Heliyon 10 (2024) e28494

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Hemodialysis and imatinib: Plasma levels, efficacy and tolerability in a patient with metastatic GIST - Case report

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ARTICLE INFO

Keywords:
GIST
Hemodialysis
Imatinib
Case report

ABSTRACT

Purpose: To study plasma levels, efficacy and tolerability of imatinib in a patient affected by metastatic GIST treated with oral Imatinib and undergoing hemodialysis.
Patients and methods: The patient suffered from metastatic GIST to the liver having a mutation of exon 9 of KIT. He was on hemodialysis and received first-line treatment with imatinib 400 mg/day.
Results: The overall mean plasma level of imatinib was 1875,4 ng/ml pre-dialysis, 1553,0 ng/ml post-dialysis and 1998,1 ng/ml post-24h. In red blood cells the overall mean level of imatinib was 619,5 ng/ml pre-dialysis, 484,9 ng/ml post-dialysis and 663,1 ng/ml post-24h. The plasma level of nor-imatinib/imatinib was 16,2% pre-dialysis, 15,6% post-dialysis and 16,4% post-24h. Comparing our findings regarding levels of imatinib in plasma and RBC, we found a statistically significant difference between pre-dialysis and post-dialysis (respectively $p < 0{,}001$ and $p = 0{,}002$), post-dialysis and post-24h (both $p < 0{,}001$), pre-dialysis and post-24h (respectively $p = 0.035$ and $p = 0{,}042$). Ultimately, regarding nor-imatinib/imatinib in plasma, we did not find any statistically significant difference between pre-dialysis and post-dialysis ($p = 0{,}091$), post-dialysis and post-24h ($p = 0{,}091$), pre-dialysis and post-24h ($p = 0.903$). Currently the patient is receiving oral imatinib 400 mg/day with radiological evidence of response.
Conclusion: In this case, hemodialysis did not affect significantly imatinib plasma levels. The statistically significant difference between pre- and post-dialysis can be explained by the fact that dialysis may likely contribute to a small portion of the normal metabolism of imatinib. The evaluation of imatinib levels in RBC and of its main metabolite in plasma also suggests that hemodialysis did not affect other aspects of the elimination of the drug.

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https://doi.org/10.1016/j.heliyon.2024.e28494
Received 26 November 2023; Received in revised form 13 March 2024; Accepted 20 March 2024
Available online 27 March 2024

1. Introduction

Gastrointestinal stromal tumors (GISTs) are a subgroup of mesenchymal tumors arising from the gastrointestinal tract, with an incidence of 0.4–2 cases per 100000 per year and a median age of 60–65 years. The most frequent location is in gastric tract (55.6%), followed by small bowel (31.8%), colorectal tract (6.0%), other (5.5%), oesophagus (0.7%), unknown (0.2%) [1–3]. *nor-imatinib*In presence of imatinib sensitive mutations, the standard treatment for locally advanced or metastatic patients is an oral treatment with imatinib [4,5].

Imatinib is a tyrosin kinase inhibitor indicated for adjuvant treatment [6–8] and in the first-line treatment of patients with metastatic/locally advanced inoperable GIST with KIT mutation and PDGRFα non-D842V, up to progression and/or intolerance [9–12]. The molecular mutation affects the response to imatinib [5]. In particular, patients with a KIT exon 11 mutation respond to treatment at the standard dose of 400 mg/day, patients who have a KIT exon 9 mutation have a better response rate and Progression Free Survival (PFS) to imatinib dose of 800 mg/day [13]. GISTs with some kinase mutations, such as PDGFRA D842V and GIST wild type (WT) for KIT and PDGRFa are resistant to imatinib [14,15]. Imatinib orally administered is well absorbed, and has an absolute bioavailability of 98% [16]. It is metabolized mainly by the cytochrome P450 (CYP) 3A4 or CYP3A5 and can competitively inhibit the metabolism of drugs that are CYP3A4 or CYP3A5 substrates [17]. Interactions may occur between imatinib and inhibitors or inducers of these enzymes, leading to changes in the plasma concentration of imatinib as well as co-administered drugs. The terminal elimination half-life is approximately 18 hours [18]. The principal metabolite of the drug, called nor-imatinib (CGP 74588), shows comparable pharmacological activity to the parent drug and is eliminated predominantly via the bile. The fecal to urinary excretion ratio is approximately 5:1 [19].

