Journal of Pharmacreations

PharmaCreations

Pharmacreations | Vol. 1 | Issue 1 | Mar - 2014

Journal Home page: www.pharmacreations.com

Academic Essay *Open Access*

Imatinib Mesylate: A Time Tested Solution For Chronic Myeloid Leukemia (CML)

***Khan N.[1], Abbas A.[1,2]**

[1]Department of Pharmacy, Health and Well being, Faculty of Applied Sciences, University of Sunderland, England, United Kingdom

[2]Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi, Sindh, Pakistan.

*** Corresponding author: Nabeel Khan.**

E-mail id: bg48mz@student.sunderland.ac.uk

ABSTRACT

Imatinib mesylate is a time tested solution for the chronic myeloid leukemic patients, it is a tyrosine kinase inhibitor which was approved from Federal Drug Agency FDA in 2001 and used in the initial phase of CML, and it can also be used in those patients who are not responding to interferon alpha-1 therapy in late stages. Imatinib mesylate has good (98%) bioavailability after oral administration. Studies showed that the drug contains mild adverse effects in animal models and was found to be suitable in all aspects for humans; however teratogenicity were also reported that is why it is not recommended for pregnant women.

Keywords: Imatinib mesylate; Chronic Myeloid Leukemia; CML

INTRODUCTION

Imatinib mesylate is a tyrosine kinase inhibitor functioned to competitively inhibit BCR-ABL tyrosine kinase activity it is suggested as the first line treatment for patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML).[1] It is a 2-phenylaminopyrimidine derivative. The pharmacology of imatinib revels that the drug inhibits the BCR-ABL tyrosine kinase and this inhibition results to reduce the uncontrolled proliferation of WBC's.[1][2] Tyrosine kinase is activated by the abnormal gene BCR-ABL on the 'Philadelphia' chromosome, it is due to fusion between Abelson (ABL) tyrosine kinase gene at chromosome 9 and break point cluster (BCR) gene at chromosome 22, resulting in the chimeric oncogene BCR-ABL and active BCR-ABL tyrosine kinase has been implicated in the pathogenesis of CML[2]. The enzymatic activity catalysed by a tyrosine kinase and imatinib blocks the site for binding so that the tyrosine kinase activity gets inhibited. It has good oral absorption, the bioavailability accounts about 98% and the peak plasma levels are achieved within 2-4 hours. 95% of the drug remains bounded with the protein and majorly to alpha-1-acid glycoprotein. Imatinib is broadly metabolized by cytochrome P450 enzymes, principally to the N-demethylated piperazine. It is primarily metabolized by CYP3A4 and to minor extent by other isoenzymes of cytochrome P540 enzyme system.[3] The elimination profile of imatinib imparts major part in the feces and most of the drug is in metabolite form. Complete elimination of the

drug from body takes around 7 to 8 days. 68 % of the dose is excreted in feces and 31% in urine. About 25% of the dose remains unchanged and 5% of the drug found in urine and 20% in faces excluding this the other excreted part are the metabolites of the drug. [1][2]

Imatinib mesylate is a good competitive inhibitor of CYP450 enzymes, noteworthy elevated peak concentration of simvastatin has been perceived during concurrent therapy. Particular caution should be exercised when imatinib is administered concomitantly.[4] It has been reported that imatinib may increase the activity of drugs that are metabolized by CYP3A4. Imatinib imparts mild to moderate adverse effects.[4][5] Most common reported adverse events includes; nausea, vomiting, diarrhoea, abdominal pain, haemorrhage, fluid disturbance /oedema, muscular cramps, arthralgia, fatigue. Unusual weight gain should be evaluated and managed appropriately. Some patient may develop neutropenia and thrombocytopenia.

