CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3620971

Available online at: http://www.iajps.com *Research Article*

PERIORBITAL EDEMA AND OPTIC DISC EDEMA SECONDARY TO USAGE OF IMATINIB MESYLATE IN CHRONIC MYELOID LEUKEMIA PATIENT

Naga Swathi Sree Kavuri*[1], Venkata Ramarao Nallani[1], Deepika Kavuri[2], A. Satish Kumar[3]

[1]Department of Pharmacy Practice, Chalapathi institute of pharmaceutical sciences, Lam, Guntur, Andhra Pradesh, India-522034., [2]MBBS, NRI institute of medical sciences, Sangivalasa, Vishakhapatnam, Andhra Pradesh, India-531162., [3]Associate Professor, Department of Radiotherapy, Government General Hospital, Guntur, Andhra Pradesh, India.

Article Received: November 2019 **Accepted:** December 2019 **Published:** January 2020

Abstract:

Chronic myeloid leukemia is a myeloproliferative disorder. Imatinib mesylate (Gleevec®) is a first line pharmacologic treatment for all phases of chronic myeloid leukemia and for advanced gastrointestinal stromal tumors (GISTs). Imatinib mesylate is generally well tolerated. Well-known ocular side effects for Imatinib are periorbital edema, epiphora, conjunctival hemorrhage, blepharoconjunctivitis, visus alterations and ocular dryness and also optic disc edema is the rare ocular event associated with Imatinib use. Here we reported a case of 58-year-old Caucasian male was diagnosed with Chronic Myeloid Leukemia (CML) and he is treating with Imatinib for 7 years. Patient was presented with moderate periorbital edema along with optic disc edema and these ocular events can be self reducible in our case after suspension of Imatinib for 1 week without any treatment. Prompt consultation with an ophthalmologist can lead to early detection, proper diagnosis and appropriate therapeutic measures.

Keywords: *Chronic myeloid leukemia, Imatinib mesylate, optic disc edema, periorbital edema.*

Corresponding author:

Naga Swathi Sree Kavuri,

Chalapathi Institute of Pharmaceutical Sciences,
Guntur, Andhra Pradesh, India-522034.
Email-Id: swathichoudary1997@gmail.com

QR code

Please cite this article in press Naga Swathi Sree Kavuri et al., ***Periorbital Edema And Optic Disc Edema Secondary To Usage Of Imatinib Mesylate In Chronic Myeloid Leukemia Patient.,*** *Indo Am. J. P. Sci, 2020; 07(01).*

INTRODUCTION:

Imatinib mesylate (Gleevec®) is the first targeted agent for Chronic Myeloid leukemia (CML) and a well-established pharmacologic treatment for advanced gastrointestinal stromal tumors (GISTs) [1]. Imatinib inhibits BCR-ABL tyrosine kinase, the fusion protein created by the Philadelphia chromosome abnormality that characterizes chronic myeloid leukemia. Competitive inhibition at the enzyme's ATP-binding site leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction [2]. Inhibition is not completely selective as imatinib also inhibits the receptor tyrosine kinases for platelet-derived growth factor and c-Kit, a stem cell factor in GIST [3] Cells that express BCR-ABL undergo growth inhibition or apoptosis but normal cells are not affected, sometimes it is generally refer as Tyrosine Kinase Inhibiting Agent (TKIA).

Imatinib mesylate is generally well tolerated, showed dramatically improvement in the prognosis of CML and GIST diseases since their approval. Most frequently occurring side effects include nausea, vomiting, musculoskeletal pain, diarrhea, fatigue, rash, dyspepsia, liver-function abnormalities and edema[4]. But edema may regularly occur anywhere, including the lower extremities and face. Severe patients with chronic myelogenous leukaemia who treated with imatinib mesylate develop mild to moderate generalized fluid retention, pulmonary edema, pericardial effusion, pleural effusion, cerebral edema, ascites, or anasarca is rare[5,6]. It as known ocular adverse events (AEs) related to its treatment are periorbital edema, epiphora, blepharoconjunctivitis, extraocular muscle palsy, and palpebral ptosis [7] Other serious side effects are also relatively uncommon, including Stevens–Johnson syndrome, hemolytic anemia, internal hemorrhage, and hepatotoxicity[8]. Additional rare ocular side effects have been reported, including cystoid macular edema, optic disc edema, and macular ischemia[9–11]. Treatment for most cases of imatinib mesylate-associated edema consists of administering diuretics, decreasing the dosage and sometimes complete cessation of therapy for few weeks, only few severe cases required surgical interventions.