In January 2021, a patient with metastatic GIST an advanced GIST patient was referred to our institution to start imatinib. However, this patient was on hemodialysis, because of concomitant chronic renal failure due to a previous ipovolemic shock occurred due to acute bleeding within the GIST mass. When deciding about the medical therapy, our clinical uncertainty was how to start therapy, at which doses and with which monitoring. Although imatinib and its metabolites are only excreted to a small extent by the kidney, we wondered what impact dialysis may have on imatinib plasma levels and whether this may affect drug efficacy, since only a few studies in literature investigated the pharmacokinetics and efficacy of imatinib in patients undergoing hemodialysis. We also wandered if dialysis could influence the equilibrium between imatinib outside and inside cells. Since red blood cells (RBC) have some

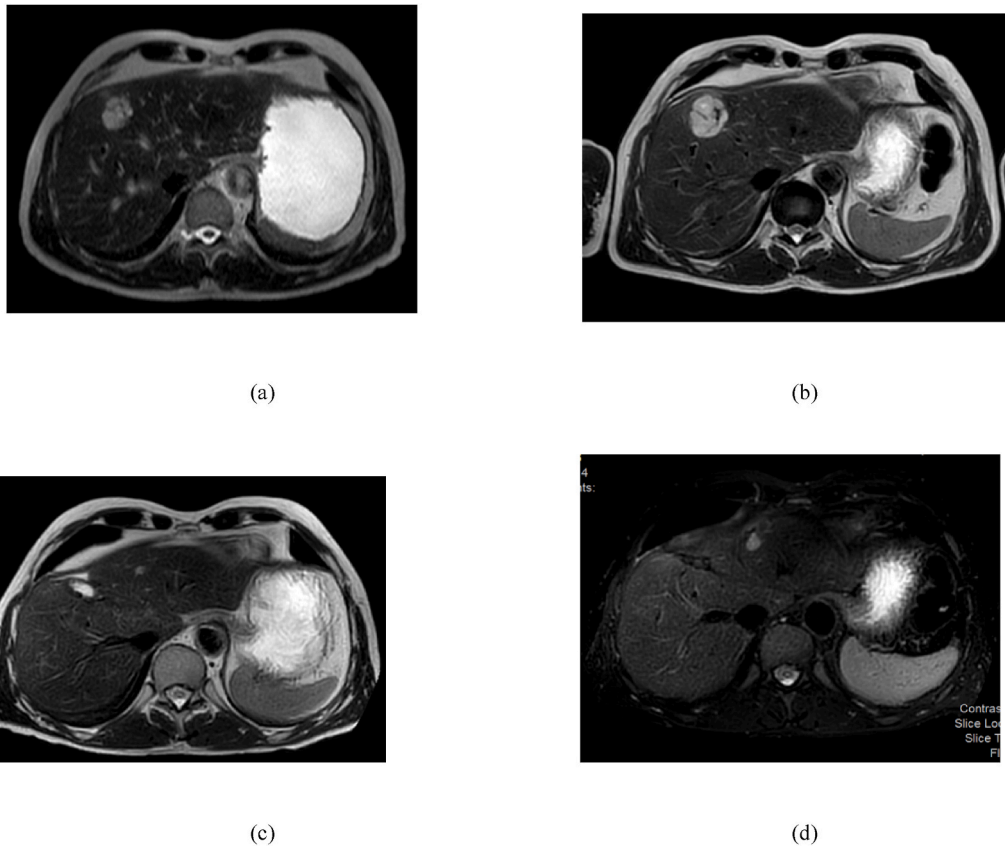

Fig. 1. December 2018: liver metastasis in the IV segment (a). May 2019: Progression of the metastasis despite RT (b). December 2019: nodule in the II segment of the liver (c). January 2021: new liver nodule in the II segment of the liver (d).

of the transporters used by imatinib to move through the cellular membrane [20,21], we decided to analyze also levels of the drug inside those cells.

We describe herein this clinical case and provide a short review about its implications.