Studies showed that it is recommended that patients on imatinib must have a complete blood count every week during initial treatment and monthly afterword.[6] Imatinib extensively metabolized in the liver, the drug may affect the transaminases and bilirubin levels hence, liver function test are recommended to monitor closely. A randomized clinical trial reported that long term use of imatinib may account for hepatic and renal toxicities and sometime immunosuppression therefore; it is recommended that patients on imatinib therapy should be closely monitored on regular basis.[7] During the initial clinical trials the drug showed teratogenic effects hence; it is not recommended in pregnancy as it is classified in pregnancy Category D. The recommended dose of Imatinib (Glivec ®) is 400 mg [1][8] once daily for patients in chronic phase of CML and 600 mg once a day for patients in accelerated phase or blast crisis.[8][9] For patients not achieving haematological remission after 3 months of management, 600 mg of imatinib is recommended for them. For paediatrics it is advised to not exceed 600 mg per day. The drug should be hold if the liver is severely damaged and if the patient is hepatically impaired then the dose should be reduced by 25%. [10]

DISCUSSION

Imatinib mesylate is mainly indicated for the treatment of Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) it is mainly indicated for newly diagnosed patients who are currently categorized into the chronic phase. Tyrosine kinase inhibitors are placed as the first line treatment for chronic phase of CML and imatinib is the most prior choice. TKI's are also indicated in the other phases of CML after the failure of interferon-alpha. The drug is orally absorbed, the bioavailability is 98% and the drug reaches the peak plasma concentration in 2-4 hours. Almost 95% of the drug remains bound with the alpha-1 acid glycoprotein and the drug got metabolized by CP450 enzyme system and the main enzyme responsible for its metabolism is CYP3A4. Major part of the drug excreted in feces. The drug is being placed in the category D of the pregnancy that is why this drug is not recommended for pregnant women. The most common adverse effects includes oedema and muscle cramps the other possible adverse effects could be nausea, vomiting, diarrhoea, abdominal pain, haemorrhage, fluid disturbance, arthralgia and fatigue. Studies showed that complete blood test and liver function test must be done on regular interval throughout the treatment.

CONCLUSION

The first-line treatment for chronic myeloid leukaemia is imatinib, which is a tyrosine kinase inhibitor, the drug imparts good response as compared with the drugs used previously. In a nut shell, this drug has fewer side effects. Many researchers are investigating on numerous aspects involved with in the drug.

REFERENCES

[1] National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. (Accessed 27 November 2013). Available from :http://guidance.nice.org.uk/TA70

[2] Hamada, S., Masago, K., Mio, T., Hirota, S, Mishima, M. Good clinical response to imatinib mesylate in atypical thymic carcinoid With KIT overexpression. Journal of Clinical Oncology. [abstract] [cited 2013 Nov 26]. 2011; (1): e9-e10.

[3] Emmanuel C Besa. Chronic Myelogenous Leukemia. http://emedicine.medscape.com/article/199425-overview#showall (accessed 25 November 2013).

[4] Khan N and Abbas A. A review of Chronic Myeloid Leukemia and its Pharmacotherapy. International Journal of Pharmacotherapy. 2014. 4(2); 65-67 P.

[5] Capdeville, R., Buchdunger, E., Zimmermann, J., Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nature Reviews Drug Discovery. [abstract] [cited 2013 Nov 30] 2002; 1(7): 493-502.

[6] Roeder, I., Horn, M., Glauche, I., Hochhaus, A., Mueller, M. C., Loeffler, M. Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications. Nature medicine. 2006; 12(10): 1181-1184.

[7] Kraft, S. (2011, June 6). "Novartis' Gleevec Cancer "Magic Bullet" Extends Life In GIST Patients." Medical News Today. Retrieved from http://www.medicalnewstoday.com/articles /227624.

[8] Wiley-Blackwell. (2012, February 27). "Leukemia Patients Who Do Not Respond To Interferon Benefit From Imatinib." Medical News Today.Retrieved from: http://www.medicalnewstoday.com /releases/ 242189

[9] Druker, B. J., Sawyers, C. L., Kantarjian, H., Resta, D. J., Reese, S. F., Ford, J. M., Talpaz, M. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. New England Journal of Medicine. 2001; *344*(14): 1038-1042.

[10] Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood. May 15 2002; 99(10):3530-9