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Pharmacokinetics of Four Tyrosine Kinase Inhibitors in Adult and Paediatric Chronic Myeloid Leukaemia Patients

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Abstract: Tyrosine Kinase Inhibitors work by blocking the tyrosine kinases responsible of the dysregulation of intracellular signalling pathways in tumour cells. This study looked at the impact of age and sex on the levels of imatinib, dasatinib, nilotinib, and ponatinib in plasma and cerebrospinal fluid samples of patients with chronic myeloid leukaemia. Imatinib and dasatinib were used to treat the majority of the enrolled patient and most of them were paediatrics. The 82.4% of patients were men; however, sex-related differences in drugs pharmacokinetics were not found. Age and imatinib plasma concentration were found to be inversely correlated. The dasatinib concentrations in plasma were found to be substantially lower than those found in cerebrospinal fluid, particularly in paediatrics. Analysing the obtained data, we can state that Therapeutic Drug Monitoring is a useful method for adjusting a patient treatment schedule depending on drug concentrations in biological fluids. The use of Therapeutic Drug Monitoring in conjunction with Tyrosine Kinase Inhibitors for the treatment of chronic myeloid leukaemia is supported by a number of sources of evidence. As a result, as the research develops, Tyrosine Kinase Inhibitors Therapeutic Drug Monitoring classification needs to be refined in terms of factors like sexes and ages.

Keywords: dasatinib; imatinib; nilotibin; ponatinib; children; therapeutic drug monitoring; sex and gender pharmacology; personalized medicine

1. Introduction

Ionizing radiation exposition is a known cause for chronic myeloid leukaemia (CML), which is a malignant neoplastic pathology by hematopoietic pluripotent stem cells [1]. In the 90% of cases the diagnosis is made thanks to abnormal values in blood tests, in particular leucocytosis. The leukocyte formula outlines: neutrophilia; decreased erythrocyte component; normal reticulocytes and increased blood platelets in the 50% of cases. The most frequent clinic symptom is splenomegaly and macule nodular or urticarious eruptions [2].

Treatment requires drugs monitoring (therapeutic drug monitoring - TDM), in order to improve the effectiveness of cancer therapy, allowing to customize doses and limit side effects [3,4].

Imatinib, commercially known as Glivec®, is a drug designed for the treatment of CML, acute myeloid leukaemia and gastrointestinal cancer. The recommended daily dose is 400-800mg, to be given orally. Imatinib bioavailability is almost complete (98%) and does not depend on food assumption. The drug absorption in the gastrointestinal tract is quick (1-2 hours after the

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administration and with a plasmatic peak after 2-4 hours) and the distribution is mostly performed by bonds with plasmatic proteins. The Imatinib metabolism is hepatic, the excretion is biliary and urinary. Imatinib's half-life is about 18 hours [5].

The development of resistances is a relevant limit to the therapy with imatinib, because of which new and more efficient drugs, such as dasatinib and nilotinib, have been developed [6].

Dasatinib, commercially known as Spycel®, is still a Tyrosine Kinase Inhibitor (TKI) approved for adult patients with CML. The initial oral dose in chronic patients is 100mg/day, while in the accelerated phase, in the myeloid blastic and lymphoid leukaemia and in the acute lymphoblastic leukaemia is 70mg (1 tab in the morning and 1 in the evening). Dasatinib is rapidly absorbed with a concentration peak in 0.5-3 hours after the administration. Dasatinib presents a high distribution volume (>3l/kg) performed by bonds with plasmatic proteins; the oral availability varies between 14-34%, and average half-life is about 1.3-5 hours. Drug metabolism is hepatic, the excretion is faecal and renal [7].

Nilotinib, commercially known as Tasigna®, like imatinib and dasatinib is a Bcr-Abl kinase selective inhibitor, capable of inhibiting the proliferation and inducting apoptosis. Nilotinib is used for the treatment of CML adults intolerants, or resistant, to the imatinib therapy. As does imatinib, nilotinib inhibits the tyrosine-kinase protein's activity, but with a strength 20-50 higher than imatinib. 400 mg of nilotinib has to be taken twice a day without food assumption for at least 2 hours before the intake and 1 hour after it; bioavailability is in fact increased through food assumption. Nilotinib's bioavailability is about 30% with a concentration peak in 3 hours after the administration. The nilotinib metabolism is hepatic, the excretion is faecal and biliary, and the average half-life is about 15 hours [8].

Ponatinib, commercially known as Iclusig®, is multi-target kinase inhibitor, anyway its primary cellular target is Bcr-Abl. Iclusig® is used also for Philadelphia-positive acute lymphoblastic leukaemia (Ph+ ALL), as no other TKI therapy is indicated. 45mg has to be taken once daily for 28 days, food assumption does not affect the absorption. Half-life is about 24 hours and the peak concentration is observed within 6 hours after the administration. Ponatinib is metabolized through multiple pathways and eliminated mostly in faeces [9].

The aim of this study was to examine the influence of age and sex on plasma and cerebrospinal fluid (CSF) concentrations of four different TKIs (imatinib, dasatinib, nilotinib and ponatinib) in CML patients.

2. Materials and Methods

2.1. Patients

After obtaining their informed consent, CML patients receiving regular doses of imatinib, dasatinib, ponatinib or nilotinib, underwent blood and, in some cases, CSF sampling for the purpose of measuring the drug concentrations at the end of dosing interval (Cthrough). These data were routinely recorded during daily clinical practice as a quality assurance measure and in order to explore improvements in the quality of services. Ethics committee approval was not required but research project was the same submitted to local ethics committee (Prot. N° 2002, approved). Confidentiality was guaranteed in data collection, analysis and dissemination phase, by presenting the results in aggregate form. Collected data were: age, sex, CML diagnosis and TKI treatments.