2. Clinical history

In July 2014, a 61-year-old man, without comorbidities or family history of inherited cancer, underwent surgery for an intestinal mass of 7 cm. The pathology report revealed a GIST with mitotic rate of 6/50 HPFs and c-kit exon 9 mutation. The clinical condition of the patient before surgery was complicated by peritonitis ad concomitant acute renal failure (with maximum levels of creatinine 12 mg/dL) which leads to chronic renal failure. Postoperative staging was negative for disease, but due to high risk of recurrence [22] on October 2014 the patient was started on oral imatinib. Due to renal condition, despite exon 9 mutation, we decided to treat the patient with imatinib 400 mg/day instead of 800 mg/day [13]. The therapy was well tolerated without any clinically relevant toxicity. The adjuvant treatment ended in September 2017 without any radiological evidence of relapse.

In December 2018, 1 year and 3 months later, an abdominal RMN showed a liver metastasis in the IV segment of the liver [Fig. 1a]. Because of renal failure, after multidisciplinary discussion we decided to treat the patient locally with ablative radiotherapy (35 Gy/7 fractions between 5 and March 13, 2019). After 4 months, due to rapid progression of the metastasis [Fig. 1b] on July 4, 2019 he also underwent surgery, with histology confirmation of liver metastasis from primitive GIST. 5 months later, in December 2019, a follow-up RMN showed a new nodule in the II segment of the liver [Fig. 1c], suspected for relapse of disease, which was treated in March 2020 with percutaneous radiofrequency. In the meanwhile, due to worsening of renal failure, in November 2020 the patient was started on hemodialysis 3 times a week. In January 2021, 10 months after last treatment, a follow-up abdominal RMN showed a new liver nodule of 14 mm [Fig. 1d]. Since the patient started dialysis and he already underwent multiple local therapies, on March 3, 2021 we decided to start a systemic treatment with oral imatinib. Because no clear guidelines regarding the dose of imatinib for dialysis patient, with precautional intention we started the treatment with a daily dose of 400 mg/day instead of 800 mg/day.

3. Materials and methods

3.1. Chemical and reagents

Imatinib mesylate and *d8*-imatinib mesylate (used as internal standard) were supplied by Spectra2000 Srl (Roma, Italy). Ammonium formate, formic acid and trifluoroacetic acid (TFA) (all LC-MS grade) were bought from Carlo Erba (Milano, Italy). Acetonitrile, isopropanol and methanol (all LC-MS grade) were obtained from Carlo-Erba (Milano, Italy). LC-MS grade water was in-house produced through Elga LabWater/VWS (UK).

3.2. Sample collection

Starting from patient treatment with imatinib, which began on March 3, 2021, blood samples were collected for 7 nonconsecutive weeks, from March 9, 2021 until April 7, 2021 (5 weeks), from May 18, 2021 until May 28, 2021 (2 weeks) and one last time in January 2022. In each of these weeks, 2 samplings were carried out at the time of hemodialysis. Each sampling consisted of 3 blood draws. The 1st immediately before dialysis (1:00 p.m.), the 2nd immediately after dialysis (5:00 p.m.) and the 3rd 24 hours after the start of dialysis (1:00 p.m. – i.e. in a non dialytic day). The blood was collected in heparinized tubes, subsequently centrifuged and divided into aliquots of plasma and red blood cells. The aliquots were stored at −80 °C until analysis.

During this period the patient took imatinib each day after dinner, at 8:30 p.m.

Control human plasma, used to prepare daily standard calibration curves and quality control (QC) samples, was provided by the transfusion unit of the National Cancer Institute (Milano, Italy) from healthy volunteers who have given their informed consent for research purposes.

3.3. Sample preparation

A calibration curve in plasma matrix was performed running 7 standard points at 3000, 2000, 1000, 500, 250, 62.48, 15.62 ng/mL. The most concentrated standard was prepared by adding 30 μL of imatinib mesylate working solutions at 1970 μL of human plasma (3000 ng/mL), the other standards were prepared by successive dilution. Standards, red blood cells and plasma samples were treated in the same way. 270 μL of precipitation solution were added to 30 μL of standards and samples and vortexed for 10 s. The mixture was centrifuged for 10 min at 16000 g and 4 °C. After that, 200 μL of the supernatant were transferred to a glass autosampler vial for the subsequent analysis. Stock and working solution preparation is described in detail in Supplementary section.