Although periorbital edema is a commonly occuring side effect of imatinib mesylate but optic disc edema is the rare form and periorbital edema is mentioned as a common side effect in the drug insert prepared by the manufacturer and in several recently published reports of clinical trials[12]. To the best of our knowledge, there are no particular published case reports to date which contains both moderate periorbital edema along with optic disc edema as a ocular side effects associated with 7 years use of Imatinib mesylate for treatment of CML.

CASE REPORT:

A 58-year-old Caucasian male was diagnosed with Chronic Myeloid Leukemia (CML) in June 2012. He was treated with Imatinib mesylate 400mg a day since that data and after 2years of initiation of therapy with Imatinib the patient was achieved minimal remission and also his White Blood Cells (WBC) count was increased in hematologic monthly follow-up. The oncologist decided to increase the dose of Imatinib to 600mg a day in order to induce remission.

Patient did not have any co-morbidities and he had not been taking any concomitant drug therapy when he started Imatinib treatment and his general condition was normal. After 5years use of Imatinib 600mg a day dose patient achieved better remission and his WBC count tend to be decreased.

On August 8th 2019 the previously normal sighted patient referred to oncology medical floors for hematologic monthly follow-up and complained about blurred vision, redness of eye, ocular heaviness and periorbital edema. The oncologist noticed periorbital edema and eye congestion in external examination of eye and referred the patient to ophthalmology department for his visual alterations and other ocular complaints. External examination of eye by ophthalmologist revealed bilateral periorbital edema along with redness of eye (Figure-1) and his visual acuity was 20/30 in the OD and 20/40 in the OS and to rule out ptosis the physician measured Marginal Reflex Distance (MRD) which is normal for both eyes 4mm of OD and 4.5mm of OS, along with normal levator function which is 15mm of OD and 16mm of OS by these the physician conformed that the patient did not have clinical ptosis. Patient fundoscopy revealed bilateral mild-moderate grade optic disc edema.

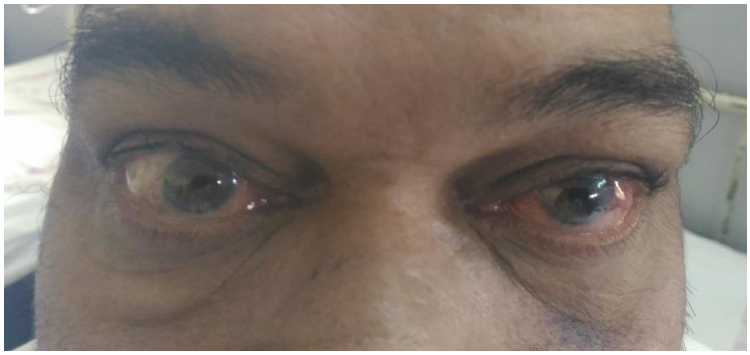

Figure-1: External photograph of patient with moderate periorbital edema and redness of eyes associated with use of Imatinib

The patient underwent neurologic and infectious disease specialist evaluation for to rule out any infective and neurological cause but no abnormality detected. He also underwent contrasted CT and MRI that resulted unremarkable and his microscopic examination of tissue reveals non malignancy. Finally, the patient was diagnosed with moderate B/L periorbital edema along with optic disc edema. No surgical intervention was required because it is moderate form of periorbital edema, as the patient reported visual improvement and new ophthalmological evaluation revealed reduction of edema after 1week of withdrawal of Imatinib and the patient achieved complete recovery and his visual alterations was normal. After recuperation the patient continue Imatinib 600mg for remission of CML.

DISCUSSION:

Imatinib belongs to category of TKIs is the first line treatment choice for patients with CML[13,14]. Most frequently occurring ophthalmological secondary side effects like periorbital edema have been reported in patients who were treated with Imatinib for CML[15]. Epiphora is so far the second most commonly presented ocular side effect of this drug and other side effects like conjunctival hemorrhage, blepharoconjunctivitis, visus alterations, and ocular dryness. Optic disc edema is a rare known ocular adverse event related to use of Imatinib [16].

