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Case Report
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Influence of Haemodialysis on Imatinib Plasma Levels in a Case of Philadelphia Positive Acute Lymphoblastic Leukemia

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Background

Imatinib is a commonly used drug for the treatment of chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) with presence of a Philadelphia chromosome (Ph+), and gastrointestinal stromal tumors (GIST). Thanks to the availability of tyrosine kinase inhibitors (TKI) including Imatinib, the standard treatment of these pathologies has changed significantly and their outcome has vastly improved. The introduction of Imatinib two decades ago constituted a revolution in the treatment of CML, both because it was the first molecularly targeted therapy in oncology and because it has allowed the field to move away from aggressive first-line therapies, including hematopoietic stem cell transplantation. The main circulating active metabolite of Imatinib in humans is the N-demethylated piperazine derivative CGP74588, also known as N-desmethyl-STI (Des-M-STI) and formed predominantly by CYP3A4. Whilst there are many studies looking at TKI usage, very little is known about the elimination and thus the safe dosage of Imatinib and its main active metabolite CGP74588 in patients receiving hemodialysis. This data is critical to predict both safety and efficacy in such clinical settings.

Imatinib is known to be primarily excreted in the faeces, with 68% eliminated from the body by this route, and only 3% to a maximum of 13% being excreted by the kidneys [1,2]. Theoretically, the potential for the drug to accumulate to toxic levels in patients with renal failure would be considered to be low. However, the ability of hemodialysis to remove Imatinib and CGP74588 from the blood has not been extensively investigated. Only rare individual case reports have been published, mainly in the context of GIST, with one single CML case described [3-6]. All published cases in the hemodialysis setting describe treatment with 400 mg of Imatinib as a single daily dose. To the best of our knowledge, no case has been described as yet for the use of Imatinib in the context of acute lymphoblastic leukemia (ALL) in a hemodialysis setting. Moreover, our patient received a daily dose of 600 mg/d rather than the usual dose dose of 400 mg/d because higher doses are recommended for ALL treatment.

We would like to share our experience of dosing Imatinib in an ALL patient receiving 600 mg/d while undergoing hemodialysis treatment.

Case Presentation

A 62-year-old man was diagnosed with Philadelphia positive, bcr-abl positive (p190) ALL. Chemotherapy was commenced according to the German Multicenter ALL protocol (GMALL), which included Imatinib 600 mg daily. During this treatment, the patient developed neutropenic sepsis with paralytic ileus, which resulted in end-stage kidney failure requiring hemodialysis. Imatinib was continued at 600 mg/d, and serial measurements of both Imatinib and CGP74588 were taken for three consecutive days, from plasma as well as from the dialysate. The patient died from paralytic ileus shortly after having started dialysis treatment. For a detailed list of measurements of Imatinib and CGP74588 in plasma and dialysate, see Table 1.

Results showed that only 0.005% of the Imatinib dose was removed during hemodialysis, demonstrating poor efficacy of hemodialysis in eliminating the drug in our clinical setting. Noteworthy, the plasma levels of both Imatinib and its main metabolite CGP74588 were found to be

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Table 1: Serial measurements of Imatinib (STI) and CGP74588 (DesM-STI) in plasma and dialysate.

	Hours after Imatinib intake	STI ng/ml	DesM-STI ng/ml	DesM-STI/STI ratio %
Day 1	21.5	363	48	13
	5	549	52	9
Day 2	21.75	368	45	12
After dialysis	23.92	338	46	14
	3.17	490	46	9
Day 3	18.92	280	39	14
	6	337	51	15
1500 ml dialysate		7 (10.5 µg absolute)		

approximately three times lower than predicted. It is unclear whether this was secondary to reduced intestinal absorption due to ileus, or to an unusual volume of distribution.

Discussion and Conclusion

Despite the fact that Imatinib constitutes the gold standard for the treatment of CML as well as GIST, data on Imatinib use in patients undergoing hemodialysis is sparse, with only a few GIST cases and one CML case described. Most of these case reports simply describe the feasibility, the efficacy against the malignancy, and the lack of major side effects of the Imatinib treatment in the context of hemodialysis [3]. Niikura and colleagues describe a 75-year-old male patient suffering from GIST with multiple metastases, achieving stable disease upon 400 mg of Imatinib daily, without major side effects. Wada et al. published the case of a 69-year-old male patient with GIST achieving a partial response without major side effects, also with daily treatment of 400 mg Imatinib. Ozdemir and colleagues published a 54-year-old female patient suffering from CML who showed an excellent response, with achievement of molecular and cytogenetic remission following 3 months of treatment with 400mg of Imatinib daily; no significant side effects occurred during follow-up [4].

Pappas et al. analyzed serial blood samples taken from a patient with GIST and metastasis to the liver, who was undergoing hemodialysis and was treated with Imatinib 400 mg/day [5]. Results were comparable to control samples taken from patients receiving the same treatment, but with normal renal function. The authors concluded that standard doses of 400 mg/day may be safely maintained in patients undergoing hemodialysis.

Regarding other TKIs, one paper on the feasibility of Nilotinib treatment in the hemodialysis setting has been published to date, with 3 cases suffering from CML [6]. Pharmacokinetics in all three patients showed no significant difference between the plasma concentrations of Nilotinib before and after dialysis, demonstrating that, just like Imatinib, Nilotinib is not cleared by hemodialysis and that treatment is feasible and effective.

Further pharmacological data on the use of TKIs in the dialysis setting is lacking. However, with a rising prevalence of CML patients receiving long-term treatment with Imatinib or other TKIs, the prevalence of such patients undergoing hemodialysis is also expected to rise, even though this is not reflected in recent studies or publications. Typically, this patient group is excluded from clinical trials of Imatinib and other TKIs.

As yet, no data has been published on Imatinib treatment in patients with Ph+ ALL undergoing hemodialysis, even though TKIs are now regularly used in combination with chemotherapy in such patients [7]. While second generation TKIs are now preferred for the treatment of Ph+ ALL, our data is still relevant for hemodialysis patients receiving treatment with Imatinib, regardless of the underlying malignancy.

Our patient died due to paralytic ileus shortly after starting hemodialysis therapy. Nevertheless, the measurements of Imatinib and CGP74599 that we conducted in plasma and dialysate suggest that Imatinib at a dose of 600 mg/d can be safely employed in patients undergoing hemodialysis. Very little of the substance was found in the dialysate, indicating that Imatinib is hardly eliminated by this route. More work is needed to determine the optimal safe dose of Imatinib in patients on hemodialysis.

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