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Case Report

Synergistic Toxicities from Multiple Therapies for Synchronous Malignancies

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Abstract
Patients may present with multiple malignancies in the setting of particular environmental and occupational exposures. These patients often require combination systemic therapy, which has not yet been studied for concurrent use. While toxicities for specific chemotherapies and immunotherapies may be well known, the possibility of exaggerated toxicity due to combination therapy exists and is understudied. Several trials are underway that may shed further light on how combination therapies affect patient toxicity. This case report outlines the unfortunate development of severe edema and rash, refractory to traditional methods of management, from combining immunotherapy and chemotherapy.

Introduction

Patients who harbor multiple malignancies are not uncommon, especially in those that have a history of environmental and/or occupational exposures. Multiple malignancies may necessitate multiple systemic therapies that have not been studied for current use. Thus, unexpected toxicity out of what is expected for each individual therapy may be encountered. Here we present a case of a patient who was concurrently treated for three advanced malignancies with hormonal therapy, systemic chemotherapy, and immunotherapy.

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Case Report

A 61-year-old Caucasian gentleman with a 15-pack-year smoking history who last smoked 20 years ago was diagnosed with a stage I squamous cell carcinoma of the lung. A video-assisted thoracoscopic surgery was performed. The left upper lobectomy specimen revealed the tumor was 1.8 cm (about 0.71 in) in greatest dimension, moderately differentiated, and with clear margins. There was no involvement of the 18 sampled multi-station lymph nodes or lymphovascular invasion. The only high-risk feature was visceral pleural invasion. A discussion about the risks and benefits of adjuvant chemotherapy ensued, including a detailed overview of the data in the stage I setting. The patient and his oncology team decided against adjuvant chemotherapy given the lack of data showing survival benefits in this setting.

The patient did well for approximately 1 year until he started experiencing diffuse bony pain, pain in the left chest, and unintentional weight loss of 20 pounds. Further workup revealed diffuse metastatic disease, sclerotic in appearance, throughout the entire skeleton. In addition, there was a large soft tissue mass encasing the left-sided 6th–8th ribs posteriorlaterally, associated with bony destruction. A prostatic-specific antigen (PSA) test came back at 35.24 ng/mL, which was previously 0.81 ng/mL a year ago. A biopsy of the left iliacus showed a high-grade small cell carcinoma in a background of prostatic adenocarcinoma, indicating neuroendocrine differentiation. The left chest wall was also biopsied and consistent with a recurrence of the patient's previous squamous cell carcinoma of the lung.

At this point, there were two concurrent advanced malignancies with three total histologies. Focus was placed on the small cell component of the prostate cancer, as this was deemed the most aggressive of the three. The patient started small cell-directed therapy with atezolizumab, carboplatin, and etoposide. Androgen deprivation therapy (leuprolide) was added for the adenocarcinoma component of the prostate cancer, and local irradiation was done to the painful left chest wall mass, but no other squamous cell systemic therapy was started initially.

An excellent partial response to the aforementioned treatment was achieved. Unfortunately, 6 months into treatment, evidence of progression of the sites known to be small cell, such as the mediastinal lymph nodes and osseous disease, began to progress. Shortly thereafter, the left chest wall lesion also started to grow and become more painful. Approximately 9 months into the small cell diagnosis, while on maintenance atezolizumab, docetaxel was added. This drug was chosen as it has known clinical benefit in small cell cancer of multiple tissue origins, squamous cell lung cancer, and prostatic adenocarcinoma. The decision was made to keep the atezolizumab going as it was still controlling some areas of known small cells based on imaging. Of note, steroid premedication for docetaxel was given. Leuprolide was continued as well, given that the patient still had a sustained PSA response of 0.03 ng/mL. The chest wall mass was re-irradiated for symptom control.

The patient experienced multiple toxicities that were out of proportion from what would be expected from each therapy alone. Peripheral edema is a well-known toxicity of docetaxel [1], but the patient gained 30 lbs. of fluid within the first cycle of docetaxel, with his legs so severely edematous he was unable to walk. Cardiac and renal evaluation revealed no abnormalities, and he did not have hypoalbuminemia. No venous compression by tumor was found either. He also had an erythematous, tender, and pruritic rash on both lower extremities. His systemic therapy was held, and he began on furosemide, but his edema proved to be refractory to these measures. Similarly, the rash was not responsive to topical corticosteroids. Ultimately, the treating team hypothesized that there was some immune component to the edema and rash, and he was started on high-dose steroids, which did lead to resolution of these symptoms.

After an extensive discussion, the patient opted to go on palliative care rather than resume any treatment and risk recurrence of these toxicities. He expired 15 months after the diagnosis of his prostate cancer and the recurrence of his lung cancer.

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Discussion

We present a case of presumed synergistic toxicity from immunotherapy and chemotherapy. This is a phenomenon that has been described previously, such as the increased rate of cytopenias when pembrolizumab is added to platinum doublet in lung cancer [2, 3]. Given that combinational chemo-immunotherapy regimens are emerging in the treatment of many cancers and patients with multiple concurrent malignancies are not an uncommon finding, we expect increase in usage of concurrent chemo-immunotherapy. Thus, treating providers must be aware of the potential for toxicity in proportion to what has commonly been seen in each drug class individually. This case illustrates refractory peripheral edema and rash so severe that quality of life was impeded to the point where it influenced the patient's decision for palliative care.

A review of the literature indicates that more data may be available soon to determine the potential incidence of our findings. A phase II trial [4] evaluating atezolizumab with a modified chemotherapy regimen including docetaxel, cisplatin, and 5-fluorouracil in advanced anal cancer is currently ongoing. Toxicity data from this trial will be insightful to evaluate if the phenomena we describe in our case report are common. Additionally, the PANDA trial [5] combines capecitabine, oxaliplatin, and docetaxel with atezolizumab in a neoadjuvant fashion for resectable gastric and gastro-esophageal junction cancers. We eagerly await the toxicity data from this study as well. The landmark POPLAR [6] and OAK [7] trials that compared atezolizumab to docetaxel in lung cancer provide a benchmark of what we can expect in terms of these toxicities from each drug alone, and this serves as a relevant basis of comparison. Finally, the PROLUNG trial [8] combining pembrolizumab and docetaxel in patients with lung cancer provides valuable information, demonstrating a doubling in incidence of rash but not peripheral edema when this combination is compared to docetaxel alone.

In summary, we hope the presentation of this patient case adds to the wealth of literature that supports the clinician when unexpected toxicity is encountered, providing potential rationale and treatment options. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529017).

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient's next of kin for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Shiven B. Patel reports receiving institutional funding from Takeda, Merck, AstraZeneca, and Janssen and consulting fees/advisory board fees from AstraZeneca, Natera, Boehringer

Ingelheim, Blueprint Medicines, TerSera Therapeutics, Takeda, Regeneron, and Sanofi. Jenny Tuan has no conflicts of interest to declare.

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Author Contributions

Shiven B. Patel is the first and corresponding author, took care of the patient in clinic and reviewed the medical record to attain information for this publication, created the figure and table, and made significant contribution to the oncology aspect of the case discussion and presentation. Katerina Butler is the pharmacist managing drug delivery and toxicities and edited the manuscript. John Esther is the oncologist taking care of patient and provided and reviewed clinical documentation that allowed for the composition of this report. Jenny Tuan composed the paper, did the final editing of the manuscript, and is the senior author. All the authors approved the final version to be submitted for publication, and all agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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