3.4. LC-MS/MS equipment and conditions

All the LC-MS/MS measurements were made by a Quantiva triple quadrupole (ThermoScientific, Milan, Italy) coupled to a LC Transcend (ThermoScientific, Milan, Italy), including an autosampler, a binary pump, and a column oven. The chromatographic separation of the analytes was conducted on a Synergi Fusion-RP column (4 μm, 2 × 50 mm) from Phenomenex (Bologna, Italy) kept in the oven at 55 °C. Mobile phase solvent A was H_2O+ 0.1% (v/v) trifluoroacetic acid+2 mM ammonium formate, mobile phase solvent

B was acetonitrile:isopropanol 80:20 (v:v)+0.1% (v/v) trifluoroacetic acid. The HPLC separation was performed in gradient mode at 0.45 mL/min (Table S1). The mass spectrometer worked in positive selective reaction monitoring (SRM) mode. The quantification was conducted using the following quantifier transitions: imatinib m/z 494.4 → 394.2, and IS (d8-imatinib) m/z 502.4 → 394.2.

3.5. Statistical analysis

The imatinib levels in plasma and red blood cells, found in the three times (pre-, post-dialysis, and 24h post-dialysis) of each sampling, were analyzed in terms of mean, median, standard deviation (SD), and coefficient of variation in % (CV%). Nor-imatinib level in plasma was evaluated as percentage ratio of nor-imatinib/imatinib %. The Wilcoxon signed-rank test was used to compare imatinib levels at the three sampling times, i.e. pre-, post-dialysis, and 24h post-dialysis in both matrices. Descriptive statistical analysis Wilcoxon signed-rank test were performed by R version 4.1.3 (2022-03-10).

4. Results

Table 1 shows mean, median, standard deviation (SD), and coefficient of variation in % (CV%) of imatinib levels found in plasma and red blood cells, and % nor-imatinib at the three times (pre-, post-dialysis, and 24h post-dialysis) of each sampling, The trend of imatinib levels in plasma and RBC during blood sampling, each consisting of three speciemens (pre-post dialysis, and 24h post dialysis), is shown in Fig. 2a and 1.2b.

Regarding levels of imatinib in plasma, we found a statistically significant difference between pre-dialysis and post-dialysis ($p < 0{,}001$), post-dialysis and post-24h ($p < 0{,}001$), pre-dialysis and post-24h ($p = 0.035$). At 6 contiguous timepoints we did not observe a statistically significant difference between post-24h and pre-dialysis of the next day (i.e. contiguous blood samples without dialysis interference, p: 0.4688). A new blood sample in January 2022 showed no progressive accumulation of imatinib (pre dialysis: 1754,9 ng/ml; post-dialysis: 1277,4 ng/ml; post-24h: 1808,7 ng/ml).

Also in red blood cells a statistically significant difference of imatinib concentration was found between pre-dialysis and post-dialysis ($p < 0{,}001$), post-dialysis and post-24h ($p < 0{,}001$), pre-dialysis and post-24h ($p = 0{,}042$). The blood sample of January 2022 showed no progressive accumulation of the drug (pre dialysis: 666,3 ng/ml; post-dialysis: 497,2 mg/ml; post-24h: 843,7 ng/ml). Ultimately, regarding nor-imatinib/imatinib in plasma, we did not find any statistically significant difference between pre-dialysis and post-dialysis ($p = 0{,}091$), post-dialysis and post-24h ($p = 0{,}091$), pre-dialysis and post-24h ($p = 0.903$).

In January 2021 an abdominal RMN showed liver progression [Fig. 3a]. The radiological evaluations after 2 months [Fig. 3b], 6 months [Fig. 3c] and 9 months of treatment [Fig. 3d] showed a dimensional regression of the metastasis with a change in its morphology without appearance of new lesions. Currently, 20 months after treatment's start, the patient is still on hemodialysis 3 times a week and he is receiving oral imatinib 400 mg/day without any clinically relevant toxicity or radiological evidence of disease progression.

5. Discussion

We report the story of a patient with a metastatic GIST to the liver having a mutation of exon 9 of KIT, who was on hemodialysis since three months earlier and received first-line treatment with imatinib at a dosage of 400 mg/day.

Our main concern was the impact that dialysis might have on the plasma levels of imatinib and consequently on the efficacy of the drug. We therefore monitored imatinib and its main metabolite nor-imatinib circulating during dialysis for a few weeks. The results obtained showed that patient was responsive to treatment with no major toxicity. Furthermore, the plasma level monitoring showed that hemodialysis did not affect significantly the drug elimination, with values comparable to patients with a normal renal function.