In the scientific literature review, Govind babu et al. reported the case of a patient who suffering from bilateral vision loss due to use of Imatinib after 26days of initiation of therapy. This case suggested the role of Imatinib in optic neuropathy along with optic disc edema[17]. According to Kusumi E et al. presented a case of optic disc edema due to use of Imatinib in early stage of initiation of treatment [18]. But in our case patient developed optic disc edema after 7 years of use of Imatinib. Another case study by Collin M mcclelland et al. reported a case of 65-years-old Caucasian women who was treated with Imatinib for 10 years later on she developed periorbital edema which was secondary to Imatinib usage [19]. Early Phases of the clinical trial of imatinib for treatment of CML and GIST, along with subsequent studies reported the side effects of Imatinib, these studied reported the incidence rates of edema in the range of 39%–74.1% in all patients who were taking Imatinib. Results specifying periocular region is the most common site for edema, presented in 47.6%–70% of patients taking Imatinib [2,3,20,21] in our present case study we also observed edema in the periorbital site along with optic disc edema. All these literature review was strongly suggestive of periorbital edema was the high frequency side effect where as optic disc edema was the least comparatively.

Although the mechanism for Imatinib-induced periorbital edema and optic disc edema were need to be elucidate, the most popular theory explained the mechanism may be due to the inhibition of platelet-derived growth factor receptor (PDGFR) signaling by the drug. PDGFR signaling tend to be increase the pressure of the interstitial fluid has been observed in the dermis of rodents [22]. The inhibition of the PDGFR signaling pathway by Imatinib treatment in human patients may similarly result in increased capillary permeability and extravasation of fluid this leads to edema. Optic disk edema may be associated to high intracranial pressure, but more often is secondary to masses in intracranial region, cerebral sinus thrombosis, or optic neuritis [16]. In the present case, there was no such complications were detected by imaging studies.

Periorbital edema secondary to Imatinib was typically mild to moderate and can usually be self managed. But several scientific findings reported that severe cases of periorbital edema have been treated by various means, using topical 1% hydrocortisone, 0.25% topical phenylephrine, including prescribing a low-salt diet, oral diuretics and sometimes surgical

intervention was also needed [5,6] optic disc edema was generally managed by using osmotic diuretics if it was due to increased intracranial pressure, or it occurred because of any abnormal masses or thrombosis that treated accordingly. In our case, moderate periorbital edema and optic disc edema appeared after 7 years of initiation of therapy, but Imatinib discontinuation for 1 week led to a gradual and almost complete reduction of the ocular symptoms without any treatment.

The correlation between the ocular event and the Imatinib usage was established by using both WHO-UMC causality assessment scale and Naranjo causality assessment scale based on series of criteria to obtain evidence of the cause-effect relationship between a certain pharmaceutical product and its secondary effect. These criteria include relationship with the dosage, response to withdrawal, by knowing toxic drug concentration using different laboratory tests, worsening after re-challenge, based on previous reports on same reaction, reaction reappear when a placebo was given, event conformed by objective evidence, possible pathophysiological mechanism, similar effects after introduction of drugs in the same family [23.24]. Applying these criteria to our patient, we identified a relationship with the dosage (progressive worsening with dosage increase); improvement after removal of the drug , the lack of an alternative pathophysiologic mechanisms that could explain the periorbital edema and optic disc edema (after extensive diagnostic tests). By considering these criteria, we therefore define the relationship of causality between Imatinib and ocular events in our patient as probable.

CONCLUSION:

Imatinib is the Tyrosine Kinase Inhibitors (TKI's) the best choice of drug to treat CML. It has wide range of ocular side effects like periorbital edema, epiphora, conjunctival hemorrhage, blepharoconjunctivitis, visus alterations, ocular dryness and Optic disc edema. Among them periorbital edema is the most common ocular event and optic disc edema is very rare, here we highlight the occurrence of moderate periorbital edema and optic disk edema due to Imatinib even after a long period of treatment and in the absence of any pathological causes. These ocular events can be self reducible in our case after suspension of Imatinib for 1 week without any treatment. The prevalence of Imatinib-induced ocular events may be expected to be increase in the future. Immediate ophthalmology consultation should be suggestive at any time of sudden visual alterations in patients with Imatinib treatment and both the ophthalmology and oncology practitioners should be aware of this common ocular side effect.

