DOI: 10.7860/JCDR/2014/9133.4975

Original Article

Pharmacology Section

Anticancer Drug Induced Palmar Plantar Erythrodysesthesia

MUTHIAH PALANIAPPAN[1], SURESHKUMAR SRINIVASAMURTHY[2], BISWAJIT DUBASHI[3], ADITHAN CHANDRASEKARAN[4]

ABSTRACT

Background: Palmar plantar erythrodysesthesia (PPE) is a dose limiting toxicity of anticancer agents. In some cases it may mandate for discontinuation of anticancer agents. Evaluation of data of PPE among reported adverse drug reactions (ADRs) from the Department of Medical Oncology could quantify the burden.

Aim: To evaluate and analyse the PPE among reported ADRs from medical Oncology.

Materials and Methods: The data of all cases of reported PPE were collected during January 2012 to September 2013 and were analysed with WHO causality assessment scale. The severity was clinically graded. The follow-up data regarding outcome of ADRs were also noted.

Results: During the study period of 21 months a total of 1418 ADRs have been reported from 1076 patients. Among them PPE was reported from 31 cases (2.9%). Majority (32.2%) of these patients were on chemotherapy for breast cancer. Patient's age ranged from 17 to 68 y and the median age was 50 y. There were 18 female (58%) and 13 male patients (42%). Capecitabine was the leading drug involved in PPE, reported with 20 cases (64.5%), and followed by docetaxel with 5 cases (16.1%). Majority (67.7%) of the reactions was categorized as certain and 64.5% was grade II severity clinically.

Conclusion: Our findings show that PPE accounts for 2.9% of total reported ADRs from Medical Oncology during 21 months. Majority of the reactions were classified as certain. Capecitabine is commonly implicated drug.

Keywords: Adverse drug reaction, Anticancer drugs, Hand foot syndrome, Palmar plantar erythrodysesthesia, Pharmacoepidemiology, Pharmacovigilance

INTRODUCTION

Palmar plantar erythrodysesthesia (PPE) or hand-foot syndrome (HFS) or acral erythema is one of the rare side effects of chemotherapeutic agent. It has been commonly reported with capecitabine, docetaxel, 5 fluorouracil, cytarabine. PPE manifests as painful erythema, preceded by paresthesia, of palms and soles during treatment with anticancer drugs. Histologically, PPE shows mild spongiosis, dyskeratotic keratinocytes, and scattered necrotic and vacuolar degeneration of the basal layer. Changes dermally seen were papillary oedema, a thin superficial perivascular lymphohistiocytic infiltrate and dilated blood vessels in the epidermis [1]. Discontinuation of therapy or dose reduction of the implicated drug usually is the mainstay of PPE management [1,2]. The prevalence of PPE was found to be 2.01% [3]. To the best of our knowledge, there is no clear data for anticancer drug induced PPE in India, though some case studies are reported. This study reports the occurrence of PPE among spontaneously reported Adverse drug reactions (ADRs) in Indian patients. Hence we aimed to evaluate the data of anticancer drugs induced PPE.

MATERIALS AND METHODS

The data of ADRs of all cases of PPE diagnosed clinically and collected during Jan 2012 to Sep 2013 were analysed. The follow up of patients with PPE was also done for outcomes. The PPE reported were analysed for WHO causality and categorized as certain, probable, unlikely, conditional and unassessable [4]. All ADRs were reported in Suspected Adverse Drug Reaction Reporting form, provided by Central Drugs Standard Control Organization, Ministry of Health & Family Welfare, Government of India.

RESULTS

During the study period a total of 1418 ADRs have been reported from 1076 patients. PPE was reported from 31 cases, so the frequency of anticancer drug induced was found to be 2.9%. Patient's age ranged from 17 to 68 of years and the median age was 50 years. There were 18 female (58%) and 13 male patients (42%). Among 31 patients, 10 were with breast cancer, 8 were with colorectal cancer, 7 were with stomach cancer, and two were chronic myeloid leukemia and one case each of angio immunoblastoma, lung cancer, ovarian cancer and renal cell carcinoma.

Twenty cases (64.5%) were reported with capecitabine followed by 5 cases of docetaxel induced PPE (16.1%). In most cases capecitabine was given with oxaliplatin as CAPOX regimen. Most of the PPE were graded as grade II (64.5%). Majority (67.7%) of the reactions were categorized as certain [Table/Fig-1]. The suspected drugs namely capecitabine and gemcitabine were stopped due to severity of PPE in two patients of breast cancer and angio- immunoblastoma respectively. In one case of breast cancer the dose of docetaxel was reduced. In all other cases drugs were continued till the completion of the regimen. The other ADRs found with these patients were diarrhea, thrombocytopenia, anaemia, myalgia, musositis, vomiting, abdominal pain, pedal oedema, insomnia, back pain, neuropathy and cough. Concomitant drugs included omeprazole, ondansetron, metoclopramide, tramadol.

