1. INTRODUCTION

Imatinib was initially approved by the US Food and Drug Administration (FDA), in 2001 for the treatment of adult Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML). In 2002, it was authorized for the treatment of gastrointestinal stromal tumors (GISTs); in 2003 for childhood chronic myelogenous leukemia (CML), and in 2006, for the treatments of dermatofibrosarcoma protuberans (DFSP), myelodysplastic/myeloproliferative diseases (MDS/MPD), aggressive systemic mastocytosis (ASM), hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL), and relapsed/refractory acute lymphocytic leukemia (Ph+ ALL). Since then, it is widely used for the management of various types of cancers.

Imatinib is a small-molecule tyrosine kinase inhibitor with activity against ABL, BCR-ABL, c-KIT and PDGFRα. Imatinib is used orally to treat CML, GISTs, other malignancies and a variety of dermatological conditions (Guilhot, 2004).

Body cells need signaling proteins (signal cascade) to survive and proliferate. The signaling proteins are activated through the addition of phosphate by a tyrosine kinase enzyme as needed. In Ph-positive CML cells, one tyrosine kinase enzyme, BCR-ABL, is stuck in the active position and these leukemic cells then keep on proliferating. Imatinib blocks this BCR-ABL enzyme and the addition of the phosphate group; therefore, these cells stop growing and even die because of apoptosis (Goldman & Melo, 2003). The BCR-ABLl tyrosine kinase enzyme exists only in cancer cells, thus imatinib is regarded as a form of targeted therapy for killing cancer cells only and is one of the first anticancer drugs to show such targeted action (Fausel, 2007; Stegmeier, Warmuth, Sellers, & Dorsch, 2010).

Similarly, in GISTs, another protein kinase, c-KIT, attains a gain-of-function mutation, leading to excessive proliferation of stromal cells. Imatinib has therapeutic effects against GISTs via inhibition of KIT, decreased glucose uptake and other yet unknown mechanisms (Tarn, Yuliya, Skorobogatko, Taguchi, Eisenberg, Von Mehren, & Godwin, 2006).

Imatinib also inhibits Platelet Derived Growth Factor Receptor (PDGFR) and appears to have the ability to treat a variety of dermatological diseases, including FIP1L1-PDGFR-alpha+ mast cell disease, hypereosinophilic syndrome, dermatofibrosarcoma protuberans and HIV related Kaposi's sarcoma (Scheinfeld, 2006). Cutaneous reactions to imatinib are common and are reported to occur in 9.5% to 69% of patient. Maculopapular eruptions, erythematous eruptions, edema, and periorbital edema are the most common adverse effects. Other common side effects include toxic epidermal necrolysis, Stevens Johnson syndrome, acute generalized exanthematous pustulosis, purpuric vasculitis and mycosis fungoides-like reaction. Relatively rare adverse effects are lichenoid reactions, pityriasiform eruptions, pityriasis rosea, psoriasis, porphyria cutanea tarda, eccrine hidradenitis, Sweet's syndrome, erythema nodosum, EBV-positive cutaneous B-cell lymphoproliferative disease, follicular mucinosis, pseudolymphoma-type drug eruptions, and malpighian epitheliomas (Scheinfeld, 2006a; Pascual, Matarredona, Miralles, Conesa, & Borras-Blasco, 2006). Regarding pigmentary changes in the skin and mucous membranes, hypopigmentation is relatively more frequently occurring, whereas, paradoxically hyperpigmentation has also been reported in occasional cases (Ayirookuzhi, Ma, Ramshesh & Mills, 2005).

Some authors have reviewed overall cutaneous reactions caused by imatinib with brief reference to color changes in the skin (Arora, Kumar, Sharma, Wadhwa, & Kochupillai, 2004; Attili, Anupama, Dadhich, Saini, Bapsy, & Batra, 2006; Brazzelli, Grasso & Borroni, 2013; Pretel-Irazabal, Tuneu-Valls, & Ormaechea-Pérez, 2014). However, it was noticed that a lot more case reports and clinical studies have been reported in the literature since then about the imatininb induced pigmentary changes in the skin and mucous membranes. Therefore, in the present article, various case reports and clinical studies pertaining to hypopigmentation and paradoxic hyperpigmentation of the skin and mucous membranes caused by imatinib are reviewed and appraised. The possible mechanisms of melanin derangements, clinical outcomes and management are also described.

2. PIGMENTARY CHANGES OF SKIN

Since the approval of imatinib for the treatment of CML, GIST and other types of cancers, its acceptance as a targeted therapy for cancer management and widespread application, many cases of hypopigmentation and occasionally hyperpigmentation related to imatinib therapy have been published in the pubmed. Below are some case reports and clinical studies pertaining to imatinib induced hypo- and hyper- pigmentation of skin and the effects of imatinib on vitiligo.

2.1 Hypopigmentation

A 70-year-old Nigerian male with severe chronic obstructive pulmonary disease and cardiomyopathy, was presented with a large bleeding gastric stromal tumor metastatic to the liver and was treated with imatinib. Within two months of onset of imatinib therapy, the patient started improving and showed 15% decrease in metastatic lesions. However, after 3 months, the patient developed hypopigmentation of the distal parts of the dorsum of both hands. Later, he was reported to have developed a generalized lightening of body