2.2. Chemicals

Imatinib, nilotinib dasatinib, ponatinib, triethylamine, methanol and acetonitrile were purchased from Sigma-Aldrich (Milan, Italy). A Milli DI system from Millipore (Milan, Italy) were used to create High Pressure Liquid Chromatography (HPLC)-grade water.

2.3. Stock Solutions, Calibration Standards (STDs), Quality Controls (QCs), Plasma Patients Samples

The Blood Bank of S. Luigi Hospital (Orbassano, Italy) generously provided blank plasma from healthy donors. This plasma was used to prepare STDs and QCs. Drug stock solutions were created

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in methanol at a final concentration of 1 mg/mL and kept at -4°C for no longer than three months. The internal standard (IS) for dasatinib, imatinib and ponatinib evaluations was nilotinib, whereas for the nilotinib evaluation, the IS was imatinib. The 50 g/mL methanol-based IS solutions were prepared and utilized right away. The highest calibration standard (STD8) and the highest quality control (QC5) were made by diluting donors' blank plasma serially with the other STDs and QCs, and the highest calibration standard (STD8) and QC5 were made by adding a specific volume of stock solutions to blank plasma. All drugs used the same calibration range and QC concentrations (STDs: 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, 10 µg/mL; QCs: 0.05, 0.5, 5 µg/mL). Prior to analysis, the STDs and QCs were kept at -4°C for no more than three months, avoiding multiple freeze-thaw cycles.

Plasma patients' samples were obtained after blood samples centrifugation at 1,500 g for 10 minutes at 4°C. Plasma patients' samples were kept at -4°C till HPLC coupled with ultraviolet detection (UV) analysis was performed. CSF samples were directly frozen till HPLC-UV analysis was performed.

2.4. Sample Preparation

Patients plasma and CSF samples, STDs and QCs were all treated with the following procedure: firstly, for dasatinib and ponatib, 50µl of IS were added to 500µl of sample. Then, 500µl of C_2H_3N were used for the deproteinization and vortexed for 30 seconds before carrying out the centrifugation (15' at 12.000rpm). The following steps need the usage of a void pump: C18 Solid Phase Extraction (SPE) columns were conditioned with 1ml of CH_3OH and 1ml of H_2O; 800µl of the obtained sample supernatant has been transferred onto the SPE columns, with 1ml of H_2O. After removing the waste, 500µl of CH_3OH was added, therefore the solution needed to evaporate until a pellet was obtained. Finally, 250µl of mobile phase was added: the solution was then ready for the HPLC-UV analysis.

Differently, for nilotinib and imatinib, 50µl of IS were added to 500µl of plasma or CSF samples. Then, 750µl of extracting solution (C_2H_3N:CH_3OH 50:50) has been added and vortexed for 30 seconds before carrying out the centrifugation (10' at 12.000rpm). The solution was then ready for the HPLC-UV analysis.

2.5. Chromatographic System and Conditions

The chromatographic analysis for the intracellular quantification of the four drugs has been carried out using a HPLC-UV system. The chromatographic separation has been realized at 40°C using a HyPURITY C18 (ThermoScientific, Monza, Italy) 150x4.6mm 3µ column. For the chromatographic run has been used a mobile phase constituted by a 40% of solution A (72.5% H_2O + 25% CH_3OH + 2.5% $C_6H_{15}N$), 40% C_2H_3N, 20% CH_3OH. The analysis was carried out at the constant flow rate of 0.9 mL/min at 35°C in an isocratic condition. The eluate was monitored at 267 nm.

2.6. Statistical analysis

For statistical analysis continuous variables were described using mean and standard deviations (SD) or median and interquartile range (IQR) according to their distribution. Categorical variables were described using frequencies and percentages. Differences between males and females were tested performing the Mann-Whitney U test or the Fisher exact test, when appropriate. Pearson linear correlation coefficient (r) was used to investigate the strength of the association between two quantitative variables. Since the analysis was carried out at visit-level, the Huber-White estimator was used to adjust correlation between multiple observations on the same patient. Odds Ratios (OR) and their 95% confidence intervals (95% CI) were reported. Firth's correction was applied to reduce the bias of the estimates due to small number of events. All the tests were performed with IBM SPSS Statistics 25.0 for Windows (Chicago, Illinois, USA). The level of significance was set at 0.05.

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3. Results

3.1. Study Population

We enrolled 153 CML diagnosed patients. The flow chart of patient's distribution is shown in Figure 1.

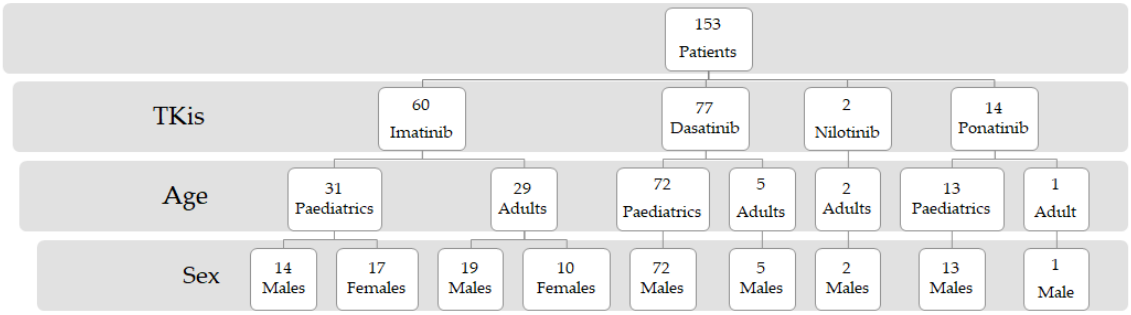

Figure 1. Flow chart of patients' distribution.

