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Combined trastuzumab and radiation therapy for HER2-positive uterine serous carcinoma: A case report

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A B S T R A C T

Overexpression of HER2 in endometrial cancer is associated with poor prognosis, aggressive disease, and resistance to standard therapies. Recent studies have shown that HER2-targeted therapies, such as trastuzumab, can be effective in treating HER2-positive endometrial cancer in combination with chemotherapy. Currently, the management of advanced-stage HER2-positive uterine serous carcinoma (USC) consists of adjuvant platinum-based chemotherapy with concurrent trastuzumab followed by trastuzumab maintenance therapy until disease recurrence or prohibitive toxicity. In the setting of persistent pelvic disease following systemic therapy, consolidation with tumor-directed radiation therapy also offers an opportunity to eradicate residual disease. With the emergence of molecular tumor classifications and systemic therapies (chemotherapy, immunotherapy, and target therapies), the landscape of adjuvant multi-modality therapy is ever changing and increasingly individualized. Currently, there is no prospective evidence to guide pelvic radiotherapy with concurrent trastuzumab in endometrial cancer, and as a result, no reported toxicity in endometrial cancer patients. In this case report, we present two patients with HER2-positive USC who received multi-agent chemotherapy with trastuzumab followed by pelvic radiation therapy and concurrent trastuzumab. Both patients tolerated this multimodal treatment without significant or persistent moderate or severe adverse events. These two cases provide insight into the safety and feasibility of administering radiation therapy with trastuzumab in endometrial cancer in the maintenance phase. Our report suggests that trastuzumab-based therapy may be a promising treatment option for HER2-positive endometrial cancer patients who receive concurrent or adjuvant chemotherapy and radiation therapy.

1. Introduction

Human epidermal growth factor receptor 2 (Her-2) is a transmembrane receptor tyrosine kinase that promotes cell growth, differentiation, and survival. It is overexpressed in certain types of cancer, including endometrial cancer with highest rates of amplification in uterine serous carcinoma (USC) (Morrison et al., 2006). Overexpression of HER2 in endometrial cancer is associated with poor prognosis, aggressive disease, and resistance to standard therapies (Slomovitz et al., 2004; Díaz-Montes et al., 2006). Recent studies have shown that HER2-targeted therapies, such as trastuzumab, can be effective in treating HER2-positive endometrial cancer in combination with chemotherapy (Fader et al., 2018). Currently, the management of advanced-stage HER2-positive USC consists of adjuvant platinum-based chemotherapy with concurrent trastuzumab followed by trastuzumab maintenance therapy until disease recurrence or prohibitive toxicity. To reduce the risk of pelvic and nodal recurrence, pelvic radiation therapy may also be considered following systemic therapy (Oaknin et al., 2022; National Comprehensive Cancer Network, 2023). Consolidation with radiation therapy offers an opportunity to reduce the risk of local recurrences. In the setting of persistent pelvic disease following systemic therapy, consolidation with tumor-directed radiation therapy also offers an opportunity to eradicate residual disease. The intersection of trastuzumab use based on biomarker testing and concurrent radiotherapy will likely increase as genetic testing and biomarker testing become the standard of care. Currently, there is no prospective evidence to guide pelvic radiotherapy with concurrent trastuzumab in endometrial cancer, and as a result, no reported toxicity in endometrial cancer patients. In this case report, we present two patients with HER2-positive USC who received multi-agent chemotherapy with trastuzumab followed by pelvic radiation therapy and concurrent trastuzumab.

Informed consent statement

Consent was obtained from the patients for publication of this case report and accompanying images.

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2. Case presentations

2.1. Case 1

A 69-year-old G2P2 woman presented with post-menopausal bleeding. Transvaginal ultrasound (TVUS) demonstrated an endometrial stripe of 2.2 cm (cm). An endometrial biopsy (EMB) was performed, revealing high-grade uterine serous adenocarcinoma. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis identified retroperitoneal adenopathy suspicious for metastatic involvement in the aortocaval space, along the right common iliac and obturator chains measuring up to 1.7 cm. