study, the use of regorafenib after failure of imatinib and sunitinib therapy resulted in occurrence of partial responses and high probability of reaching permanent stabilisation of the disease. The grade 3/4 CTC side effects include: arterial hypertension, diarrhoea and palmar-plantar erythrodysesthesia, impotence, changes of the voice timbre/hoarseness, and tiredness [26]. The patient gave her consent for the proposed treatment, which in Polish reimbursement rules was founded by the patient's private financial means. A significant clinical improvement was observed after the first course of therapy. The main observed side effect was hand-foot syndrome and diarrhoea in maximal grade 2 CTC. The side effects were observed mostly in the third week of the therapy. A radiological evaluation of the response is shown in Figure 1. The patient continued on regorafenib for 10 months. She first achieved a partial response, followed by disease stabilisation.

Subsequent progression of the disease was diagnosed in May 2017. According to the clinical data from the GIRD study [27, 28], which suggested the validity of the continuation of regorafenib therapy in patients with radiological progression of the disease and confirmed clinical benefit, the patient continued the treatment for another three months. In July 2017 regorafenib was stopped due to further clinically important progression of the disease detected by the CT imaging of the abdomen and of the true pelvis. We plan to enrol this patient into a clinical trial. The presence of *KIT* gene mutation in exon 11 was detected by the mutation analysis of a new neoplastic tissue sample.

Summary

In the presented case the efficacy of sequentially used tyrosine kinase, as well as the tolerance of each therapy, was shown. The results of therapy obtained in the Department of Soft Tissue/Bone Sarcoma and Melanoma in the Maria Skłodowska-Curie Institute — Oncological Centre in Warsaw are similar to the ones previously cited. The optimal sequence of using the individual drugs as well as combinations of targeted agents, in subsequent lines of therapy, requires further investigation. In the majority of cases even during progression on therapy with one tyrosine inhibitor, the GIST cells remain partially sensitive to another TKI.

It is crucial to refer GIST patients with disease progression and good performance status to clinical trials involving new molecularly targeted agents in monotherapy or combined with immunotherapy. Based on the data from clinicaltrials.gov, there are some ongoing studies with use of ponatinib or DCC-2618. In the case of presence of V842V mutation of the *PDGFRA* gene, the efficacy of crenolanib r Blu285 is being tested. There are also some ongoing studies evaluating the efficacy of immunotherapy, involving accessible anti PD-1/PDL-1 antibodies such as nivolumab or pembrolizumab as well as the anti-CTLA4 antibody — ipilimumab, used in monotherapy or in combination [29].

Our patient was offered participation in a II phase clinical trial: 'Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients with Solid Tumours Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)'. The study includes testing the mutation profile. In patients harbouring the tested mutations the response rate to entrectinib equals about 80%. The aforementioned data are from a I phase clinical study involving 119 patients among whom 25 had a positive result of testing for presence of TRK1, NTRK2, NTRK3, ROS1, or ALK gene mutations. Very good tolerance of treatment with entrectinib should also be mentioned.

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