Demographics and pharmacological characteristics were reported in Table 1 stratified by drug assumed and age (paediatrics and adults).

Table 1. Demographics and pharmacological characteristics of the enrolled patients.

	All	Imatinib	Dasatinib	Nilotinib	Ponatinib
N	153	60	77	2	14
Males (N, %)	126, 82.4	33, 55	77, 100	2	14
Females (N, %)	27, 17.6	27, 45	0	0	0
Median age (years; IQR)	14 (12-17)	15 (25-56.75)	13 (12-17)	52 (50-54)	14 (13-16.5)
Paediatrics (N, %)	116, 75.8	31, 51.7	72, 93.5	0	13, 92.9
Median paediatric age (years; IQR)	13 (12-14)	13 (9-14)	13 (12-14)	/	14 (13-14)
Adults (N, %)	37, 24.2	29, 48.3	5, 6.5	2, 100	1, 7.1
Median adult age (years; IQR)	54 (42.5-58)	57 (50.5-59)	18 (18-48)	52 (50-54)	/
Plasma sampling (N, %)	111, 72.5	60, 100	39, 50.6	2, 100	10, 71.4
Plasmatic concentrations (μg/mL)	/	1.82 (0.88-2.93)	0.06 (0.03-0.33)	0.19 (0.16-0.22)	0.19 (0.15-0.51)
Cerebrospinal fluid sampling (N, %)	42, 27.5	0	38, 49.4	0	4, 28.6
Cerebrospinal fluid concentrations (μg/mL)	/	/	0.11 (0.06-0.32)	/	0.65 (0.18-1.65)

* IQR: Interquartile range.

3.2. Imatinib Pharmacokinetics

A border line correlation between imatinib plasma concentration and age has been observed: p=0.073, r=-0.233. No significant influence of sex and age groups (paediatrics versus adults) has been observed with the Mann-Whitney test. No statistically significant results have been observed considering paediatrics and adults separately.

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3.3. Dasatinib Pharmacokinetics

With Mann-Whitney test, age groups significantly influence dasatinib plasma concentrations (p=0.022): in paediatrics (N=36; median 0.05 µg/mL, IQR 0.27-0.13 µg/mL) drug concentrations are higher than in adults (N=3; median 0.4 µg/mL, IQR 0.28-0.74 µg/mL) as showed in Figure 2.

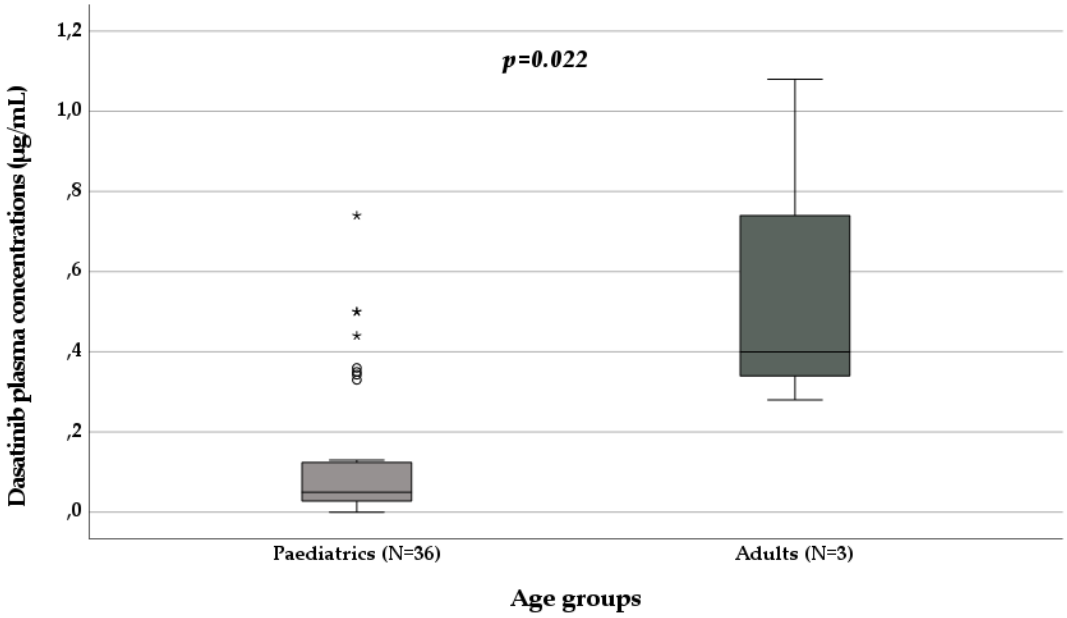

Figure 2. Influence of age on dasatinib plasma concentration [µg/mL] (p=0.022). Box plot of dasatinib plasma concentration distribution in paediatric and adult patients; boxes and black lines in boxes represent respectively interquartile ranges (IQR) and median values; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Considering plasmatic and CSF matrices, a statistically significant influence has been observed on drug concentrations (p=0.038): plasmatic levels (N=39; median 0.06 µg/mL, IQR 0.03-0.33 µg/mL) are lower than CSF ones (N=38; median 0.11 µg/mL, IQR 0.06-0.32 µg/mL) as showed in Figure 3.

