CASE REPORT

Successful sequential treatment of a patient with advanced gastrointestinal stromal tumor using four different molecularly targeted drugs

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Abstract A 60-year-old woman was admitted to a medical clinic because of epigastric pain. Esophagogastroduodenoscopy revealed a submucosal tumor in the upper gastric corpus and, the tumor was subsequently resected using partial gastrectomy. The pathological findings revealed that the tumor was a gastrointestinal stromal tumor. After 4 months of observation without any adjuvant treatment, the patient was found to have liver metastasis and she was admitted to our hospital for treatment. We successfully treated the patient through sequential drug therapies, including imatinib, nilotinib, sunitinib, and regorafenib, and maintaining disease control for more than 5 years.

Keywords Gastrointestinal stromal tumor · Imatinib · Nilotinib · Sunitinib · Regorafenib

Introduction

Gastrointestinal stromal tumor (GIST) is a relatively rare disease, and the annual incidence is approximately 10 per million in Western countries [1]. First-line therapy for

GIST limited to the local site is always complete surgical resection. Until about the year 2000, the optimal therapy for patients with unresectable GIST or recurrent metastasis was not established, and cytotoxic anticancer drugs such as ifosfamide were used. However, the response rate to these drugs was low (<30 %) and there was no therapeutic drug that contributed to the prolongation of the survival.

Since the twenty-first century, a molecular target agent, imatinib, is available. Its efficacy for unresectable or recurrent metastatic cases with regard to median overall survival time, median progression-free survival period, and disease control rate, was 57, 20 months and 82.2 %, respectively [2, 3]. Imatinib was approved for GIST treatment by the US FDA and Japan in 2002 and 2005, respectively.

The efficacy of sunitinib in cases of imatinib-resistant GIST with regard to median progression-free survival period, and disease control rate, is 27.3 weeks and 71.3 %, respectively. Its usage was subsequently approved as the second therapeutic drug by the US FDA and Japan in 2006 and 2008, respectively [4].

Furthermore, the efficacy of regorafenib in cases of GIST resistant to imatinib and sunitinib with regard to median progression-free survival period and disease control rate, is 4.8 months and 52.6 %, respectively, and was approved as the third therapeutic drug by the US FDA and Japan in 2013 [5].

There are still few reports that show the long-term efficacy by treatments with these new molecular target drugs, particularly in Japanese populations with gastrointestinal stromal tumors. Here, we report a case of recurrent GIST in a Japanese patient who sequentially received imatinib, nilotinib, sunitinib, imatinib reintroduction, and regorafenib therapy, leading to a long-term disease control and survival.

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Case report

The patient was a 60-year-old woman. There were no family or medical histories relevant to this case. In November 2008, the patient presented with epigastric pain. A submucosal tumor was found in the upper part of the stomach through endoscopy of the upper gastrointestinal tract in a previous hospital and subtotal gastrectomy was performed in the same month. Histopathological and immunohistochemical analyses revealed that the tumor was 60 × 70 mm in size, CD34-positive, KIT-positive, vimentin-positive, S-100-negative, desmin-negative, and α -SMA-negative. The number of the nuclear divisions was 2–3/50 HPF, and the MIB-1 index was 2–3 %, evaluated as intermediate risk (modified Fletcher classification [6, 7]). The patient was postoperatively followed up without adjuvant drug treatment.

In March 2009, multiple liver metastases were found as recurrent neoplasm by abdominal computed tomography (CT). The patient consulted our department of the Tohoku University Hospital in April 2009. There were no relevant abnormal findings with regard to blood tests performed at the initial diagnosis. By enhanced CT, multiple liver metastases were found in S2, S3, S4, S6, and S8 (Fig. 1a), indicating no option to perform curable resection for the liver metastases because of their multiple occupation beyond the both lobes of liver.

