Cytarabine and Doxorubicin-Induced Palmoplantar Erythrodysesthesia Syndrome: The Possible Role of Voriconazole Interaction

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Cite this article as: *Tavakoli-Ardakani M, Haghighi S, Shokouhi S, et al. Cytarabine and Doxorubicin-Induced Palmoplantar Erythrodysesthesia Syndrome: The Possible Role of Voriconazole Interaction. Eurasian J Med 2019; 51(3): 313-5.*

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Received: December 13, 2018
Accepted: April 26, 2019

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DOI 10.5152/eurasianjmed.2019.18459

ABSTRACT

Palmoplantar Erythrodysesthesia Syndrome (PPES) caused by chemotherapeutic agents is rarely life threatening and requires a reduction in dose or discontinuation of chemotherapy. The use of cytarabine and doxorubicin in the treatment of acute myeloid leukemia (AML) along with voriconazole can potentially alter the metabolism of the drugs and cause some interactions. In this study, we presented a case of AML who received cytarabine and doxorubicin as a chemotherapy regimen and voriconazole as a prophylactic anti-fungal. In this combination, voriconazole probably inhibits the P-glycoprotein pump, which leads to an increase in the cytarabine concentration. The emphasis of this report is the awareness of clinicians and pharmacotherapists about these interactions.

Keywords: Cytarabine, doxorubicin, voriconazole, palmoplantar, erythrodysesthesia syndrome

Introduction

Palmoplantar Erythrodysesthesia Syndrome (PPES) or hand-foot syndrome (HFS) is an adverse event associated with numerous classic chemotherapeutic agents and newer molecular targeted agents [1]. The primary symptoms, which appear in 3-5 days, are dysesthesia or tingling in the hands or feet with erythema. These symptoms may get worse over the time, thereby occurring desquamation or ulceration. Besides, by progressing PPES, the pain level also increases, especially by grasping objects or walking, which affects the life quality of the patient [2]. PPES seems to be dose-dependent and related to drug concentration and total cumulative dose. Nevertheless, in some cases, no direct relation between dose and severity of PPES was observed [1]. Cytarabine is an anti-metabolite drug, which has an essential role in the treatment of AML. This agent is substrate for cytochrome P450 (CYP) isoenzymes or P-glycoprotein efflux pumps [3]. In myelosuppressive chemotherapy, neutropenia is a major concern that leads to a devastating infection. Hence, the patients need prophylactic antimicrobial agents such as voriconazole [4]. In some patients, voriconazole can inhibit CYP3A4, CYP2C9, and CYP2C19 in different degrees. Another uncertain interaction mechanism of voriconazole is with the P-glycoprotein efflux pumps [5]. Therefore, this combination therapy can lead to an increase in the concentration of cytotoxic agents in the cells, thereby increasing adverse effects of chemotherapy such as PPES. Here, we describe an AML case with PPES who was received cytarabine, doxorubicin, and voriconazole.

Case Presentation

This is the case of AML-M5 who was a 29-year-old man admitted to hematology ward of Blinded Hospital. Lab data revealed hyperleukocytosis (WBC=155×10^6 cells/L). Hydroxyurea (CYTODROX; Cipla) capsule 1 g four times daily was started for cytoreduction before initiating chemotherapy. Also, the prophylactic anti-microbial regimen was started based on the last guideline of National Comprehensive Cancer Network (NCCN, version 1.2018), which consist of acyclovir 400 mg tablet (Aciclovir; Ruzdarou) twice day, ciprofloxacin 500 mg (Ciprofloxacin; Farabi) twice a day, and voriconazole 200 mg tablet (Vonafend; Tehrandarou) twice a day. Although the standard antifungal prophylaxis is posaconazole, it is not available in Iran. After seven days of routine evaluation, treatment by cytarabine (Cytosar; Pfizer) at dose 300 mg daily for seven days and doxorubicin (Adriamycin; Pfizer) at dose 80 mg daily for three days as induction regimen was started; and appropriate premedication and supportive medication were considered. After nine days, the chemotherapy complications affected the patient, and the number of white blood cells