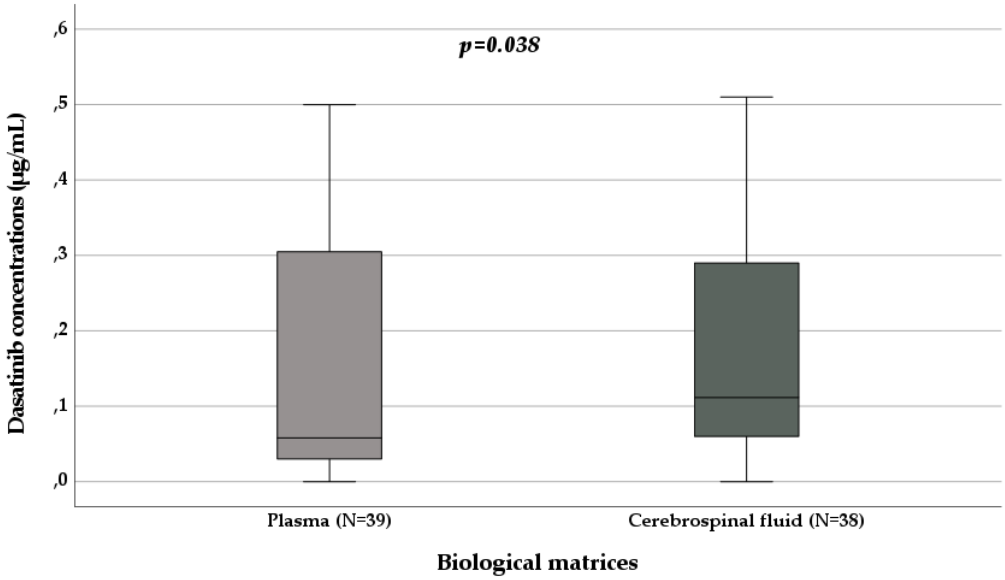

Figure 3. Distribution of dasatinib levels in plasma and CSF samples [µg/mL] (p=0.038). Box plot of dasatinib plasma concentration distribution in plasma and CSF samples; boxes and black lines in

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boxes represent respectively interquartile ranges (IQR) and median values; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Separating adults and paediatric patients, the significant difference has been retained only in paediatrics: plasmatic levels (N=36; median 0.05 μg/mL, IQR 0.03-0.13 μg/mL) are lower than CSF ones (N=36; median 0.11 μg/mL, IQR 0.05-0.29 μg/mL) as showed in Figure 4.

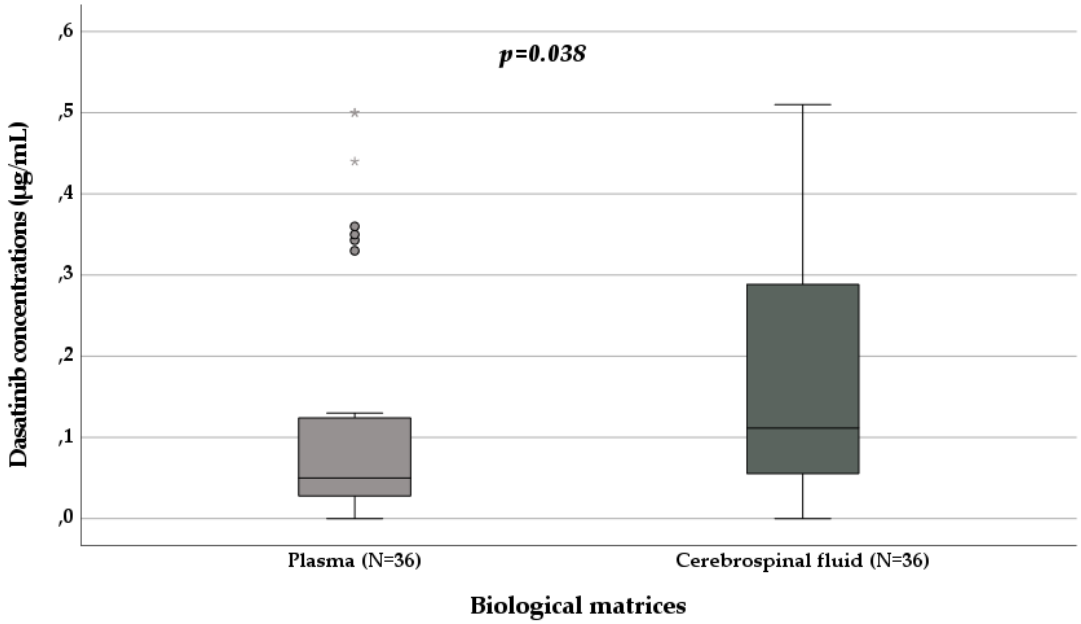

Figure 4. Distribution of dasatinib levels in plasma and CSF samples [μg/mL] (p=0.038), considering paediatric patients. Box plot of dasatinib plasma concentration distribution in plasma and CSF samples; boxes and black lines in boxes represent respectively interquartile ranges (IQR) and median values; open dots and stars represent outlier values. Median values (horizontal line), IQR (bars), patient values (black square), highest and lowest value (whiskers) and p value are shown.

Pearson correlation showed no significant results between the considered variables.

3.4. Nilotinib and Ponatinib Pharmacokinetics

No factors significantly influenced or were correlated with nilotinib an ponatinib concentrations.

