Short Communication

Hypersensitivity Reactions to Platinum Based Drugs in NSCLC – When and What?
Prakruti Dash
Department of Biochemistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha.

ABSTRACT
Platinum based chemotherapeutic agents like carboplatin and cisplatin are highly recommended drugs in ovarian cancers and now has become an integral part of adjuvant chemotherapy regimen in lung cancer patients. Hypersensitivity reactions developing immediately or a few days later have been sporadically reported in many literatures which included both ovarian and lung cancer patients. Knowledge and preparedness to tackle these adverse reactions which may also be life threatening at times is essential for the care givers. This case also very typically suffered from hypersensitivity reactions upon repeated administration of carboplatin which was effectively tackled by anti-allergic medications and the treatment could be completed by timely intervention.

Key words: Hypersensitivity, Platinum based Drugs, NSCLC

Address for Correspondence:
Prakruti Dash
Department of Biochemistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.
E mail: dashdrprakruti@gmail.com
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INTRODUCTION
Lung cancer has reached alarming proportions, now being one of the primary cause of cancer deaths in developed countries and is rising at a disquieting in the developing countries [1]. Treatment of ovarian cancer with platinum based systemic chemotherapy like Cisplatin and Carboplatin is a well-accepted regimen [2]. Hypersensitivity to these drugs has been recognised in the ovarian cancer patient, commonly after having a prior exposure to platinum chemotherapy and subsequently treated for relapse [3, 4, 5].

Over the years, the treatment strategy for non-small cell lung cancer (NSCLC) has been restructured based on the results of large clinical trials which have demonstrated a survival benefit from the use of adjuvant chemotherapy with platinum based drugs like carboplatin and cisplatin. This change in lung cancer treatment has steered many patients to receive more than one course of platinum chemotherapy in their lifetime: after the initial surgical resection as adjuvant chemotherapy, and then later in the event of recurrent or metastatic cancer [6, 7].

In light of the incidences of hypersensitivity reaction seen in ovarian cancer patients receiving repeated cycles of Platinum drugs, it is vital that clinicians are aware of the possibility of such adverse reactions when administering platinum based therapy to lung cancer patients and have adequate preparedness and protocols to prevent and manage these reactions, so that their impact on further treatment is minimized.

CASE
A 40 year old male patient was diagnosed with Non-small cell adenocarcinoma of right lungs in Stage 4 with multiple metastases to brain. He had a very small lesion in the right lung at the bifurcation of middle bronchus with collapse of the middle lobe. His MRI scan of brain showed a large cystic lesion in brain (4×4×5 cm) in the left temporal lobe with perilesional edema and
midline shift along with a few small lesions in the right front parietal lobe and left occipital lobe of brain. Initial treatment comprised of WBRT (whole brain radiation therapy) along with chemotherapy with carboplatin and pemetrexed.

**Treatment History:** The patient after completion of WBRT took 3 cycles of Carboplatin with pemetrexed in an interval of 21 days. He tolerated the chemotherapy well with occasional nausea and vomiting. On PET-CT scan his lung lesion was still active while the brain lesions had disappeared with only the bigger cystic lesion in the left temporal lobe found to be present but PET-CT negative. He took another cycle of carboplatin and pemetrexed along with localised radiation therapy to the lungs lesion. Tolerance to the treatment was good. On evaluation, the lungs lesion was PET-CT negative and small lesions in the brain had vanished with the big cystic lesion in brain slightly shrunken in size and PET-CT negative.

**Follow-up** the patient did well with no symptoms for 1 year and repeated follow-up scans showed stable disease.

**Recurrence of brain lesion** after 1 year and 2 months of initial diagnosis, the brain cystic lesion increased in size with gross perilesional edema and mid-line shift for which immediate decompression surgery was performed. Patient fared well after the surgery and remained symptomless till he had a recurrence of the same cystic lesion 6 months after the first surgery. He was reoperated followed by stereotactic radiation at the operated site. He did well for 6 months after which the brain lesion again showed progression in MRI follow-up scan.

**Chemotherapy with Carboplatin and Pemetrexed:** Patient this time was given chemotherapy with the same drug combination carboplatin and pemetrexed for 6 cycles. He well tolerated the first two cycles but developed a mild skin rash and hypersensitivity reaction at the 3rd cycle (7th cycle from initial treatment) after taking around 100ml of the scheduled dose. The drug administration was temporarily stopped and Inj. Avil with Dexamethasone was given by which the reaction subsided and infusion restarted and completed.

**Hypersensitivity reaction in the next 3 cycles:** The next cycle after 21 days again lead to skin rash with a slightly more aggravated hypersensitivity reaction with itching after infusion of 100ml. Infusion was again temporarily stopped and anti-allergic medicines given which subsided the reaction. The infusion was restarted but had to be discontinued before completion as the hypersensitivity reaction reappeared this time.

**Prevention:** Anticipating a more aggravated reaction with cisplatin, Carboplatin was continued in the next cycle as the patient was responding well to the treatment but brand of the drug was changed. The patient was given prior anti-allergic medications and other precautionary measures were kept ready. The patient was able to take the therapy without any measure adverse reactions.

**DISCUSSION**

The platinum coordination complexes carboplatin and cisplatin wield their anticancer properties through crosslinking of DNA mostly at N7 of Guanine residue. Type I, IgE mediated hypersensitivity is the one reported to be associated with the platinum compounds where the IgE acts upon tissue mast cells and basophils in peripheral blood, stimulating the release of SRSs (slow reacting substances of anaphylaxis) like histamines, leukotrienes and prostaglandins that leads to capillary dilation and the rapid contraction of smooth muscle, facial flushing, and pruritus. However, some patients may suffer from severe reactions like angioedema, symptomatic bronchospasm, hypotension, and cardiac dysfunction, which need immediate intercession. Typically symptoms usually develop during or within a few hours of drug infusion as was the case in this patient, but may also occur a little later after administration. As a preventive measure intradermal skin testing has also been used to predict hypersensitivity to carboplatin. Platinum chemotherapeutics inducing allergic hypersensitivity reactions have been widely reported with much of the literatures related to its application in ovarian cancer. The incidence of carboplatin hypersensitivity is not exactly known but it is quite evident from various literatures that the reactions usually occur in patients who are exposed to more number of cycles and also related to repeated exposures after a gap.

This patient very typically experienced the allergic reaction after he was exposed to Carboplatin after a gap of 2 years on his 7th cycle. In our case the reaction was mild and temporary stoppage of infusion of Carboplatin and administration of anti-allergic medications stopped the adverse reactions. Interestingly, after that the patient could continue with the treatment and took the full dose with no further anaphylaxis. Prior administration of anti-allergic...
medications before initiation of infusion protected this patient from adverse reactions during infusion in the last cycle and he could continue with the treatment uninterruptedly with a good response.

**CONCLUSION**

This case showed that the NSCLC patients experienced hypersensitivity reactions to carboplatin and such reactions occurred in a pattern consistent with that described by various oncology literatures. Patients previously exposed to multiple cycles of platinum chemotherapy are at risk of a reaction, and patients who are being treated for relapsed cancer (having a prior exposure to platinum chemotherapy and a treatment-free interval, as in this case) with platinum-based chemotherapy are at greater risk. Hence, it is important that all lung cancer patients must be informed about the risk of platinum hypersensitivity, and in case of any adverse reactions should report to their treatment team immediately. Clinicians and hospital staff should be aware of these risks and be able to respond urgently in the event of a reaction to avoid any major mishap. Pre-treatment with anti-allergic medications and/or skin testing may prevent many such adverse reactions, aiding the patient to continue with the treatment.

**REFERENCES**