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Mirvetuximab after anaphylaxis to Paclitaxel: A case report

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ABSTRACT

Introduction: Patients with platinum resistant epithelial ovarian cancer have limited treatment options which are further limited by hypersensitivity reactions to first line medications such as paclitaxel. Paclitaxel is a taxane that inhibits microtubules and has a high incidence of hypersensitivity reactions. Mirvetuximab soravtansine-gynx (MIRV) is a folate receptor alpha (FRα) directed antibody and microtubule inhibitor that is approved for patients with FRα positive platinum resistant recurrent epithelial ovarian cancer. Both medications are microtubule-targeting agents with similar binding sites, therefore a theoretical risk of cross reactivity between paclitaxel and MIRV may exist. Additionally, phase II clinical trial, SORAYA, did not include data on patients with prior hypersensitivity to paclitaxel.

Case: This is the case of a 33-year-old female with recurrent stage IIIC epithelial ovarian cancer with a history of severe anaphylaxis to paclitaxel. She was deemed eligible for MIRV after progression on multiple regimens, but MIRV was given with caution given her severe reaction history. With proper pre-treatment and monitoring, she was treated with MIRV without a reaction.

Discussion: It is suspected that most paclitaxel reactions are due to the cremophor solvent rather than paclitaxel itself; however, cross reactivity with docetaxel which is suspended in a polysorbate solution can also occur. Therefore, there is no clear way to determine the risk of cross reactivity between paclitaxel and similar medications. MIRV is also suspended in polysorbate and has a similar mechanism to taxanes, therefore it was unknown if a patient with a prior grade 5 reaction to paclitaxel would also have a reaction to MIRV. Though this is one case, patients with a history of severe hypersensitivity to paclitaxel and meet the criteria for MIRV could be treated with MIRV with careful monitoring.

1. Introduction

Ovarian cancer is the second most common gynecologic cancer, and approximately 90 % of cases are epithelial ovarian cancer (Desai et al., 2014). The standard of care chemotherapy for epithelial ovarian cancer is platinum-based chemotherapy, most commonly carboplatin combined with taxanes, such as paclitaxel or docetaxel (Armstrong et al., 2021). Platinum based therapy has an 80 % response rate in the frontline setting (Yang et al., 2022) and the addition of taxanes improves overall survival (McGuire et al., 1996). For platinum-sensitive disease, platinum-based therapy remains standard of care (Armstrong et al., 2021). In the context of platinum-resistant disease, typically single agent therapy is employed with paclitaxel, liposomal doxorubicin, topotecan and gemcitabine, but all have only a 10–20 % objective response rate (Armstrong et al., 2021; McGuire et al., 1996; Davis et al., 2014; Picard et al., 2014). Hypersensitivity or anaphylactic allergies to chemotherapy regimens further limit treatment options.

Taxanes are a class of cytotoxic chemotherapy that are isolated from the bark of the pacific yew tree (Markman, 1991). The mechanism of action is inhibition of mitosis by binding to and stabilizing tubulin, which subsequently inhibits microtubule function and prevents cell division (Markman, 1991). Paclitaxel is associated with a high incidence of hypersensitivity reactions, therefore, all patients receiving paclitaxel are pre-medicated with corticosteroids and antihistamines to prevent reactions, which can reduce reactions from 30 % to 2 % (Markman et al., 2000; Pagani et al., 2021). The exact mechanism of hypersensitivity

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reactions to taxanes is not fully known, but it is thought to be a direct complement activation to the solvent the medication is suspended in (cremophor or polysorbate) as taxanes are poorly soluble in typical solvents (Weiszhar et al., 2012). This leads to a nonspecific mast cell and basophil degranulation that occurs within a few minutes of medication administration (Picard et al., 2014). However, there is some data that suggests the taxane, rather than the solvent, leads to complement activation (Essayan et al., 1996) and IgE-mediated severe hypersensitivity reaction (Garcia and Pineda de la Losa, 2010). Though there are many theories regarding the mechanism of action of taxane hypersensitivity reactions, there are clear management guidelines regarding reaction treatment. For mild reactions, it is recommended to stop the infusion, give corticosteroids and restart at a slower rate, retreatment has a success rate of 93 % (Picard et al., 2014; Markman et al., 2000). For patients in whom retreatment is unsuccessful, desensitization protocols have been established or one can try a different taxane that uses a different solvent (Feldweg et al., 2005). Though severe cross reactivity has been documented between paclitaxel and docetaxel in breast and ovarian cancer patients, there is no reliable way to determine if cross reactivity will occur when switching between taxanes (Pagani et al., 2021). For severe hypersensitivity reactions, guidelines recommend to permanently discontinue taxane therapy (McGuire et al., 1996). Ultimately, taxane hypersensitivity can significantly limit treatment options in the frontline and recurrent setting.

