Case Report

Nightmares ~~caused by~~associated to nevirapine during chemoradiotherapy for carcinoma tongue

Abstract

Nevirapine, an NNRTI (add the whole word with abbreviation between brackets) is a drug used in the management and treatment of HIV. It ~~and~~ is considered safe for use in conjunction with platinum-based chemotherapy. Chemotherapy is a staple of cancer treatment and is used routinely in the management of malignancies of the head and neck. However, managing HIV-positive cancers presents challenges due to individual side effects and drug interactions. Drug interactions can potentiate or reduce drug metabolism, reduce excretion, or cause adverse ~~events~~drug reactions.
Herein, we describe a case of new-onset nevirapine-induced nightmares that was noted in a patient undergoing chemoradiotherapy with cisplatin.

Keywords: case report, nevirapine, radiotherapy, chemotherapy, cisplatin, toxicity, adverse drug reaction

Introduction

Highly active antiretroviral therapy (HAART) has radically changed the approach to treating individuals who are positive for human immunodeficiency virus (HIV-positive). The usage of various lines of drugs which include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FI), and others, has helped manage the illness, reduce transmission, and has also decreased the incidence of AIDS-defining cancers (ADCs).[1] Nevirapine, which is an NNRTI, acts by forming a hydrophobic pocket near the active site of the reverse transcriptase, thereby causing a structural deformation on the substrate binding site and affecting the formation of HIV viral DNA. It is considered to be safe for administration along with chemotherapeutic drugs.[2]

Chemotherapy is a mainstay in the management of cancers. Squamous cell carcinomas of the head and neck are treated with the use of cisplatin either in the neoadjuvant setting or in concurrence with radiotherapy which is administered as an adjuvant treatment after surgery or with radical intent. [3]

Cancers in HIV-positive patients that require chemotherapy pose a challenge in management which can be attributed to the individual side effects of the drugs and their interactions. Drug interactions may either potentiate or reduce the metabolism of the drug, reduce excretion, or ~~react to~~ cause adverse ~~events~~ drug reactions (ADR)that may belong to one of the drugs or both.[4] In this report, we describe a case of nevirapine-induced nightmares that was noted as a fresh complaint in a patient undergoing chemoradiotherapy with cisplatin.

Case Report

A 50-year-old male, who has been a tobacco chewer for 27 years and HIV positive for 8 years ~~and~~ on nevirapine, presented to the oncology outpatient department with complaints of a large ulceroproliferative growth over the left border of the tongue. The patient also had multiple hard swellings over the neck. Clinical examination confirmed the findings of the lesion and enlarged lymph nodes in bilateral levels IB, and ipsilateral levels II and III. A biopsy was done on a sample taken from the tongue lesion that revealed it to be a moderately differentiated squamous cell carcinoma. A contrast-enhanced computed tomography (CECT) scan and an 18-fluorodeoxyglucose positron emission tomography (18FDG PET) scan was performed that showed a locally advanced lesion with multiple involved lymph nodes in the neck. No other lesions were noted. The disease was staged as cT3N2bM0. The patient was taken up for radical chemo-radiotherapy (CTRT) to a dose of 72 Gy in 40 fractions at 1.8 Gy per fraction delivered daily with concurrent cisplatin at 40 mg/m2 delivered weekly.

During the routine weekly review at week 1, the patient complained of debilitating nightmares on the day of receiving chemotherapy, and on the next day as well. The patient had no complaints for the rest of the week. The patient did not have any other complaints. Upon discussion at the institutional tumor board, the patient was allowed to continue treatment without any further intervention. At the next follow-up one week later, the patient's nightmares on days 0 and 1 of the current cycle of chemotherapy had not resolved and mucositis had developed. He was prescribed topical lignocaine for the ulcers, oral paracetamol for the ulcer pain, and pregabalin as an analgesic and to help the patient sleep. On week 3, the patient's nightmares were on days 0, 1, and 2 of the chemotherapy cycle. The patient now had florid mucositis and had developed erythema of the skin. Upon detailed investigations of the medications and history, the patient did not have any issues with nightmares affecting sleep ever in the past since starting the nevirapine. The case was discussed again at the tumor board and it was concluded that the nightmares were due to the overlapping of the administration of nevirapine and either cisplatin or low-dose dexamethasone. For the next cycle, the dose of dexamethasone was reduced and the patient had nightmares again indicating that the adverse event could be due to the interaction between cisplatin and nevirapine.

The patient was advised to meet the physician prescribing the nevirapine to change it to a different line of antiretroviral therapy (ART) and was advised that as long as the nevirapine continued these nightmares would persist.(how was the outcome after cessation of nevirapine and before cessation of CTRT? Or nevirapine was not stopped?) He was also given olanzapine to improve sleep quality. The nightmares persisted till the end of treatment and resolved within 1 week after CTRT.

Discussion

Nevirapine is ~~a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is~~(that was said in introduction) a non-competitive inhibitor of HIV-1 reverse transcriptase. Nevirapine is metabolized by the CYP3A and CYP2B6 enzymes and has a half-life of 25-30 hours.[2][5] ~~Nevirapine~~ It is known to cause vivid dreams, and when taken in high doses has been shown

to cause mania as well.[6] In patients with an altered CYP2B6, neurotoxicity has also been noted.[7]

Cisplatin is an alkylating agent that is routinely used to treat malignancies of the head and neck, including the tongue, in the neoadjuvant setting or concurrence with radiotherapy. Cisplatin toxicities include nephrotoxicity, myelosuppression, ototoxicity, and gastrointestinal toxicity, but no psychiatric toxicities have been noted.[8]

While both nevirapine and cisplatin are inducers of CYP3A4, cisplatin is known to be a minor inhibitor of CYP2B6.[4] Cases were found to have 85% of the enzyme activity as compared to the controls (sentence not clear, you can change it like this: the enzyme activity was decreased to 85% compared to the controls) add reference. This inhibition could potentiate the longer action of nevirapine, precipitating its ~~adverse events~~ADR in the form of vivid dreams or nightmares. The addition of steroids post-chemotherapy may affect the normal sleep cycle of the patient and lead to the exacerbation of these vivid dreams. (reference?)

Switching to alternative ART regimens that have no interactions may benefit HIV-positive patients undergoing chemotherapy.[9] While most ARVs do not have any interaction with the platinum-based chemotherapeutic drugs, upon onset of symptoms a review of the drug being used must be conducted.

To date, no reports of interactions between cisplatin (and nevirapine) have been published, which led to the delay in identifying the interaction and the cause in this case. Further research into drug interactions is required to shed light on this subject.

Conclusion

The use of nevirapine along with cisplatin may potentiate its toxicity and must be used with caution. Switching to an alternate ART may prove to be beneficial by minimizing toxicities.

General comments:

- Explain more the mechanism of nightmare with nevirapine and its usual presentation (delay, outcome..)
- Accentuate that it is your hypothesis that the nightmare may be due to an interaction with CYP2B6 inhibition by cisplatin as it is not reported in literature. In fact, in the reference 4, it is stipulated that “The cisplatin, although it is able to inhibit partly the activities of CYP enzymes (to 75% of activity of CYP2C9, at 400 mmol/l), is not expected to elicit a clinically relevant interaction because of low plasma levels of this drug”

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Consent

As per international standards or university standards, patient written consent has been collected and preserved by the author(s).

Ethical Approval

It is not applicable.

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