



THREE CASE REPORTS OF 5-FLUOROURACIL INDUCED SERPENTINE SUPRAVENOUS HYPERPIGMENTATION

Swathi T^{*1}, Sucharitha R¹, Vijaya Kumar Subash¹, A.Y. Rao², C.S.K Prakash²

¹Department of Pharmacy Practice, Vaagdevi College of Pharmacy, MGM Hospital, Warangal, Andhra Pradesh, India.

²Department of Oncology, Kakatiya Medical College / MGM hospital, Warangal, Andhra Pradesh, India.

ABSTRACT

The toxicity of the 5-fluorouracil is strongly influence by the dosage used, the rate and duration of drug administration. However, common side effects of 5-fluorouracil include nausea, vomiting and diarrhoea, leucopenia and thrombocytopenia. We report two cases with inoperable carcinoma of stomach who developed serpentine supravenuous hyperpigmentation at the 4th cycle of chemotherapy.

Key words: Chemotherapy, Cancer, Cell-cycle, Dark streak.

INTRODUCTION

5-fluorouracil was designed, synthesized and patented by Charles Heidelberger in 1957 [1,2]. It is a chemotherapeutic agent used in the management of many neoplastic conditions. It is used in the treatment of breast, gastric, colorectal, pancreas cancers and superficial basal cell carcinoma. 5-fluorouracil is a pyrimidine analogue often combined with radiotherapy [3]. The mode of action of 5-fluorouracil as a pyrimidine analogue, it is transformed inside the cell into different cytotoxic metabolites which are then incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis by inhibiting the cells ability to synthesize DNA. It is an S-phase specific drug and only active during certain cell cycles. In addition to being incorporated in DNA & RNA, the drug has been shown to inhibit the activity of the exosome complex, an exorubonuclease complex of which the activity is essential for cell survival. The side effects of 5-fluorouracil include nausea, vomiting and diarrhea, leucopenia and thrombocytopenia, hand-foot syndrome, mucositis and cardiac toxicity [4].

Case presentation

Case 1

Mrs. CA, a 48yrs old farmer present as a serpentine supravenuous hyperpigmentation to the oncology unit. He had been diagnosed with squamous cell carcinoma of stomach inoperable and was treated with chemotherapy. The following drugs are administered to the patient 5-Fluorouracil for 5 days the total dose of 5-Fluorouracil 750mg d1-d5, followed by calcium leucovorin 50mg d1-d5, and oxaloplatin 150mg on day 1. A good partial remission was attained, little haematological, no gastrointestinal or central nervous toxicity were experienced. The patient did experience diffused hyperpigmentation of face and hand markedly increased pigmentation of skin over the course of the veins used for the multiple 5-Fluorouracil infusion was noted. Because of it unusual experience of drug toxicity the name serpentine supravenuous 5-fluorouracil hyperpigmentation is suggested for this entity. Many irregular dark streaks were found on the patients left and right hand occurs extremity extending from the hand or distal forearm to the shoulder. This dark streaks were 1-1.5 cm wide and were serpiginous in their course. Figure (1,2). When tourniquet were placed around the arm it became obvious. Each of

this hyperpigmented bands over line a vein into one or more dose of 5-Fluorouracil.

Case 2

Mrs. AA a 42yrs old women presented to his physician with stomach pain and fatigue. She is 155cm height, 49kgs weight and had no medical history of diabetes, hypertension, tuberculosis and seizures. She was referred to the oncologist and found that she had stomach cancer, her cancer stage was inoperable. She was treated according to the WHO guidelines. She had initially 4 cycles of 5-fluorouracil 750mg, calcium leucovorin 50mg, followed by oxaliplatin 150mg. She had taken I.V 5-fluorouracil 750mg in normal saline for 5 days, calcium leucovorin 50mg in DNS for 5 days followed by oxaliplatin 150mg were continued for the 3rd cycle. Two days after the 4th cycle the patient noted for the first time asymptomatic pigmentation retracing venous streaks of left and right arm from fore arm to shoulder. Clinical examination revealed serpiginous hyper pigmented streaks along the course of the superficial vein (Figure.3) There were no apparent leakage of medical agents in surrounding

skin and no other mucocutaneous abnormality.