Mirvetuximab soravtansine-gynx (MIRV) is a folate receptor alpha (FRα) directed antibody and microtubule inhibitor conjugate (Moore et al., 2021). MIRV is FDA approved to treat FRα positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, in those who have received one to three prior systemic treatment regimens and is reported to have an overall response rate of 31.7 % (Moore et al., 2021). FRα is highly expressed on epithelial ovarian cancer cells and is unique to cancer cells, thus it does not target non-cancer cells (Moore et al., 2021). MIRV binds FRα on cancer cells, subsequently internalizing the antibody-drug conjugate into the cell and releases the payload, DM4, which is a potent cytotoxic tubulin inhibitor (Moore et al., 2021). Tubulin is vital for creating microtubules required for DNA separation during mitosis, thus inhibiting mitosis triggers cell death (Moore et al., 2021). There is a theoretical risk of cross-reactivity between MIRV and paclitaxel, given they both target the microtubule for anti-cancer activity with adjacent binding sites on the tubulin. The incidence of infusion-reactions with mirvetuximab was 9 % with only one incidence of a class 3 or higher hypersensitivity reaction (Matulonis et al., 2023). However, history of taxane allergy was not tracked or evaluated in the trial, nor was tolerability of mirvetuximab in patients with history of allergies to other chemotherapies (Matulonis et al., 2023).

This is the case of a 33-year-old female with recurrent stage IIIC epithelial ovarian cancer with a history of severe anaphylaxis to paclitaxel who was successfully treated with MIRV after platinum resistant recurrence.

2. Case

A 33-year-old woman with a history of obesity and polycystic ovarian syndrome presented to an outside hospital for abdominal pain and adnexal mass found on ultrasonography. Computed topography (CT) of the abdomen and pelvis revealed a 4.9 cm left ovarian mass, peritoneal carcinomatosis, extensive omental caking, small to moderate ascites and a left pleural effusion. After undergoing diagnostic laparoscopy with omental, diaphragm and falciform biopsies, final pathology revealed stage IIIC high grade serous ovarian carcinoma. Germline genetic testing revealed BRCA1 mutation. Due to extensive disease, neoadjuvant chemotherapy with carboplatin and paclitaxel was planned. Of note, she had no known history of drug allergies but did have a family history of breast cancer in her maternal grandmother and great grandmother.

She returned to an outpatient chemotherapy infusion center for cycle 1 of paclitaxel and carboplatin chemotherapy. She was appropriately pre-medicated with famotidine, dexamethasone and diphenhydramine and the infusion began. Soon after initiation of paclitaxel infusion, she reported shortness of breath, with wheezing and flushing noted on exam. The infusion was immediately stopped, and she was medicated with corticosteroids and diphenhydramine. Her symptoms improved and re-treatment began one hour later at half the rate. She again reported shortness of breath to family in the room and quickly became unresponsive. Rapid response team was called and the patient was found to be pulseless and in ventricular fibrillation. Emergency medical services was called to the outpatient infusion center and advanced cardiac life support (ACLS) protocol was initiated. Ultimately, she was intubated and received several defibrillation shocks prior to being transferred to the emergency department. Return of spontaneous circulation was obtained after 50 min of ACLS. She was in the intensive care unit for one week but ultimately recovered without deficits. Her episode was attributed to a severe paclitaxel allergy and the decision was made to permanently discontinue taxane chemotherapy.