significantly decreased to 20×10^6 cells/L. In addition, severe nausea, vomiting, diarrhea, abdominal pain, microsites, and hiccups appeared in the patient. The patient became feverish (39.5) and was diagnosed with febrile neutropenia. Therefore, broad- spectrum antimicrobial was added to his regimen. In this time, erythema, edema, and palmoplantar thickening with sharp demarcation line in the wrist appeared. The lesions were tender in palpation, and few bullous lesions were seen on the fingers. However, there were no ulcerative or necrotic lesions in this area (Figure 1). These symptoms were seen on feet with less severity (Figure 2). In addition, some rash appeared in his genital areas. These clinical findings were consistent with a diagnosis of PPES. His treatment was continued, and his antifungal regimen was changed into amphotericin (Ambisome; Gilead Sciences) 80 mg daily. In addition, topical Mometasone (Megacorte; kish-medipharm) 0.1% was prescribed for his PPES. All medications were received at a certain dose and were not changed during hospitalization. After 11 days, PPES recovered following peeling of the affected area, and gradually febrile neutropenia was resolved. Finally, after one month, he was discharged, and his clinical condition was stable (Figure 3). To report this case, the informed consent of the patient was obtained.

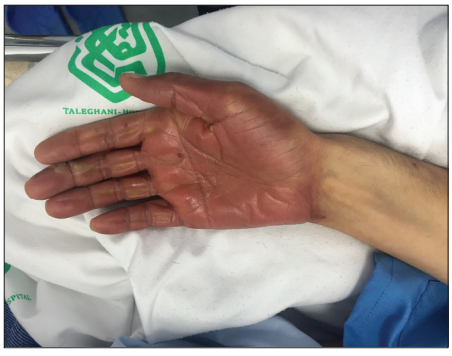

Figure 1. Palmoplantar Erythrodysesthesia Syndrome in both hands following induction regimen for treating acute myeloid leukemia (AML).

Discussion

In this study, we presented a case of PPES following induction therapy for AML. This study aimed to show the possible interaction between voriconazole and chemotherapy regimen. It is documented that cytarabine and doxorubicin are substrates for cytochrome P450 isoenzymes or P-glycoprotein efflux pumps [3, 6]. Some cells such as hematopoietic cells and squamous skin cells are more susceptible to chemotherapy. Mrozek Orlowski et al. [7] introduced a reasonable mechanism for this phenomenon. They described that cytotoxic drugs may be excreted in sweat fluid, making hands and feet more susceptible to PPES. These areas are saturated with many eccrine glands. On the other hand, voriconazole can inhibit CYP3A4, CYP2C9, CYP2C19, and probably P-glycoprotein efflux pump. Hence, this process leads to increased adverse effects of chemotherapy on healthy cells. Previous reports regarding PPES following cytarabine or doxorubicin have been summarized in Table 1. Recently, Alzghari et al. [8] reported a case of cytarabine and posaconazole interaction-induced severe PPES and aplasia. Posaconazole inhibits the P-glycoprotein pump, which leads to an increase in the cytarabine concentration. In 2016, Sakurada et al. [9] reported an AML case with PPES who were treated with high-dose

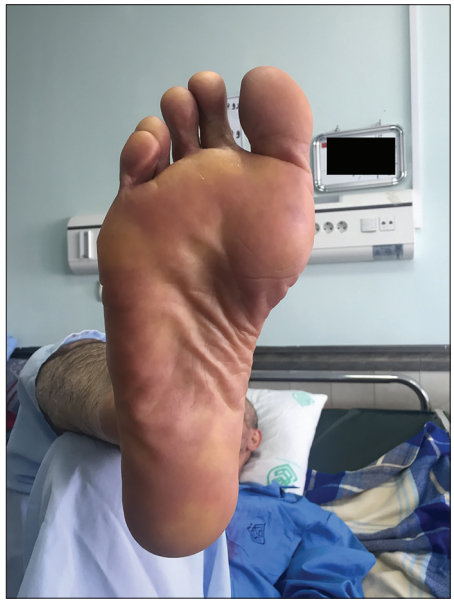

Figure 2. Palmoplantar Erythrodysesthesia Syndrome in feet with less severity following induction regimen for treating acute myeloid leukemia (AML).

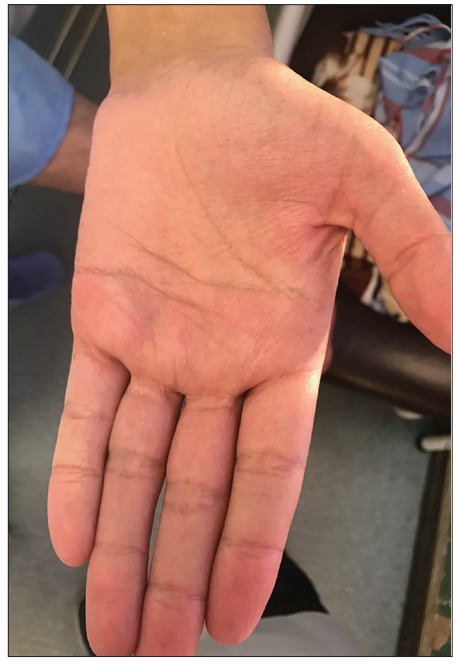

Figure 3. Hand of the patient after PPES recovery.