At our knowledge, among GIST patients, there are only three cases with advanced GIST undergoing medical treatment with imatinib 400 mg/day while they were on dialysis. Plasma levels of imatinib and its metabolite were evaluated only in one study, but the analysis was performed only at the start of treatment and after one week [23]. In one patient, the levels of imatinib fell within the range of pharmacokinetics values of patients with a normal renal function and the disease remained stable for several months without major side effects [23]. In another case report, the drug was used as an adjuvant, again without toxicity [24]. In the last case available, the patient progressed after 4 months but it is unknown if the underlying mutation was sensitive to imatinib [25]. Among chronic myeloid leukemia patients, in one study a progressive increase of plasma levels of imatinib was reported, causing severe adverse effects

Table 1
Mean, median, SD, and CV% of imatinib levels in plasma and RBC, and % nor-imatinib at the three times of each sampling.

	Plasma imatinib ng/ml		RBC imatinib ng/ml				Plasma % Nor-imatinib[a]		
	pre-dialysis	post-dialysis	pre-dialysis	post-dialysis	24h-post dialysis	24h-post dialysis	pre-dialysis	post-dialysis	24h-post dialysis
Mean	1875,4	1552,9	619,5	484,9	663,0	1998,1	16,2	15,6	16,3
Median	1907,7	1509,8	610,1	468,6	665,9	1938,4	16,3	16	16,3
SD	247,4	173,6	51,9	59,7	64,6	357,7	1,5	1,4	1,5
CV%	13,2	11,2	8.4	12.3	9.7	17,9	9,4	8,9	9,0

[a] = Not-imatinib/imatinib %.