Case 3

Miss AA a 35yrs old women with inoperable carcinoma of stomach. She was treated with adjuvant chemotherapy of 5-fluorouracil and leucovorin. She is 155cm in height 40kgs weight and had no history of hypertension and diabetes and asthma. She was treated with 5-fluorouracil 500mg (in 5% dextrose slow infusion over 22 hrs) along with dexamethasone 8mg and ondansetron 16mg, leucovorin 200mg (in 5% dextrose). This treatment is repeated for 5 days ,after 2 cycles of chemotherapy a good response to treatment were observed and the patient did not show any cutaneous toxicity , the treatment was continued . during the 2nd day of 3rd cycle of chemotherapy she used to experience severe pain around the injection site. During the 3rd cycle of chemotherapy she noticed serpiginous asymptomatic pigmentation of the right forearm. There was gradual progression of the pigmentation. Examination revealed hyperpigmentation streaks along the course of the superficial veins in the forearm [Figure.4].hematologic and other systemic examinations were normal.

Fig 1. Serpentine supravenuous hyperpigmentation of left hand



Fig 3. Serpentine supravenuous hyperpigmentation of hands



Fig 2. Serpentine supravenuous hyperpigmentation of right hand



Fig 4. serpentine supravenuous hyperpigmentation of left hand



DISCUSSION

Fluorouracil is pyrimidine antimetabolites that produce its toxic destructive effects by interfering with ribonucleic acid and deoxyribonucleic acid synthesis [5]. Its specificity of action relates directly both to the metabolic rate of the cells exposed to it and the extracellular and intracellular concentration attained [6].

It is well known that chemotherapeutic drugs may induce various patterns of hyperpigmentation of the skin, mucosa, and epidermal appendages. For example, 5-FU-induced hyperpigmentation occurs in 42% of Caucasian patients [7]. In a recent study, skin hyperpigmentation occurred in 26% of biliary tract carcinoma patients following weekly 24-hour infusions of high-dose 5-FU and leucovorin [8]. However, linear hyperpigmented streaks over the arm veins used for injections without previous erythematous changes have rarely been reported [7].

Serpentine supravenuous hyperpigmentation was first described in 1976 by Hrushesky as an unwanted side effect of intravenous 5-Fluorouracil [9]. Other chemotherapeutic agents suggests vinorelbine, fotemustine and docetaxel have also found to cause serpentine supravenuous hyperpigmentation [9,10].

CONCLUSION

Our case reports suggest that subclinical nerve-fiber injury during chemotherapy of stomach cancer patients. There is no specific treatment for serpentine supravenuous hyperpigmentation although they may disappear gradually. However most of the authors suggest that central venous access route could potentially be useful to protect the skin overlying the peripheral vein from the darkening of the patients.

REFERENCES

1. Chu E. Ode to 5-fluorouracil . *Clinical Colorectal Cancer*, 6(9), 609.
2. National Academy of Sciences, Biographical memoirs, 80, 135.
3. Van Kuilenburg AB. Dihydropyrimidine Dehydrogenase and the efficacy and toxicity of 5-fluorouracil. *European Journal of Cancer*, 40, 2004, 939–950.
4. Teixeira L, Barry S, Debourdeau P, Cohen A, Tournigand C. Cardiotoxicity of 5-fluorouracil. *Bulletin du Cancer*, 91, 2004, 154–158.
5. Miller E. The Metabolism and Pharmacology of 5-fluorouracil. *J Surg oncol*, 3, 1971, 309-315.
6. Shelley WB, Shelly ED. Scrotal dermatitis caused by 5-fluorouracil (Efudex). *J Am Acad Dermatol*, 19, 1988, 929-931.
7. Vukelja SJ, Bonner MW, McCollough M *et al.*, Unusual serpentine hyperpigmentation associated with 5-fluorouracil: case report and review of cutaneous manifestations associated with systemic 5-fluorouracil. *J Am Acad Dermatol*, 25, 1991, 905-908.
8. Chen JS, Jan YY, Lin YC *et al.*, Weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract carcinomas. *Anti-Cancer Drugs*, 9, 1998, 393-397.
9. Hrushesky WJ. Letter: Serpentine supravenuous hyperpigmentation. *JAMA*, 236(2), 1976, 138.
10. Rao R, Balachandran C. serpentine supravenuous pigmentation. A rare vasulo-cutaneous effect induced by systemic 5-fluorouracil. *Indian J Dermatol venereal leprol*, 76(6), 2010, 714-715.