Table 1. Previous cases of PPES induced by Cytarabine or Doxorubicin

Author	Year	Sex	Age (Years)	Diagnosis	Cytotoxic agent	Dose	Possible Interaction with chemotherapy	Affected area
Alzghari et al. [8]	2017	Female	24	AML	Cytarabine	HiDAC	Posaconazole	Both hands and feet
Sakurada et al. [9]	2016	Female	40	AML	Cytarabine	HiDAC	Not mentioned	Both hands and feet
Sharma et al. [10]	2013	Female	28	AML	Cytarabine	Standard	Not mentioned	Both hands and feet
Hwang et al. [11]	2012	Female	51	AML after breast cancer	Cytarabine	HiDAC	Colfarabine	Trunk and limbs
Swenson et al. [12]	2010	Female	69	Ovarian cancer	Liposomal Doxorubicin	50 mg/m^2	Not mentioned	Feet, behind knees, axillary regions and breasts
Rosenbeck et al. [13]	2011	Male	52	AML	Cytarabine	HiDAC	Not mentioned	Both hands and feet
Damasiewicz et al. [14]	2007	Female	43	Breast cancer	Doxorubicin	60 mg/m^2	Cyclophosphamide	Both hands and feet
Crawford et al. [15]	2002	Male	21	ALL	Cytarabine	HiDAC	Not mentioned	Hands
Gordon et al. [16]	1995	Male	30	Kaposi's sarcoma	Liposomal Doxorubicin	20 mg/m^2	Not mentioned	Both hands and feet
		Male	38	Kaposi's sarcoma	Liposomal Doxorubicin	20 mg/m^2	Not mentioned	Hands

Hi-DAC: High-Dose Cytarabine

cytarabine (HiDAC) regimen. This case had a mild rash in her induction therapy phase; so the clinicians decided to prevent the probable PPES with heparinoid lotion and hypoallergenic soap. Their strategy was not completely successful. In 2013, Sharma et al. [10] reported PPES in an AML case after receiving the standard dose of cytarabine. This case received topical ointment, pyridoxine, and soft pads on her lesions. Hwang et al. [11] reported an interesting case of PPES with the affliction of trunk and limbs. She received clofarabine and cytarabine concomitantly. This combination might affect clofarabine or cytarabine metabolism. This case was the first mortality report of severe PPES [11]. Swenson et al. [12] reported a liposomal doxorubicin-induced PPES in a case of ovarian cancer. Her oncologist held the liposomal doxorubicin and reduced its dose by 25% when her treatment resumed. Rosenbeck et al. [13] reported a case of HiDAC-induced PPES. This case received supportive care, and PPES was finally resolved by receiving the last dose of cytarabine after 20 days. In 2007, Damasiewicz et al. [14] reported a case of doxorubicin-induced PPES. This case received doxorubicin and cyclophosphamide for her breast cancer. Crawford et al. [15] reported an ALL case with recurrent PPES. The initial manifestation was a generalized body rash, and they concluded that PPES is a dose-dependent phenomenon in which peak concentration and cumulative dose of cytarabine are involved. Gordon KB et al. [16] also reported two case of Kaposi's sarcoma who inflicted to PPES after liposomal doxorubicin administration. They found that Kaposi's sarcoma may trigger PPES in this situation. Current case emphasized the probable interaction between voriconazole as a P-glycoprotein inhibitor and cytarabine-doxorubicin. It should be kept in mind that this was a probable interaction, and hand-foot syndrome recovered after medication modification. To the best of our knowledge, this is the first report of PPES that emphasizes on the interactions of cytarabine and doxorubicin with voriconazole in chemotherapy regimen of patient with AML. Therefore, it is necessary for clinicians and pharmacotherapists to be aware of these interactions and predict the possible complications.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.T, S.H, S.S., R.H; Design - A.S, M.M., B.A; Supervision - M.T, S.H., S.S; Data Collection and/or Processing - M.M, R.H., A.S; Analysis and/or Interpretation - M.T, S.H, B.A., S.S; Literature Search - A.S, M.M., B.A; Writing Manuscript: M.M, R.H., A.S; Critical Review - M.T, S.H, B.A., S.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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