DISCUSSION

PPE is a dermatologic reaction associated with anti cancer drugs that can limit the use of these drugs. It occurs at any age group, and there are no known gender differences. There is also no data of PPE being associated race or population groups [5]. PPE most commonly manifests with dysesthesia, usually with a tingling sensation of the palms and soles, which can progress in 3–4 days to burning pain; clear symmetric swelling and erythema. The hands tend to be usually affected than the feet. In some patients only hands might be affected [2]. Blistering and desquamation, shedding of scales or small sheets could be seen in some cases [6].

The PPE is graded clinically as follows: numbness, dyesthesia,

S. No	Drug	No. of Cases (n=31)	Grade			Causality	% (95% CI)
			I	II	III		
1	Capecitabine	20	12	5	3	Certain	64.5 (45.4 – 80.8)
2	Docetaxel	5	4	0	1	Possible	16.1 (5.4 – 33.7)
3	Imatinib	2	2	0	0	Possible	6.5 (7.9 – 21.4)
4	Flurouracil	1	1	0	0	Possible	3.2 (0.07 – 16.7)
5	Gemcitabine	1	1	0	0	Possible	3.2 (0.07 – 16.7)
6	Liposomal Doxorubicin	1	0	1	0	Possible	3.2 (0.07 – 16.7)
7	Sorafenib	1	0	0	1	Certain	3.2 (0.07 – 16.7)

[Table/Fig-1]: Drugs involved in PPE with their grading and causality
CI: Confidence Interval

tingling, in the hands and feet as grade 1; painless erythema with swelling of palms and soles as grade 2; moist desquamation, ulceration, blistering, with severe pain as grade 3 [6]. For Grade 1 PPE, usually the drugs are continued, skin barrier cream and moist exposed burn ointment is prescribed. For Grade 2 PPE, either dose is maintained or 25% of dose is reduced. Moist exposed burn ointment and Supportive care are also advised. Management of grade 3 PPE, includes interrupted of one cycle followed by dose adjustment along with moist exposed burn ointment and supportive care [7].

Treatment suspension or reduction of dose remains the only method shown to effectively manage PPE, but supportive measures to shrink the pain and forbid secondary infection are extremely important. Many other cautionary and treatment strategies have been tested, with pyridoxine and COX-2 inhibitors being the most anticipating therapies in case reports and retrospective studies [8].

PPE is commonly reported with 5-fluorouracil (5 Fu), capecitabine, cytarabine, docetaxel etc., and it was rarely reported with liposomal doxorubicin [9], imatinib [10], sorafenib [11], sunitinib [12], gemcitabine and vinorelbine [13]. We also report PPE with gemcitabine, imatinib, liposomal doxorubicin and sorafenib along with capecitabine, docetaxel, fluorouracil.

Various mechanisms have been proposed for PPE. It is hypothesized that the presence of elevated thymidine phosphorylase expression in the palms of the hands along with an increased basal cell proliferation rate could contribute to capecitabine induced PPE [14]. Further thymidine phosphorylase is also responsible for preferential conversion of capecitabine to 5 Fu in tumor tissue. Local delivery of high drug concentrations though eccrine glands has been involved in the etiology of PPE induced by sorafenib [15]. Various studies have described a connection between the antitumour efficacy of epidermal-growth-factor receptor inhibitors and cutaneous side-effects [16]. The doxorubicin liposomes are carried to skin surface by the normal sweat function, presumably favoured by the hydrophilic coating. From the skin surface, the sweat containing the drug may get through into the stratum corneum and also it functions as a source for the entry of doxorubicin into deeper skin layers and reacts with epidermal cells [17]. The exact mechanism of docetaxel, gemcitabine induced PPE is not clearly known [18,19].

PPE with anti cancer drugs is dose dependent [20]. In our cases, oral capecitabine involved in 20 cases of PPE, among them 7 cases were with the dose of 3000 mg per day. But in the case of PPE with other drugs like gemcitabine, imatinib and sorafenib, these drugs were given in normal doses. A study by Hueso et al., found that the most commonly implicated drugs in causing PPE were 5Fu with 36.3% including both infusion as well as bolus followed by docetaxel (13.6%), however in their study capecitabine was not included [3]. We found that capecitabine a pro-drug of 5FU to be the most commonly implicated drug (64.5%). Similarly a study by Kadoyama et al., found that PPE is most commonly associated with capecitabine than 5 Fu [21]. Both 5Fu and capecitabine are metabolized by the enzyme dihydropyrimidine dehydrogenase (DPD).

In this study we found, overall 112 patients reported ADRs due to 5 Fu among them one developed PPE (0.9%); 59 patients developed ADR due to capecitabine including 20 case of PPE (33.9%), 57 case of docetaxel induced ADRs with 5 PPE (8.8%); 53 cases of gemcitabine induced ADRs with 1 PPE (1.9%); 2 (1%) cases of imatinib induced PPE among 196 cases.

CONCLUSION

Our findings show that PPE accounts for 2.9% of total reported ADRs from Medical Oncology during 21 mnth. Capecitabine is commonly implicated drug followed by docetaxel. Majority of the reactions were classified as certain. Early detection may help in management of PPE.