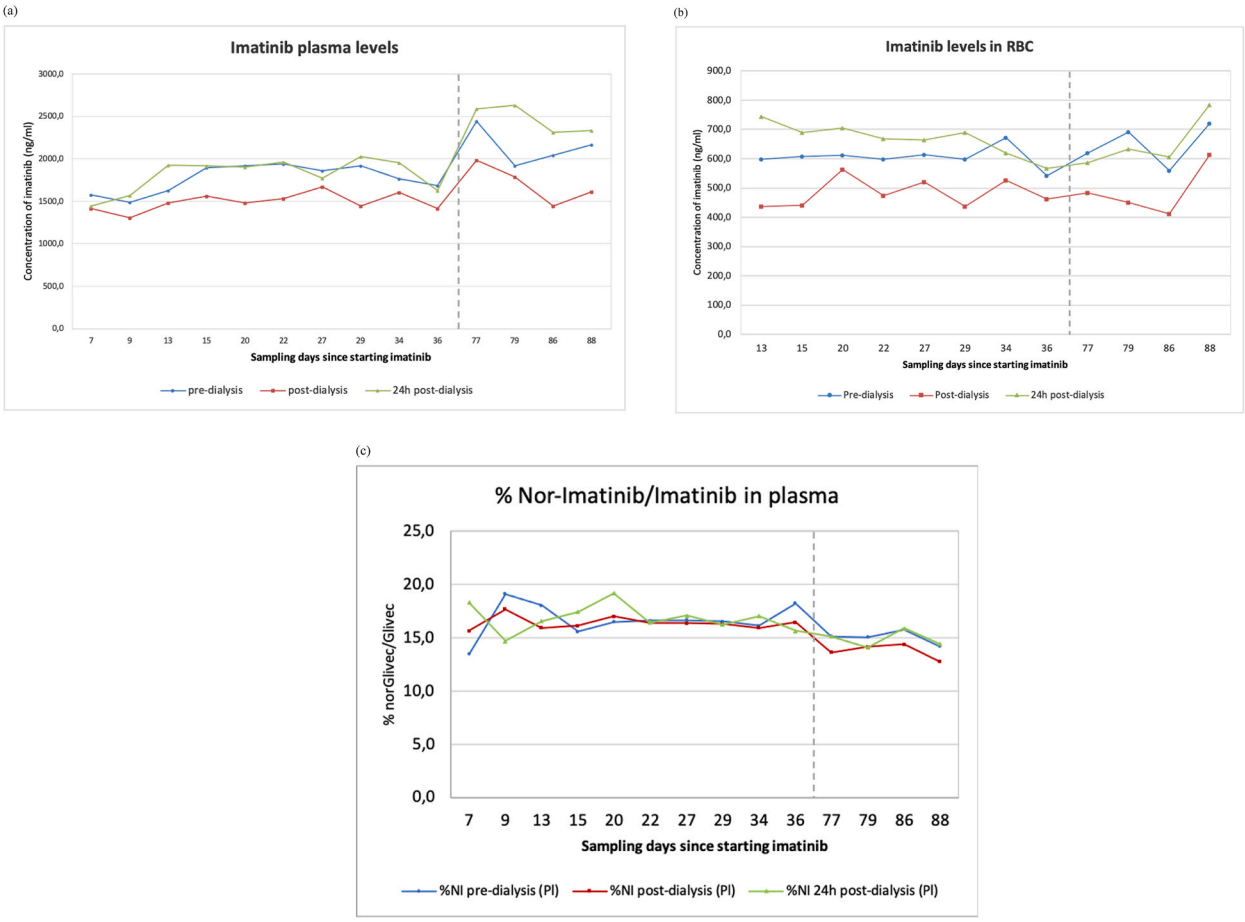

Fig. 2. Trend of imatinib levels during blood sampling, each consisting of three specimens: 1st specimens, pre-dialysis ((blue line), 2nd specimens, post-dialysis yellow line) and 3rd specimens, post24h-dialysis (gray line). (a) Concentration in plasma, (b) Concentration in RBC, and (c) % nor-imatinib/imatinib. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

requiring dose reduction [26]. In a more recent study, levels of imatinib were evaluated with a single analysis at day 8 and 28, with evidence of a large fluctuation of values, thought to occur because the steady state was reached on day 28 after re-administration [27]. The patient did not experience any clinically relevant toxicity.

In our patient, plasma levels fell in the range between Cmax and trough concentration of patients with a normal renal function [28].

As we expected, since the elimination half-life of imatinib is 18 h and the kidneys normally represent a minor pathway for the elimination of imatinib (as reported in literature they remove about 5–10% of it [29]), we found a statistically significant difference between pre and post dialysis. Even though we do not have data regarding urinary elimination, we could suggest that dialysis may likely contribute to a small portion of the normal elimination of imatinib.

Interestingly, we also found a significant difference between pre-dialysis and post-24h, with increasing values from the former to the latter, with the theoretical threat of progressive accumulation of the drug. As a matter of fact, the patient had no clinical toxicity and the blood samples that were collected in January 2022 excluded any increase of imatinib plasma levels, since the levels remained in the range between Cmax and trough concentration of patients with normal renal function. Moreover, statistical analysis at 6 contiguous timepoints in days without potential dialysis interference (i.e. between post-24h of Wednesday and pre-dialysis of Thursday) did not show any statistically significant difference. Probably, as hypothesized in a LMC study [27], due to hemodialysis, the steady state was not yet reached after one week from the start of treatment, as it normally happens in patients with normal renal function. Since RBC have some of the transporters used by imatinib to move through the cellular membrane [20,21] we also analyzed levels of imatinib in those cells, which remained relatively constant over time. Interestingly, comparing pre-dialysis, post-dialysis and post-24h, even in this case we found a statistically significant difference between pre, post dialysis and post-24h. As reported for plasma levels, the blood sample of January excluded an increase of imatinib in RBC. Finally, it is interesting to notice that in the second period of analysis (18–28 May 2021) we observed an increase in the levels of imatinib in pre-dialytic blood samples while the levels in RBC remained stable over time, which could suggest that the steady state was reached more quickly in RBC rather than in plasma. So even though we do not have data regarding patients with a normal renal function, the stability of the values over time suggests that hemodialysis did not affect either the equilibrium between imatinib outside and inside cells like RBC.