In May 2009, the patient was enrolled in the international joint phase III study (the ENESTg1 study) developed

to compare the efficacy and safety of the drug nilotinib with the standard drug imatinib [8], and she was assigned to the imatinib group. Treatment was started with imatinib 400 mg/day, but imatinib was reduced to 300 mg/day because of drug eruption of grade 3 2 months later. A mutation in exon 11 of the *KIT* gene was subsequently found by genetic screening performed in the study associated with this trial. The total administration period of imatinib in this trial was 27 months, and the best overall response was SD (28 % of maximal reduction ratio, Fig. 1b). Because an AST (81 U/L) increase of grade 1 and an ALT (109 U/L) increase of grade 2 were shown, imatinib treatment was discontinued for 1 month, but was able to be reinitiated subsequently during other periods without a dose reduction. Progression of liver metastasis was detected by enhanced CT performed in December 2011, and it was classified as a progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) [9] (Fig. 1c), and the patient was switched to nilotinib treatment.

Nilotinib was initiated at 800 mg/day, but the dose was reduced to 400 mg/day because of a lipase increase (120 U/L) of grade 3. Progression of liver metastasis was detected in May 2012 by enhanced CT (Fig. 1d), showing PD, and nilotinib was discontinued. The total administration period of nilotinib was 7 months.

Sunitinib 50 mg/day was initiated as the third treatment, but due to fever, stomatitis, and hand-and-foot syndrome,

Fig. 1 CT scans showing liver metastases during drug treatments. **a** A metastatic lesion of 23.4 mm was detected in the liver S5 area at the time when the patient was referred to our department. **b** The size of the liver tumor was decreased to 17.0 mm (SD) 15 months after initiation of imatinib treatment. **c** The liver tumor enlarged (PD), 27 months after imatinib, **d** 7 months after nilotinib, **e** 10 months

after sunitinib, and **f** 4 months after imatinib re-administration treatments began. **g** The sizes of the liver tumors were not decreased (SD), but the CT value of the tumors was decreased 3 months upon initiation of regorafenib treatment, suggesting efficacy of regorafenib treatment. **h** The liver tumors subsequently enlarged (PD) 15 months after initiation of regorafenib treatment

Fig. 2 The patient's clinical course showing drug treatments, laboratory data (AST, ALT, and LDH), and drug toxicities

the dose was reduced to 37.5 mg/day. Progression of liver metastasis was detected by enhanced CT (Fig. 1e) showing PD, and sunitinib was subsequently discontinued. The total administration period of sunitinib was 10 months. Imatinib 300 mg/day was reintroduced as the fourth treatment, but PD was revealed by CT in July 2013 (Fig. 1f).

Therefore, we switched to regorafenib 160 mg/day as the fifth treatment. However, the dose was reduced to 120 mg/day due to hand-and-foot syndrome of grade 3 after the first course of enforcement. In enhanced CT, 3 months later, enhanced effect of the liver metastasis decreased, although its size did not change significantly (Fig. 1g). Because of the fact total bilirubin levels increased along with the progression of liver metastasis, and obstructive jaundice developed in January 2015, regorafenib was discontinued (Fig. 1h). The total administration period of regorafenib was 15 months.

Eventually, anti-cancer drug treatment was discontinued, and only palliative care was subsequently given. The patient died because of hepatic failure due to liver metastasis in February 2015. An outline of the episode of care is shown in Fig. 2.

Discussion

Because this patient was positive for a mutation in *KIT* gene exon 11 conferring susceptibility to imatinib [10], efficacy of imatinib was initially expected. Disease was

controlled for 27 months by imatinib assigned to control group in an international joint study (see above).

Next, we participated in a crossover study by nilotinib, but the patient was refractory. Nilotinib is a multi-target kinase inhibitor targeting ABL1, BCR-ABL1, KIT, PDGFR, DDR-1, and DDR-2. In the study in which the present patient participated, the efficacy of nilotinib as primary therapy for GIST was shown to be inferior to imatinib (2-year progression-free survival: 51.6 vs. 59.2 %) [8]. As a result, nilotinib was not approved as primary therapy for GIST.