Acknowledgement:

All the authors of this article like to take the privilege of expressing cordial thanks to management of Chalapathi Institute of Pharmaceutical Sciences and Government General Hospital, Guntur and also convey sincere gratitude for enabling to prepare this article under the close supervision of department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences. We sincerely thank to Dr. N. Venkata Rama Rao, HOD of Pharmacy Practice department for encouraging us to perform this project and thanks to Dr. A. Satish Kumar, Associate professor of oncology, Government General Hospital, Guntur, Andhra Pradesh, India.

REFERENCES:

1. Druker BJ, Sawyers CL, Kantarjian H, et al. 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. *N Engl J Med*. 2001;344(14):1038–1042.
2. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347(7):472–480.
3. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344(14):1031-7.
4. Van Oosterom AT, Judson I, Verweij J, Stroobants S, Di Paulo ED, Dimitrijevic S et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumors: a phase I study. Lancet 2001; 358: 1421–1423.
5. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003;21(8):1637–1647.
6. Guilhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist*. 2004;9(3):271–281.
7. Fraunfelder, F. W., J. Solomon, B. J. Druker, B. Esmaeli, and J. Kuyl. 2003. Ocular side-effects associated with imatinib mesylate (Gleevec). J. Ocul. Pharmacol. Ther. 19:371–375.
8. Scheinfeld N. Imatinib mesylate and dermatology Part 2: A review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol*. 2006;5(3):228–231.
9. Masood I, Negi A, Dua HS. Imatinib as a cause of cystoid macular edema following uneventful

phacoemulsification surgery. *J Cataract Refract Surg*. 2005;31(12):2427–2428.
10. Georgalas I, Pavesio C, Ezra E. Bilateral cystoid macular edema in a patient with chronic myeloid leukaemia under treatment with imanitib mesylate: Report of an unusual side effect. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(10):1585–1586.
11. Kwon SI, Lee DH, Kim YJ. Optic disc edema as a possible complication of Imatinib mesylate (Gleevec). *Jpn J Ophthalmol*. 2008;52(4): 331–333.
12. Hasselbalch HC. STI571 (Gleevec), a new drug for the treatment of chronic myeloid leukemia. Ugeskr Laeger 2002; 164: 2914–2917.
13. Kantarjian H, Pasquini R, Lévy V, Jootar S, Holowiecki J, Hamerschlak N, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). Cancer 2009;115(18):4136–47.
14. Abbott BL. Dasatinib: from treatment of imatinib-resistant or intolerant patients with chronic myeloid leukemia to treatment of patients with newly diagnosed chronic-phase chronic myeloid
1. leukemia. Clin Ther 2012;34(2):272–81.
15. Fraunfelder FW, Solomon J, Mehelas TJ. Ocular adverse effects associated with cyclooxygenase-2 inhibitors. Arch Ophthalmol 2006;124(2):277–9.
16. Kwon, S. I., D. H. Lee, and Y. J. Kim. 2008. Optic disc edema as a possible complication of Imatinib mesylate (Gleevec). Jpn. J. Ophthalmol. 52:331–333.
17. Govind Babu K, Attili VS, Bapsy PP, Anupama G. Imatinib-induced optic neuritis in a patient of chronic myeloid leukemia. Int Ophthalmol 2007;27(1):43–4.
18. Kusumi, E., A. Arakawa, M. Kami, D. Kato, K. Yuji, Y. Kishi, et al. 2004. Visual disturbance due to retinal edema as a complication of imatinib. Leukemia 18:1138–1139.
19. Collin M McClelland,George J Harocopos,Philip L Custer. Periorbital edema secondary to imatinib mesylate. Clinical Ophthalmology. 2010:4 427–431.
20. Valeyrie L, Bastuji-Garin S, Revuz J, et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: A prospective study of 54 patients. *J Am Acad Dermatol*. 2003;48(2): 201–206.
21. Fraunfelder FW, Solomon J, Druker BJ, et al. Ocular side-effects associated with imatinib mesylate (Gleevec). *J Ocul Pharmacol Ther*. 2003;19(4):371–375.
22. Pietras K, Ostman A, Sjoquist M, et al. Inhibition of plateletderived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. *Cancer Res*. 2001;61(7):2929–2934.
23. WHO-UMC causality assessment scale. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
24. Naranjo causality assessment scale. https://ephor.nl/wp-content/uploads/2018/12/naranjo-causality-scale.pdf