One month later, she was admitted for carboplatin desensitization inpatient, and had no signs of hypersensitivity. After the third cycle of carboplatin, she underwent an interval cytoreduction surgery with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal stripping and splenectomy, with complete resection. She then received three additional cycles of carboplatin. She had a complete response to treatment, and she was started on niraparib maintenance therapy. She was on maintenance therapy for ten months with no evidence of disease until imaging and an elevated Ca125 indicated her first recurrence. She received five cycles of carboplatin and liposomal doxorubicin after inpatient desensitization, but the sixth cycle was held due to hematologic toxicity. Fortunately, she had stable disease for three months, but her next CT scan revealed evidence of progression. At this point in her treatment, she was deemed platinum resistant. She received four cycles of gemcitabine; however, continued to have biopsy confirmed progression. She then received four cycles of pembrolizumab for PD-L1 positivity based on molecular tumor board recommendations; however, she again had progression of disease on imaging. At this time, bevacizumab and cyclophosphamide were added on to pembrolizumab and she received eight cycles of the combination regimen until she had rising Ca125 levels and progression on imaging.

As she had exhausted all other medication options, FRα testing was then performed using the FDA approved companion assay and confirmed 90 % positivity, and the patient was started on MIRV (Food and CfDaRH, 2022). Both MIRV and paclitaxel bind to tubulin and affect microtubule stability, therefore there is a theoretical risk for anaphylactic cross reactivity. Since paclitaxel allergy was not tracked in the original MIRV trial, she was admitted for an inpatient trial of MIRV (Matulonis et al., 2023). Prior to the infusion, she was premedicated with intravenous diphenhydramine 25 mg and dexamethasone 12 mg, oral lorazepam 0.5 mg and acetaminophen 650 mg, orally disintegrating ondansetron 16 mg and prednisolone eyedrops. She was started at an administration rate of 1 mg per minute and subsequently progressed to 3 mg per minute and then 5 mg per minute after tolerating each infusion rate for an hour. During her infusion, she had hemodynamic monitoring and tolerated the medication well with no evidence of hypersensitivity. She received cycle 2 of MIRV in an outpatient infusion center without issues.

3. Discussion

MIRV is a novel antibody drug conjugate for patients with FRα positive recurrent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. MIRV and paclitaxel bind to the same protein at different sites and inhibit tubulin thus inhibiting microtubules and mitosis (Markman, 1991; Moore et al., 2021). It has been suggested that reactions occur to paclitaxel due to suspension in cremophor

however, cross reactivity with docetaxel still occurs despite being suspended in polysorbate (Pagani et al., 2021). Due to the cross reactivity between taxanes, a grade 5 reaction to paclitaxel would preclude taxane use entirely and another medication class would need to be considered for treatment (Armstrong et al., 2021). MIRV is suspended in a polysorbate solution, like docetaxel, and both paclitaxel and MIRV bind to the same protein and have similar structure. Cross reactivity between taxanes and MIRV is plausible, and it was unknown if someone with a prior hypersensitivity reaction to paclitaxel would also have a hypersensitivity reaction to MIRV infusions. The clinical trial for MIRV included data of infusion reactions with none reported as a class 3 or higher hypersensitivity reaction. They did not, however, track or evaluate for prior taxane allergy and there are no reports in the literature of patients with hypersensitivity to paclitaxel receiving MIRV (Matulonis et al., 2023; Moore et al., 2023). It is unclear why the safety of MIRV in patients with severe taxane allergy was not evaluated in the trial as this is a more common chemotherapy allergy in patients with ovarian cancer. Given our patient had limited treatment options, decision was made to give MIRV with close inpatient monitoring after discussing risks and benefits.

Though this is only one report, future patients with a history of severe hypersensitivity to paclitaxel and meet the criteria for MIRV could be treated with MIRV with careful monitoring. Further research should be done to determine the incidence of a hypersensitivity to MIRV in the setting of prior hypersensitivity to paclitaxel or other taxane therapy. Further research should also be conducted to determine all the mechanisms in which paclitaxel causes a hypersensitivity reaction, as there are studies showing it may not just be the solution it is suspended in.

4. Conclusion

This is the first report of safety of MIRV in patients with a severe anaphylactic reaction to paclitaxel. Although this is only one report, this case demonstrates safe administration of MIRV in the context of a patient with a prior taxane reaction with careful monitoring and appropriate premedication.

Informed Consent

Patient was deceased at time of publication. Written informed consent was obtained from the patient's next of kin for publication of this case report.

CRediT authorship contribution statement

Megan A. Stewart: Writing – review & editing, Writing – original draft, Investigation. **Taylor A. Rives:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Kimberly Blanton:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Conceptualization. **Lauren Baldwin:** Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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