

Application of hypersensitivity skin testing in chemotherapy-induced pneumonitis

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Skin testing has been utilised to determine the culprit allergenic agent in drug reactions. Its application in the setting of hypersensitivity reaction relating to combination chemotherapeutic regimens may help identify the causative drug, allowing drug that is safe to be continued and avoiding limiting treatment options for patients. We report what we believe to be the first published case of hypersensitivity skin testing for gemcitabine-induced pneumonitis in a patient with metastatic leiomyosarcoma and another case of docetaxel-induced pneumonitis in a patient with metastatic HER2-positive breast cancer.

Key words: Skin Tests; Lung Diseases, Interstitial; Antineoplastic Agents; Antibodies, Monoclonal; Hypersensitivity

INTRODUCTION

Skin testing is a method of diagnosing drug hypersensitivity and has not been utilized in the field of medical oncology where multiple antineoplastic agents may be implicated in a hypersensitivity reaction. We describe two cases of drug-induced pneumonitis secondary to combination chemotherapeutics and the application of skin testing in determining the culprit agent. Testing enabled identification of the non-causative agent for patients whose therapeutic options were already limited.

CASE REPORTS

Case 1

A 65 year-old woman with metastatic leiomyosarcoma had progressive disease after receiving systemic therapy with doxorubicin and then pazopanib. She had no medical comorbidities, regular medication or known drug allergy. Third-line combination gemcitabine and docetaxel was initiated. Five days after the third cycle was given, she presented with acute respiratory distress. Congestive cardiac failure and septic causes were excluded. Blood tests revealed stable liver and renal

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function tests. Computed tomography pulmonary angiography (CTPA) excluded pulmonary emboli but demonstrated bilateral pulmonary infiltrates consistent with drug-induced pneumonitis. On treatment with corticosteroid, her condition improved.

Subsequently, she underwent skin prick testing with gemcitabine and docetaxel at the concentration of 0.2 mg/mL and 0.4 mg/mL, respectively, equivalent to the concentration at which the drugs were infused. Histamine was used as positive control and saline was used as negative control. As neither drugs elicited a positive reaction, intradermal testing was performed at a dilution of 0.02 mg/mL and 0.04 mg/mL for gemcitabine and docetaxel respectively. Readings taken thirty minutes after the injection was positive for gemcitabine, with a 5-mm increase in the diameter of the original bleb and a surrounding flare response, implicating gemcitabine as the culprit agent for the pneumonitis. A reading 24 hours later found no delayed response. Docetaxel was recommenced and led to clinically apparent and ongoing meaningful disease control.

Case 2

A 59-year-old woman was found to have recurrent hormone receptor positive and HER2 positive breast cancer with malignant pleural effusion and bony metastases. She proceeded with combination trastuzumab and docetaxel, and completed five cycles uneventfully with a good clinical and tumour marker response. Six days prior to the sixth cycle, she developed acute respiratory distress. Chest x-ray revealed a stable pleural effusion and a new reticular density throughout the lung fields. CTPA excluded pulmonary emboli but confirmed widespread bilateral ground-glass opacities and interstitial septal thickening consistent with acute pneumonitis. Treatment with prednisolone was commenced with improvement in her symptoms. Septic screening detected *Escherichia coli* bacteriuria but no other sources of infection. A gated heart pool scan revealed a normal left ventricular ejection fraction.

She underwent similar skin testing with a delayed reading at 48 hours; intradermal testing was performed with an incremental increase in the docetaxel concentrations. Saline, as negative control, and 0.02-mg/mL docetaxel did not induce a wheal or a flare response. Docetaxel at 0.2-mg/mL and 2-mg/mL concentration did not induce a wheal but at 48-hour reading induced a wheal and flare response. Skin prick and intradermal testing was negative for trastuzumab. She thereafter continued on treatment with trastuzumab, with the addition of pertuzumab

with radiological and clinical improvement of her pneumonitis one month later.

DISCUSSION

In the treatment of metastatic soft tissue sarcoma, the combination of gemcitabine and docetaxel has been shown to improve response rate and survival in comparison to single agent gemcitabine [1]. Meta-analysis on this combination regimen (n = 5,065) has estimated the incidence of pulmonary toxicity to be 2.7% [2]. Even though either drug could induce pneumonitis, there has not been a previous attempt to determine the causative drug among this combination in any patient. Docetaxel, trastuzumab, and pertuzumab are the recently established standard first-line treatment for metastatic HER2-positive breast cancer [3], and there have been case reports of drug-induced pneumonitis with the use of trastuzumab [4]. The development of drug-induced pneumonitis, without identification of the causative agent, could hinder the continuation of this effective combination regimen.

Immunological skin testing is an objective investigation to determine the culprit antigen of hypersensitivity reactions [5], and it has been utilised in the diagnosis of hypersensitivity pneumonitis [6]. In testing for hypersensitivity reactions, a skin prick test is performed to assess for IgE mediated sensitization, and intradermal testing is useful in assessing both IgE mediated and delayed type hypersensitivity reactions [7]. Patch testing could be performed as well and this involves mixing the drug to be tested in petrolatum or 0.9% saline and applying the mixture to the skin under occlusion for 48 hours to elicit a wheal-and-flare response [8]. While patch testing is more specific for diagnosing delayed drug hypersensitivity [5], the preparation is more difficult to make. The dilution of chemotherapeutic agents to be used for skin prick testing and intradermal testing can be prepared at each individual testing centre. The downside is the lack of standardisation for the results to be reproducible.

The positive response on intradermal testing with gemcitabine in the first case is more suggestive of an immediate hypersensitivity reaction rather than a delayed, cell-mediated hypersensitivity reaction generally presumed to be the cause of hypersensitivity pneumonitis. This suggests the probable lack of a clear delineation with regards to immediate and delayed hypersensitivity responses. An analogy to this is the pathogenesis involving a combination of IgE and T-cell mediated response in allergic bronchopulmonary aspergillosis. Exposure to *Aspergillus* spores leads to a T-cell

response in the bronchoalveolar lymphoid tissue and also, in atopic individuals, IgE formation [9]. T-cell generated cytokines in turn stimulate a further increase in IgE and eosinophilia [10], thus obscuring the dichotomy between immediate, IgE-mediated, and delayed, T cell-mediated, hypersensitivity reactions.

None of the agents we tested was a vesicant or irritant, which would have contraindicated intradermal injection. Administering a series of dilutions may be performed, as in the second case, to confirm the reaction elicited to be a true positive, not merely a result of skin irritation. Testing on control subjects to ensure a nonirritant concentration may not be appropriate for cytotoxic agents.

To our knowledge, there has not been any previous published report of skin testing for combination chemotherapeutics in the setting of hypersensitivity reactions. Gemcitabine is widely used, mostly in combination with other chemotherapeutic agents, in many solid tumours, and regimens including anti-HER2 monoclonal antibodies are standard of care in the treatment of HER2-positive breast cancers. On developing hypersensitivity reactions to these combination regimens, identifying the culprit drug may allow the continuation of the noncausative agents, maximising the potential benefit of the treatment without the risk of inducing recurrent reactions. Our two cases highlight the usefulness of skin testing, for nonvesicants or non-irritants, when hypersensitivity reactions occurred.

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