4. Discussion

TK protein are enzymes able to transfer the ATP terminal phosphate to a substrate protein. Those proteins play a relevant role as pathways modulators in the cellular signal transduction, since they are able to mediate events such as differentiation, proliferation and communication between cells. Therefore, an oncogenic mutation of TK proteins leads to a cellular deregulation, and consequent imbalance between cellular division, growth and apoptosis. TK proteins seems to be an important therapeutic target in cancer fight [10].

Here we describe the Ctrough concentration at the end of dosing interval of four different TKIs, imatinib, dasatinib, nilotinib and ponatinib, in CML patients. The data have been presented also considering paediatrics (with less the 18 years old) and adults, and plasma and CSF samples separately.

The current aim of CML patient's treatment is to increase quality of life and survival while minimizing late problems related to TKIs use. As a result, the cessation of TKIs therapy, also known as treatment-free remission (TFR), has garnered interest. TFR was listed as a new treatment objective in the 2020 European LeukemiaNet guidelines for CML patients who have achieved a deep molecular

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response [11]. In order to induce a deeper therapeutic response at an earlier time, the treatment milestones following TKIs administration were also modified [11]. Imatinib has been the sole available TKI treatment since the early 2000s. However, third-generation TKI ponatinib with significant efficacy for T315I mutations, for which imatinib and second generations TKIs are resistant, as well as second-generation TKIs, with higher affinity for BCR-ABL1, became accessible and it has been introduced in clinical practice. Because of these developments, the treatment strategy could be shifted to another TKI agent even in the event of a significant adverse event or the BCR-ABL1 mutation, which is the primary reason for resistance. As a result, the first-line treatments for CML include imatinib and a second-generation TKI, such as nilotinib and dasatinib. The response to second-generation TKIs is quicker than imatinib in the first-line treatment of CML [12–14]. Conversely, in previous clinical trials of second-generation TKIs and imatinib, except for the 5-year progression-free survival and overall survival of nilotinib 400 mg BID group in the ENESTnd trial [15], the outcomes were equivalent [14,16,17]. Therefore, clinical trials have not demonstrated the benefits of utilizing second-generation drugs from the standpoint of survival. Despite the observational study drawbacks, it was found that the nilotinib and dasatinib outcomes of the New TARGET observational study 1 were significantly better than those of the imatinib [18]. Contrarily, second-generations are typically thought to cause more severe side effects than imatinib, including cardiovascular complications. Comorbidities of patients and TKIs side effects should be carefully considered while choosing a TKI. In the case of vascular illness, nilotinib and ponatinib are contraindicated for the treatment of CML [9,11,19,20]. Imatinib is still the first-line treatment that is advised in these situations. As showed in Figure 1, the most patients included in our study were treated with imatinib and dasatinib.

In addition, TKIs treatment choices depend in part on the CML patients ages. This target therapy may be stopped in younger individuals if a full molecular remission is achieved permanently. In this case, second-generation TKIs might be preferable over imatinib due to their higher rate of full molecular remission. On the other hand, older people are unaffected when TKI medication is stopped [21]. In our cohort most of the patients were under 18 years of age.

Sex pharmacology approach in a wide field, often very difficult to pursue. It is yet unclear how sex differences, particularly those resulting from sex-specific immunological responses to CML, can affect patients' clinical outcomes. As reported in literature, men are more likely than women to develop CML, with M:F ratio ranging between 1.2 and 1.7 [22–24]. In younger age groups, the incidence of the sex difference is less pronounced. This sex-related incidence is confirmed in our study, where the 82.4% of enrolled patients were males. Evaluating drugs pharmacokinetics, we did not observe sex-related differences. In imatinib pharmacokinetic investigations, no sex differences have been seen [25]. Also, treatment-related toxicity and quality of life improvement do not seem to be sex-specific [26]. Women appear to have a better outcome or at least a comparable outcome when presenting with less favorable prognostic variables, in contrast, there are sex-related differences in clinical outcome following imatinib therapy [27,28]. Evaluating dasatinib, although the STIM trial found that male sex was a positive predictive factor for treatment free remission, most TKI discontinuation trials found that patient sex had no effect on this type of remission [29–31]. While female patients who stopped TKIs therapy were predominately enrolled in the D-NewS Study, male and female patients were roughly equally represented in the first-line DADI and DASFREE studies [29–31].

Based on population pharmacokinetic studies, imatinib volume of distribution appears to be slightly influenced by age; it increases by 12% in people over 65, although this effect is not thought to be clinically significant [32]. Additionally, it has been demonstrated that limited clearance and low bodyweight are associated [33,34]. Thirty-one children participated in a phase I research for the treatment of Ph+ leukaemia in youngsters [35]. The findings demonstrated that imatinib administered once daily to children produced plasma concentrations at steady state and mean area under the concentration that were equivalent to those observed in adults. We observed an inverse correlation between age and imatinib plasma concentration: drug levels decreased with increasing age of patients. On the contrary, Wilkinson and Larson reported that patients with elevated imatinib trough

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values were more likely to be 50 years of age or older, which is likely connected to an impaired liver or metabolism in older patients [36,37].

Eventually, we evaluated plasma and CSF concomitant samples at the Ctrough drug point; we observed that plasma dasatinib concentrations were significantly lower than those reported in CSF. Particularly, separating adult and paediatrics, the difference has been retained only in children. Dasatinib property to substantially cross the blood brain barrier is not universally agreed upon, and central nervous system reactions have been inconsistent [38–40]. Due to the liver quick cytochrome P450 metabolism, only a very little drug amount is found in plasma. Targeted therapy blood brain barrier penetration is difficult to predict, however there are a few important physiochemical traits known to affect central nervous system penetration: agent must be small, lipophilic and without affinity for the main blood brain barrier efflux pumps, such as p-glycoprotein (PGP) and breast-cancer resistance protein (BRCP). Dasatinib is a substrate of PGP and BCRP, small (506 g/mol) and lipophilic (consensus logP 2.8) [41]. Studies on dasatinib levels in CSF, however, were above all restricted to case reports [38,42–45].