REFERENCE

[1] Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. Incidence, recognition and management. *Am J Clin Dermatol*. 2000;1(4):225-34.
[2] Yvonne L, Paulo H. Management of hand-foot syndrome in patients treated with capecitabine (Xelodas). *Eur J Oncol Nurs.* 2004;8:31–S40.
[3] Hueso L, Sanmartin O, Nagore E, Botella-Estrada R, Requena C, Llombart B, et al. Chemotherapy-Induced Acral Erythema: A Clinical and Histopathologic Study of 44 Cases. *Actas Dermosifiliogr.* 2008;99:281-90.
[4] Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf.* 1997;17(6):374-89.
[5] Janusch M, Fischer M, Marsch WCh, Holzhausen HJ, Kegel T, Helmbold P. The hand-foot syndrome--a frequent secondary manifestation in antineoplastic chemotherapy. *Eur J Dermatol.* 2006;16(5):494-99.
[6] Blum JL, Smith SE, Buzbar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol.* 1999;17(2):485–93.
[7] Hyun-Sook S, Woo YL, Won-Suk L, Seong HY, and Ho-Kyung C. Compliance and Effective Management of the Hand-Foot Syndrome in Colon Cancer Patients Receiving Capecitabine as Adjuvant Chemotherapy. *Yonsei Med J.* 2009;50(6):796–802.
[8] Sarah M Gressett, Brad L Stanford, Fred Hardwicke. Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract.* 2006;12:131-41.
[9] Lopez AM, Wallace L, Dorr RT, Koff M, Hersh EM, Alberts DS. Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia. *Cancer Chemoth Pharm.* 1999;44(4): 303-06.
[10] Battistella M, Frémont G, Vignon-Pennamen MD, Gornet JM, Dubertret L, Viguier M. Imatinib-induced hand-foot syndrome in a patient with metastatic gastrointestinal stromal tumor. *Arch Dermatol.* 2008;144(10):1400-02.
[11] Hyun L, Sung HN, Sun YK, Kyu YJ, and Pyoung HH. Hand-Foot syndrome induced by sorafenib, a multitargeted tyrosine kinase inhibitor, in a patient with advanced renal cell carcinoma. *Korean J Pediat*. 2009;52(1):119-23.
[12] Fife DJ, Wu JJ, Behnam SE, Linden KG. Sunitinib-induced hand–foot syndrome: a new, distinct form. *Clin Exp Dermatol.* 2010;35(2):200–01.
[13] Laack E, Mende T, Knuffmann C, Hossfeld DK. Hand-foot syndrome associated with short infusions of combination chemotherapy with gemcitabine and vinorelbine. *Ann Oncol.* 2001;12(12):1761-63.
[14] Gérard M, Marie-Christine, Etienne-Grimaldi, Mireille M, Sandra L, Jean-Louis F, et al. Candidate mechanisms for capecitabine-related hand–foot syndrome. *Br J Clin Pharmacol.* 2008;66(1):88–95.
[15] Lai SE, Kuzel T, Lacouture ME. Hand-foot and stump syndrome to sorafenib. *J Clin Oncol.* 2007;25(3): 341-43.
[16] Robert C, Soria JC, Spatz A, Le CA, Malka D, Pautier P, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;6(7):491-500.
[17] Jacobi U, Waibler E, Schulze P, Sehouli J, Oskay-Özcelik G, Schmook T, et al. Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome? *Ann Oncol.* 2005;16(7):1210-11.
[18] Jain A, Dubashi B. Docetaxel-induced hand foot syndrome. No dose is a safe dose. *J Pharmacol Pharmacother.* 2012;3(2):200–01.
[19] Laack E, Mende T, Knuffmann C, Hossfeld DK. Hand-foot syndrome associated with short infusions of combination chemotherapy with gemcitabine and vinorelbine. *Ann Oncol.* 2001;12(12):1761-63.
[20] Jia C. Prevention and management of hand-foot syndromes. Oncology Nurse Advisor. 2010. 17-22. (cited: 3 October 2013); Available from: http://media.oncologynurseadvisor.com/documents/32/ona_ce_0710-0712_7954.pdf.

[21] Kadoyama K, Miki I, Tamura T, Brown JB, Sakaeda T, Okuno Y. Adverse Event Profiles of 5-Fluorouracil and Capecitabine: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS, and Reproducibility of Clinical Observations. *Int J Med Sci.* 2012;9(1):33-39.

PARTICULARS OF CONTRIBUTORS:
1. Technical Associate – Pharmacovigilance, Department of Clinical Pharmacology, JIPMER, Pondicherry, India.
2. D.M., Department of Clinical Pharmacology, JIPMER, Pondicherry, India.
3. Assistant Professor, Department of Medical Oncology, JIPMER, Pondicherry, India.
4. Head of the Department, Department of Clinical Pharmacology, JIPMER, Pondicherry, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Muthiah Palaniappan,
ADR Monitoring Centre, Department of Clinical Pharmacology, JIPMER, Pondicherry – 605006, India.
Phone : 9965926162, E-mail : muthu_pharmacist@yahoo.co.in, krplmuthu@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 02, 2014**
Date of Peer Review: **Jul 02, 2014**
Date of Acceptance: **Jul 02, 2014**
Date of Publishing: **Oct 20, 2014**