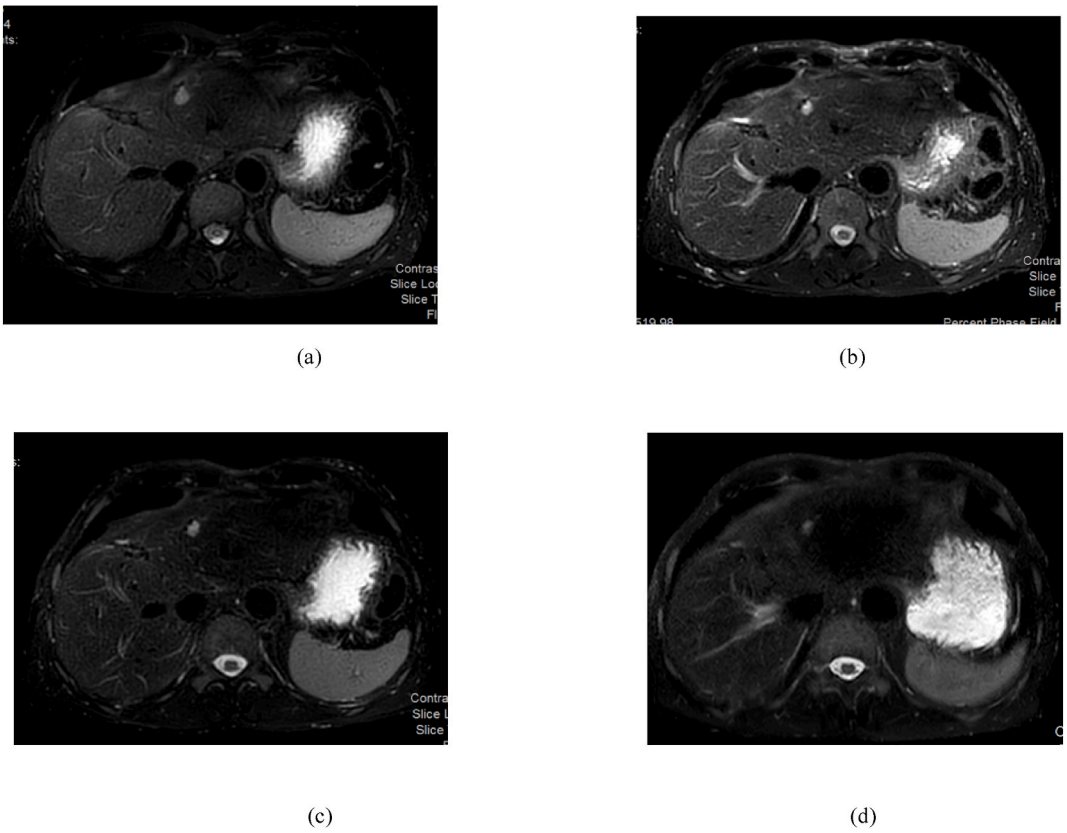

Fig. 3. January 2021: new liver nodule in the II segment of the liver, January 2021 (a). May 2021 (b), September 2021 (c), December 2021 (d).

Finally, since the principal metabolite of imatinib (CGP 74588) shows comparable pharmacological activity to the parent drug, we decided to analyze the percentage of Nor-imatinib/imatinib in plasma. This ratio remained stable over time and showed no difference comparing pre-dialysis, post-dialysis and post-24h, suggesting that Imatinib and its main metabolite are eliminated by hemodialysis in the same extent.

Clinically, the patient had a dimensional tumor response, which is ongoing at the moment, and no major toxicity.

In general, plasma level monitoring during imatinib therapy in GIST patients is not routinely made, in the lack of any prospective evidence pointing to its efficacy. Only retrospective evidence is available. The most significant study was from Demetri et al., retrospectively correlating plasma levels above a threshold at 1110 ng/ml to a better PFS in 73 patients with advanced GIST receiving either 400 or 600 mg/day. Plasma levels of imatinib and its major metabolite CGP745888 were assessed at day 1 and 29 [28]. Currently, imatinib plasma level assessment is not routinely performed though it is recommended in patients taking concomitant medications, in those with unexpected toxicities, in those failing to respond while having sensitive genotypes [30].

Imatinib is a drug with a wide therapeutic window and is generally well tolerated, while the other drugs currently indicated in the treatment of metastatic GIST are marked by more side effects. These may well require a modulation of the dose and/or schedule. Evaluation of plasma levels, however, could be even more useful with more toxic agents such as sunitinib, regorafenib, ripretinib and avapritinib.

An interesting review of 73 articles was recently published summarizing all clinical studies available in the treatment of adult patients using sunitinib in the approved indications (GIST and metastatic renal cell carcinoma), addressing the need to introduce appropriate and robust monitoring of therapeutic levels of sunitinib and its major metabolite, N-desetylsunitinib [31]. According to the evidence presented in this review, plasma level-guided sunitinib dose modification could provide a better treatment outcome while preventing sunitinib toxicity. For the other drugs used in the treatment of metastatic GIST, there are no works about plasma level monitoring.

