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Case Series

ADVERSE REACTIONS OF DACARBAZINE IN PEDIATRIC ONCOLOGY; A CASE SERIES FROM A TERTIARY CARE CANCER SPECIALTY HOSPITAL, PAKISTAN.

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Abstract

Hodgkin's lymphoma in pediatric patients involves chemotherapy drug regimens containing Dacarbazine as a backbone of the therapy. Adverse drug events are the major concerns in the treatment plan of chemotherapy. Here in this case series, we present five cases of Hodgkin's lymphoma of pediatric age group getting treated with Dacarbazine based chemotherapy either COPDac or ABVD. All patients developed shivering during the infusion. Three of them had fever spikes and one patient happened to have tachycardia. All the events were managed conservatively followed by safe administration of chemotherapy. Four patients are continuing to have treatment as per the plan and one patient is with end of treatment and on follow up. Naranjo's scale was used for probability assessment of the events and score of 6 was given to all the events, indicating the adverse drug reactions to be probable. A very scarce data and our case series are evocative of further studies to review the administration time of the Dacarbazine as well as the addition of pre-medication before initiation of Dacarbazine infusion.

Key words: Pediatric Hodgkin's Lymphoma, Adverse Drug Reactions, Dacarbazine, Case Series

Abbreviations: PHL (Pediatric Hodgkin's Lymphoma), COPDac (Cyclophosphamide, Vincristine, Prednisone, Dacarbazine), ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), OEPA (Vincristine, Etoposide, Prednisone, Adriamycin), ADR (Adverse Drug Reaction)

Introduction:

Cancers originating from blood cell lineage in pediatric population are remediable and are treated with combinations of chemotherapy drugs (1). Adverse drug events usually happen during the course of chemotherapy and are the utmost reason of interruption in the treatment plan of chemotherapy. In one recent study higher incidence of ADRs in pediatric patients as compared to adult patients has been documented (2). Many of these ADRs are anticipated and in many cases are avertable (3). Dacarbazine as a part of many protocols is used in pediatric malignancies in our hospital as per the guidelines (1). We describe, after written informed consents from the patient's attendants, five cases of PHL population who during treatment with Dacarbazine, experienced symptoms like fever, tachycardia and shivering during infusion.

Case series:

Case 1

A 6-years-old child presented with a history of left sided neck mass with enlarged cervical lymph nodes and no B-symptoms, was diagnosed to have Mixed cellularity Classical Hodgkin's lymphoma, stage IIA. Patient was planned to start chemotherapy COPDac alternating with ABVD. On the day of administration of ABVD cycle 1 day 1 on 5th Sep 2017, during the infusion of Dacarbazine, patient complained of shivering and fever. Dacarbazine infusion was held. Patient was examined and found shivering with fever of 39C°and warm extremities. Rest of the systemic exam was unremarkable. Intravenous paracetamol 180mg, ceftriaxone 1400mg was advised along with pheniramine maleate 20mg and hydrocortisone 40mg and administered immediately to the patient. Blood

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sample was taken and sent to lab for any microbial culture sensitivity. Patient was observed and found to be stable and afebrile after conservative management. Remaining infusion of chemotherapy was resumed and finished safely about after 3 hours of the reactions. Antibiotic administration was advised and followed to have for at least 48hrs of getting afebrile after fever spike. Since patient had no further fever spike and shivering episode also microbial culture were negative for any sensitivity, antibiotic was discontinued after 48 hours. Patient was given appointment for ABVD cycle 1 D15 accordingly and received Dacarbazine safely.

Case 2

Patient aged 6-years-old came with a history of on and off fever, generalized body weakness, right cervical lymphadenopathy in association of B-symptoms. Cervical lymph nodes biopsy and further work-up was done and a diagnosis of classical Hodgkin's lymphoma, stage IIIB was established. Chemotherapy COPDac alternating with ABVD each of four cycles was planned. On 18th Aug 2017, day 15 of 2nd cycle of ABVD was planned when patient started shivering, became febrile and developed tachycardia just after 5 minutes of Dacarbazine infusion was started. Chemotherapy was held till further orders. Fever of 38.5 C° with a raised in blood pressure up to 140/90 mm/Hg with three consecutive readings and a pulse of 125/min was documented. Apart from stopping the infusion, blood sample was taken and sent for microbial analysis and patient was managed with immediate intravenous administrations of pheniramine maleate 25mg, hydrocortisone 50mg, paracetamol 250mg and antibiotic ceftriaxone 1725mg. in order to manage hypertension, a calcium channel blocker nifedipine 10mg was administered with an hourly monitoring of blood pressure for three hours. Once patient became hemodynamically stable after 3 hours of reactions, remaining infusion of dacarbazine was administered slowly and safely. Blood cultures were followed and found negative for any sensitivity. Patient was given appointments for next chemotherapy as per therapy schedule and received further doses safely.

Case 3

5-years-old boy with a history of bilateral palpable cervical and inguinal lymphadenopathy for last 1.5 years and no B-symptoms was diagnosed as a case of Classical Hodgkin's Lymphoma stage III-AS. Patient was planned for three cycles of chemotherapy COPDac alternating with ABVD. Cycle 3 of chemotherapy COPDac was scheduled on 19th Aug 2017 and just after starting the administration of day 1 Dacarbazine, patient developed shivering. After clinical assessment, Dacarbazine infusion was stopped with the advice of administration of injection pheniramine maleate 15mg and injection hydrocortisone 30mg I/V. Patient's vitals were monitored and were found clinically unremarkable after every 15 min for the next hour. About after one hour of the reaction when patient was found clinically stable, remaining chemotherapy was resumed and administered safely. The subsequent infusions of Dacarbazine on day 2 and day 3 were administered as per protocol with no episode of untoward events.

Case 4

Patient aged 7-years-old young boy presented with swelling of right sided neck with no B-symptoms from last three months. Biopsy from right cervical lymph node was done and a diagnosis of Mixed Cellularity Classical Hodgkin's Lymphoma, stage IIA was made. Patient was planned to be started on chemotherapy COPDac alternating with ABVD for each of three cycles. On 7th Sep 2017, day 1 of first cycle of ABVD, patient developed shivering immediately after the Dacarbazine infusion has been started. Chemotherapy infusion was stopped followed by vitals checking, which were found unremarkable. Injection pheniramine 20mg and injection hydrocortisone 40mg were administered to manage the symptoms conservatively. Patient was observed clinically for symptoms for next hour, and after that was considered fit for the remaining chemotherapy once became asymptomatic.

Next chemotherapy on day 15 was administered as per protocol without happening of the adverse event.

Case 5

A young boy, aged 8-years with eleven months history of left cervical lymphadenopathy but no B-symptoms was diagnosed with Classical Hodgkin's Lymphoma of Mixed Cellularity type stage IIIAS. Patient was planned to be started on chemotherapy COPDac alternating with ABVD each of three cycles. 3rd cycle of chemotherapy COPDac was planned on 18th Aug 2017 and just after the start of day 1 Dacarbazine infusion, patient started shivering. Chemotherapy infusion was stopped and patient was assessed clinically. Upon clinical assessment, patient was found afebrile and hemodynamically stable. To manage the symptoms of shivering, intravenous administration of pheniramine maleate 22mg and hydrocortisone 40mg was advised. Symptoms were resolved after conservative management, but patient was kept under observation for next half an hour. Vitals monitoring was ensured during the observation and once patient was considered fit enough for chemotherapy, the remaining infusion was resumed as per the protocol and finished safely. Subsequent doses on day 2 and day 3 of this cycle were administered safely with no happening of adverse event.

Discussion:

According to the WHO guidelines, an ADR is defined as "any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy (4).

From the class of alkylating agents (Triazene compounds), Dacarbazine shows its antineoplastic activity after conversion to an active alkylating metabolite MTIC [(methyl-triazene-1-yl) - imidazole-4-carboxamide]. MTIC causes methylation of O6 guanine, which leads to double stranded DNA breaking and ultimately apoptosis (5).

In our institution, PHL patients are divided into different treatment groups according to the presentation of disease at the time of diagnosis. Patients then receive a current regimen which was adapted due to excessive toxicity perceived with OEPA/COPDac; i.e. COPDac/ABVD alternating courses for a particular number of cycles defined as per their treatment group (6). As per the protocol recommendations for Dacarbazine in COPDac, the dosing recommendations for Dacarbazine is 250mg/m2 from Day 1 to day 3, to be delivered over 30 minutes after dilution in 100ml sodium chloride 0.9%. Whereas in ABVD, the dosing and administration of Dacarbazine is as 375mg/m2 on day 1 & 15 diluted in 100ml of sodium chloride 0.9% and to be administered in 15 minutes.

Up to our knowledge, no documented data is available reporting shivering and tachycardia resulting from Dacarbazine infusion. Only fever has been documented as a part of flu like syndrome, as infrequent/post marking adverse event according to the drug monograph (7). In our case series, case 1, 2 & 4 were scheduled for ABVD, whereas 3 & 5 were given appointments for COPDac when the reactions were observed. All patients developed shivering with an additional fever spike which was documented in case 1 and 2. Case 2 also reported tachycardia which was managed with the administration of antihypertensive drug. Although the reactions were observed in quite similar dates, but it is of particular interest that Dacarbazine has been infused to other pediatric patients as well on the same days but with no episode of reaction indicating that the batch for Dacarbazine shouldn't be hold accountable for these reactions. Also, processes for reconstitution, further dilution by pharmacy technician and for nursing administration were retrieved and found done according to the defined protocol and chemotherapy administration guidelines of our institution.

Our cases belong to the adverse reactions induced by Dacarbazine infusion which was kept held after the reaction and then the reactions were managed after administering

antihistamine and corticosteroid. All the cases were continued with remaining chemotherapy as resolution of symptoms occurred within 1-3 hours of reactions. Follow up also showed no issue with chemotherapy. The ADRs are type B and are probable with a score of 6, as estimated by Naranjo's adverse drug reaction probability scale (8) and related to the administration time defined for Dacarbazine infusion. Since a range of 15 to 60 minutes with other infusion durations as well has been recommended as infuse over time (7), thus it is suggested to review either the delivered over time allowed for Dacarbazine in ABVD and COPDac chemotherapy protocols or the consideration of antihistamine and corticosteroid as pre-medication. Our case series will serve as local study to support and initiate further investigational studies for the purpose of identifying safe infusion of Dacarbazine in PHL population.

Conclusion:

This case series reveals that administration of Dacarbazine infusion was associated with shivering, fever and tachycardia in PHL patients. These adverse reactions need to be considered while infusing Dacarbazine.

Disclaimer:

The abstract or any part of this case series has not been published or presented previously in any conference.

Conflict of interest:

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