5. Conclusions

Analysing the obtained data, we can state that TDM is a useful method for adjusting a patient treatment schedule depending on drug concentrations in biological fluids. The use of TDM for TKIs for the treatment of CML is supported by many literature scientific evidences. As a result, as the research develops, TKIs TDM classification needs to be refined in terms of factors like sexes and ages. For these reasons, further studies collecting demographical, pharmacological, especially for co-administered drugs, and genetic information are needed to confirm the observed results. Following the introduction of safe and effective targeted medications, more and more patients are experiencing positive results, which is accompanied by an increase in requests for dose reduction. The era of directing reduction by TDM and putting it into clinical practice in the near future to improve patients' quality of life will dawn upon us when we expand the current knowledge with new studies in the area of personalized medicine.

Author Contributions: Conceptualization, S.A. and S.D.F.; methodology, E.D.; software, F.C..; validation, S.A., and S.D.F.; formal analysis, E.D. and F.C.; data curation, X.X.; writing—original draft preparation, E.D.; writing—review and editing, S.A. and E.D; supervision, S.D.F.; project administration, S.D.F. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Local Ethics Committee of San Luigi Gonzaga University Hospital in Orbassano (Torino) (protocol code Prot. N° 2002, 07/02/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data are not publicly available due to ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gale, R.P. Radiation and leukaemia: Which leukaemias and what doses? *Blood Rev* **2023**, *58*, 101017, doi:10.1016/j.blre.2022.101017.
2. Senapati, J.; Sasaki, K.; Issa, G.C.; Lipton, J.H.; Radich, J.P.; Jabbour, E.; Kantarjian, H.M. Management of chronic myeloid leukemia in 2023 - common ground and common sense. *Blood Cancer J* **2023**, *13*, 58, doi:10.1038/s41408-023-00823-9.
3. Rosti, G.; Castagnetti, F.; Gugliotta, G.; Baccarani, M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol* **2017**, *14*, 141-154, doi:10.1038/nrclinonc.2016.139.

4. Groenland, S.L.; Mathijssen, R.H.J.; Beijnen, J.H.; Huitema, A.D.R.; Steeghs, N. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. *Eur J Clin Pharmacol* **2019**, *75*, 1309-1318, doi:10.1007/s00228-019-02704-2.
5. Clarke, W.A.; Chatelut, E.; Fotoohi, A.K.; Larson, R.A.; Martin, J.H.; Mathijssen, R.H.J.; Salamone, S.J. Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology consensus guidelines for imatinib therapy. *Eur J Cancer* **2021**, *157*, 428-440, doi:10.1016/j.ejca.2021.08.033.
6. Cheng, F.; Li, Q.; Cui, Z.; Hong, M.; Li, W.; Zhang, Y. Dose optimization strategy of the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib for chronic myeloid leukemia: From clinical trials to real-life settings. *Front Oncol* **2023**, *13*, 1146108, doi:10.3389/fonc.2023.1146108.
7. He, S.; Bian, J.; Shao, Q.; Zhang, Y.; Hao, X.; Luo, X.; Feng, Y.; Huang, L. Therapeutic Drug Monitoring and Individualized Medicine of Dasatinib: Focus on Clinical Pharmacokinetics and Pharmacodynamics. *Front Pharmacol* **2021**, *12*, 797881, doi:10.3389/fphar.2021.797881.
8. Tian, X.; Zhang, H.; Heimbach, T.; He, H.; Buchbinder, A.; Aghoghovbia, M.; Hourcade-Potelleret, F. Clinical Pharmacokinetic and Pharmacodynamic Overview of Nilotinib, a Selective Tyrosine Kinase Inhibitor. *J Clin Pharmacol* **2018**, *58*, 1533-1540, doi:10.1002/jcph.1312.
9. Poch Martell, M.; Sibai, H.; Deotare, U.; Lipton, J.H. Ponatinib in the therapy of chronic myeloid leukemia. *Expert Rev Hematol* **2016**, *9*, 923-932, doi:10.1080/17474086.2016.1232163.
10. Zhong, L.; Li, Y.; Xiong, L.; Wang, W.; Wu, M.; Yuan, T.; Yang, W.; Tian, C.; Miao, Z.; Wang, T.; et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal Transduct Target Ther* **2021**, *6*, 201, doi:10.1038/s41392-021-00572-w.
11. Hochhaus, A.; Baccarani, M.; Silver, R.T.; Schiffer, C.; Apperley, J.F.; Cervantes, F.; Clark, R.E.; Cortes, J.E.; Deininger, M.W.; Guilhot, F.; et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* **2020**, *34*, 966-984, doi:10.1038/s41375-020-0776-2.
12. Hughes, T.P.; Saglio, G.; Kantarjian, H.M.; Guilhot, F.; Niederwieser, D.; Rosti, G.; Nakaseko, C.; De Souza, C.A.; Kalaycio, M.E.; Meier, S.; et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood* **2014**, *123*, 1353-1360, doi:10.1182/blood-2013-06-510396.
13. Jabbour, E.; Kantarjian, H.M.; Saglio, G.; Steegmann, J.L.; Shah, N.P.; Boqué, C.; Chuah, C.; Pavlovsky, C.; Mayer, J.; Cortes, J.; et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood* **2014**, *123*, 494-500, doi:10.1182/blood-2013-06-511592.
14. Cortes, J.E.; Gambacorti-Passerini, C.; Deininger, M.W.; Mauro, M.J.; Chuah, C.; Kim, D.W.; Dyagil, I.; Glushko, N.; Milojkovic, D.; le Coutre, P.; et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. *J Clin Oncol* **2018**, *36*, 231-237, doi:10.1200/JCO.2017.74.7162.
15. Hochhaus, A.; Saglio, G.; Hughes, T.P.; Larson, R.A.; Kim, D.W.; Issaragrisil, S.; le Coutre, P.D.; Etienne, G.; Dorlhiac-Llacer, P.E.; Clark, R.E.; et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia* **2016**, *30*, 1044-1054, doi:10.1038/leu.2016.5.
16. Kantarjian, H.M.; Hughes, T.P.; Larson, R.A.; Kim, D.W.; Issaragrisil, S.; le Coutre, P.; Etienne, G.; Boquimpani, C.; Pasquini, R.; Clark, R.E.; et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia* **2021**, *35*, 440-453, doi:10.1038/s41375-020-01111-2.
17. Cortes, J.E.; Saglio, G.; Kantarjian, H.M.; Baccarani, M.; Mayer, J.; Boqué, C.; Shah, N.P.; Chuah, C.; Casanova, L.; Bradley-Garelik, B.; et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol* **2016**, *34*, 2333-2340, doi:10.1200/JCO.2015.64.8899.
18. Kizaki, M.; Takahashi, N.; Iriyama, N.; Okamoto, S.; Ono, T.; Usui, N.; Inokuchi, K.; Nakaseko, C.; Kurokawa, M.; Sumi, M.; et al. Efficacy and safety of tyrosine kinase inhibitors for newly diagnosed chronic-phase chronic myeloid leukemia over a 5-year period: results from the Japanese registry obtained by the New TARGET system. *Int J Hematol* **2019**, *109*, 426-439, doi:10.1007/s12185-019-02613-1.
19. Baccarani, M.; Abruzzese, E.; Accurso, V.; Albano, F.; Annunziata, M.; Barulli, S.; Beltrami, G.; Bergamaschi, M.; Binotto, G.; Bocchia, M.; et al. Managing chronic myeloid leukemia for treatment-free remission: a