However, by subgroup analysis limited to *KIT* gene exon 11 mutation cases, progression-free survival of nilotinib was approximately equivalent to that of imatinib [8]. Therefore, for certain GIST subtypes, the possibility may remain that nilotinib becomes the drug of choice in primary therapy [8]. The patient in the present report survived for additional 3 years even after nilotinib treatment, which was apparently longer than the overall survival of Japanese patients who received nilotinib treatment in a phase II study (10 months) [10], suggesting that the late line therapies contributed to the favorable outcome in this patient as well as the initial imatinib treatment.

The efficacy of sunitinib as the second-line treatment for imatinib-resistant GIST has been demonstrated [4]; however, the effect of sunitinib was insufficient in the present case. For patients with imatinib/sunitinib-resistant GIST, reintroduction of imatinib has been shown to extend progression-free survival as compared with placebo [11]. In this

case, reintroduction of imatinib was carried out as the third treatment, but the expected effect was not obtained. One of reasons that reintroduction of imatinib for imatinib/sunitinib-resistant GIST was effective could be that GIST is often more bulky than other tumors and thus imatinib-sensitive cells may remain after some cells have become resistant. The liver metastasis of this patient was not large, and the greatest dimension was 16.4 mm (when controlled by imatinib) and 33.7 mm (at the time of PD judgment). Also, as a result of the primary therapy with imatinib lasting 27 months, imatinib-resistant cells accounted for most of the tumors, and imatinib reintroduction might therefore not be effective. Approximately 90 % of patients who received imatinib treatment as first-line treatment get disease control, but most of them experience secondary resistance to imatinib, with median progression-free survival of 20 months [3]. Secondary mutations occur in kinase regions of either KIT or PDGFR in about two-thirds of patients with secondary resistance to imatinib [12]. The tumor in this patient might have acquired such a secondary mutation in *KIT* or *PDGFR* gene.

Regorafenib is a multi-target kinase inhibitor inhibiting KIT, VEGFR, PDGFR, RET, RAF-1, BRAF, and TIE2. In patients with imatinib/sunitinib-resistant GIST, regorafenib extended progression-free survival time regardless of the site of the primary mutation in the *KIT* gene and of the number of treatment regimens [5]. The reason might be the effect of regorafenib that inhibits the multiple target molecules, which are important to the mechanism of GIST onset/progression [5]. It is unclear whether the effect of regorafenib differs depending on the type of secondary resistance mutations.

Fortunately, a benefit of regorafenib treatment was thought to be obtained in this patient, in the light of the favorable progression-free survival of 15 months in this patient as compared with median progression-free survival of 4.8 months in all populations and even 7.1 months in Japanese populations in the international phase III study (GRID) [5, 13]. In addition, it should be noted that our patient benefited from regorafenib treatment that was given as the fifth-line therapy after the preceding four lines of treatment including imatinib, nilotinib, sunitinib, and imatinib reintroduction, which seems to concur with the result of subgroup analysis in the GRID study that some patients who received regorafenib as fourth-line therapy or later was likely to benefit from regorafenib, as well as those who received regorafenib as third-line therapy after imatinib and sunitinib [5]. The reason why regorafenib was particularly effective in this patient remains unclear, however, we consider that the regorafenib treatment contributed to the prolongation of survival as well as the first-line imatinib treatment did, in this patient.

This case report is an example of a Japanese patient with GIST, who successfully achieved long-term disease

control and long-term survival, through the sequential use of four types of molecular target drugs together with the appropriate management for various side effects of these treatments. Further studies are warranted to clarify the long-term outcome of Japanese patients with GIST who received these newly introduced molecular target drugs.

Compliance with ethical standards

Conflict of interest C. Ishioka reports receiving lecture fees from Taiho, Chugai, Takeda, Bayer, Pfizer, Mochida, Asahikasei, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, and Novartis, and grant support from Chugai, Taiho, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, Yakult, Ono, and Novartis.

Research involving Human Participants and/or Animals This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient for the publication of the report that describes her case.

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