Our patient received imatinib 400 mg/day, despite having an exon 9 of KIT, and responded to treatment. The standard of treatment for the subgroup of patients with exon 9 mutation is imatinib at 800 mg/day, because it has been shown that at this dose the patients have a significantly higher response rate and better PFS, with a trend in OS. In the meta-analysis, although these data were not shown, it was also found that time to definitive imatinib failure did not differ between the two treatment arms 400 *vs* 800 mg/day [13]. Thus, which is the best therapeutic strategy between starting treatment at a dosage of 800 mg/day or starting at 400 mg/day and then increasing the dose as it progresses is an open question. In our case, in consideration of the important comorbidity, we started the treatment at 400 mg/day and since the patient obtained a radiological response to the disease, we decided to continue the treatment at

the same dose, with a view to a dose escalation only in case of progression.

Indeed, our patient had received imatinib 400 mg/day as an adjuvant, being unable to start at a dosage of 800 mg, in consideration of the high levels of creatinine. The patient had a recurrence of the disease one year and three months after the end of the adjuvant treatment. It is possible that imatinib, even if administered at the dose of 400 mg/day, somewhat prolonged Recurrence Free Survival (RFS). Imatinib 800 mg/day is proposed as adjuvant therapy in GIST patient with an exon 9 mutation on the basis of data extrapolated from the advanced setting [13]. However, a recent retrospective study demonstrate a daily dose of imatinib 800 mg in GIST patients with exon 9 mutation is not better in terms of survival than imatinib 400 mg/day [32].

Interestingly, our patient was treated locally for 3 times due to the risk of worsening renal function. This approach led to postpone the start of imatinib by 2 years, until the time the patient was on hemodialysis. The potential benefit of this approach would theoretically be to postpone secondary progression to imatinib by starting the drug later, thereby prolonging OS. Since a correlation between initial tumor volume and OS was shown in the advanced disease [13], the potential risk could be a shorter benefit should a bigger tumor be in place when starting imatinib. On the other side, limited effectiveness of surgery of metastatic GIST is confined to focal progressions on imatinib [33,34], while surgery of residual disease responding to imatinib has never been prospectively validated, in the lack of any prospective randomized trials [33–35].

This is the first case report in which were assessed the levels of imatinib and its metabolite in plasma and RBC before, after and 24h post-dialysis monitoring the patient over a period of 7 weeks showing that in this specific case hemodialysis did not affect significantly imatinib metabolism. The weakness is that these results are limited to a single patient, reducing accuracy of the conclusions. Other limits are that the analysis were conducted only in blood samples and not in urine, thus reducing the accuracy of our conclusions regarding the potential minor role of dialysis in the elimination of imatinib. It is also a limit that our considerations regarding RBC are supported only by a few of other papers in which it was analyzed the equilibrium of specific drugs within and without those cells. We also do not have data regarding RBC in patients with a normal renal function. For those reasons there will be need of more studies to confirm these hypothesis.

In conclusion, we reported the case of a GIST patient on hemodialysis that received 400 mg/day imatinib mesylate with a tumor response at the moment and no major toxicity. Monitoring of imatinib plasma levels could confirm that hemodialysis did not affect significantly the elimination of the drug.

Ethics statement

Written informed consent was obtained from the patient for the publication of all images, clinical data and other data included in the manuscript. We also obtained human ethics committee approval (number of protocol 4892949–August 05, 2022).

Funding

This research received no funding.

Institutional review board statement

This study was conducted in accordance with the declaration of Helsinki, and our patient signed informed consent for scientific research purposes. The work was submitted to the Ethics Committee of our Center and received approval.

Data aviability statement

Our data have not been deposited into a publicly available repository. They will be made available on request.

CRediT authorship contribution statement

Ida De Luca: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Daniela Miliziano:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Giulia Guerra:** Writing – original draft, Methodology, Formal analysis, Data curation. **Roberto Colombo:** Methodology, Data curation, Conceptualization. **Carlo Morosi:** Visualization, Validation, Data curation. **Carlo Sposito:** Visualization. **Marco Fiore:** Visualization. **Elisabetta Venturelli:** Writing – review & editing, Data curation. **Claudia Sangalli:** Visualization. **Paolo G. Casali:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology. **Adalberto Cavalleri:** Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elena Fumagalli:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28494.

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