proposal from the GIMEMA CML WP. *Blood Adv* **2019**, *3*, 4280-4290, doi:10.1182/bloodadvances.2019000865.

20. Oehler, V.G. First-generation vs second-generation tyrosine kinase inhibitors: which is best at diagnosis of chronic phase chronic myeloid leukemia? *Hematology Am Soc Hematol Educ Program* **2020**, *2020*, 228-236, doi:10.1182/hematology.2020000108.
21. Jabbour, E.; Kantarjian, H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am J Hematol* **2020**, *95*, 691-709, doi:10.1002/ajh.25792.
22. Höglund, M.; Sandin, F.; Hellström, K.; Björeman, M.; Björkholm, M.; Brune, M.; Dreimane, A.; Ekblom, M.; Lehmann, S.; Ljungman, P.; et al. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: report from the population-based Swedish CML registry. *Blood* **2013**, *122*, 1284-1292, doi:10.1182/blood-2013-04-495598.
23. Rohrbacher, M.; Hasford, J. Epidemiology of chronic myeloid leukaemia (CML). *Best Pract Res Clin Haematol* **2009**, *22*, 295-302, doi:10.1016/j.beha.2009.07.007.
24. Berger, U.; Maywald, O.; Pfirrmann, M.; Lahaye, T.; Hochhaus, A.; Reiter, A.; Hasford, J.; Heimpel, H.; Hossfeld, D.K.; Kolb, H.J.; et al. Gender aspects in chronic myeloid leukemia: long-term results from randomized studies. *Leukemia* **2005**, *19*, 984-989, doi:10.1038/sj.leu.2403756.
25. Peng, B.; Lloyd, P.; Schran, H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* **2005**, *44*, 879-894, doi:10.2165/00003088-200544090-00001.
26. Aziz, Z.; Iqbal, J.; Aaqib, M.; Akram, M.; Saeed, A. Assessment of quality of life with imatinib mesylate as first-line treatment in chronic phase-chronic myeloid leukemia. *Leuk Lymphoma* **2011**, *52*, 1017-1023, doi:10.3109/10428194.2011.560310.
27. Lee, J.P.; Birnstein, E.; Masiello, D.; Yang, D.; Yang, A.S. Gender and ethnic differences in chronic myelogenous leukemia prognosis and treatment response: a single-institution retrospective study. *J Hematol Oncol* **2009**, *2*, 30, doi:10.1186/1756-8722-2-30.
28. Björkholm, M.; Ohm, L.; Eloranta, S.; Derolf, A.; Hultcrantz, M.; Sjöberg, J.; Andersson, T.; Höglund, M.; Richter, J.; Landgren, O.; et al. Success story of targeted therapy in chronic myeloid leukemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. *J Clin Oncol* **2011**, *29*, 2514-2520, doi:10.1200/JCO.2011.34.7146.
29. Yamaguchi, H.; Takezako, N.; Ohashi, K.; Oba, K.; Kumagai, T.; Kozai, Y.; Wakita, H.; Yamamoto, K.; Fujita, A.; Igarashi, T.; et al. Treatment-free remission after first-line dasatinib treatment in patients with chronic myeloid leukemia in the chronic phase: the D-NewS Study of the Kanto CML Study Group. *Int J Hematol* **2020**, *111*, 401-408, doi:10.1007/s12185-019-02801-z.
30. Kimura, S.; Imagawa, J.; Murai, K.; Hino, M.; Kitawaki, T.; Okada, M.; Tanaka, H.; Shindo, M.; Kumagai, T.; Ikezoe, T.; et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. *Lancet Haematol* **2020**, *7*, e218-e225, doi:10.1016/S2352-3026(19)30235-2.
31. Shah, N.P.; García-Gutiérrez, V.; Jiménez-Velasco, A.; Larson, S.; Saussele, S.; Rea, D.; Mahon, F.X.; Levy, M.Y.; Gómez-Casares, M.T.; Pane, F.; et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. *Leuk Lymphoma* **2020**, *61*, 650-659, doi:10.1080/10428194.2019.1675879.
32. Lyseng-Williamson, K.; Jarvis, B. Imatinib. *Drugs* **2001**, *61*, 1765-1774; discussion 1775-1766, doi:10.2165/00003495-200161120-00007.
33. Dagher, R.; Cohen, M.; Williams, G.; Rothmann, M.; Gobburu, J.; Robbie, G.; Rahman, A.; Chen, G.; Staten, A.; Griebel, D.; et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* **2002**, *8*, 3034-3038.
34. Pindolia, V.K.; Zarowitz, B.J. Imatinib mesylate, the first molecularly targeted gene suppressor. *Pharmacotherapy* **2002**, *22*, 1249-1265, doi:10.1592/phco.22.15.1249.33482.
35. Champagne, M.A.; Capdeville, R.; Krailo, M.; Qu, W.; Peng, B.; Rosamilia, M.; Therrien, M.; Zoellner, U.; Blaney, S.M.; Bernstein, M.; et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. *Blood* **2004**, *104*, 2655-2660, doi:10.1182/blood-2003-09-3032.
36. Larson, R.A.; Druker, B.J.; Guilhot, F.; O'Brien, S.G.; Riviere, G.J.; Krahnke, T.; Gathmann, I.; Wang, Y.; Group, I.I.R.I.v.S.S. Imatinib pharmacokinetics and its correlation with response and safety in chronic-

phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood* **2008**, *111*, 4022-4028, doi:10.1182/blood-2007-10-116475.

37. Wilkinson, G.R. Cytochrome P4503A (CYP3A) metabolism: prediction of in vivo activity in humans. *J Pharmacokinet Biopharm* **1996**, *24*, 475-490, doi:10.1007/BF02353475.
38. Porkka, K.; Koskenvesa, P.; Lundán, T.; Rimpiläinen, J.; Mustjoki, S.; Smykla, R.; Wild, R.; Luo, R.; Arnan, M.; Brethon, B.; et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood* **2008**, *112*, 1005-1012, doi:10.1182/blood-2008-02-140665.
39. Frigeri, F.; Arcamone, M.; Luciano, L.; Di Francia, R.; Pane, F.; Pinto, A. Systemic dasatinib fails to prevent development of central nervous system progression in a patient with BCR-ABL unmutated Philadelphia chromosome-positive leukemia. *Blood* **2009**, *113*, 5028-5029, doi:10.1182/blood-2008-11-191080.
40. Papageorgiou, S.G.; Pappa, V.; Economopoulou, C.; Tsirigotis, P.; Konsioti, F.; Ionnidou, E.D.; Chondropoulos, S.; Vasilatou, D.; Papageorgiou, E.; Economopoulos, T.; et al. Dasatinib induces long-term remission in imatinib-resistant Philadelphia chromosome-positive acute megakaryoblastic leukemia but fails to prevent development of central nervous system progression. *Leuk Res* **2010**, *34*, e254-256, doi:10.1016/j.leukres.2010.03.032.
41. Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep* **2017**, *7*, 42717, doi:10.1038/srep42717.
42. Zhou, H.S.; Dai, M.; Wei, Y.; Wang, Q.; Xu, N.; Yin, C.; Meng, F. Isolated central nervous system relapse in patient with blast-crisis chronic myeloid leukemia in durable complete cytogenetic remission on dasatinib treatment: pharmacokinetics and ABL mutation analysis in cerebrospinal fluid. *Leuk Lymphoma* **2013**, *54*, 1557-1559, doi:10.3109/10428194.2012.745933.
43. Kondo, T.; Tasaka, T.; Matsumoto, K.; Matsumoto, R.; Koresawa, L.; Sano, F.; Tokunaga, H.; Matsuhashi, Y.; Nakanishi, H.; Morita, K.; et al. Philadelphia chromosome-positive acute lymphoblastic leukemia with extramedullary and meningeal relapse after allogeneic hematopoietic stem cell transplantation that was successfully treated with dasatinib. *Springerplus* **2014**, *3*, 177, doi:10.1186/2193-1801-3-177.
44. Levêque, D.; Becker, G.; Bilger, K.; Natarajan-Amé, S. Clinical Pharmacokinetics and Pharmacodynamics of Dasatinib. *Clin Pharmacokinet* **2020**, *59*, 849-856, doi:10.1007/s40262-020-00872-4.
45. Gong, X.; Li, L.; Wei, H.; Liu, B.; Zhou, C.; Zhang, G.; Liu, K.; Lin, D.; Gong, B.; Wei, S.; et al. A Higher Dose of Dasatinib May Increase the Possibility of Crossing the Blood-brain Barrier in the Treatment of Patients With Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia. *Clin Ther* **2021**, *43*, 1265-1271.e1261, doi:10.1016/j.clinthera.2021.05.009.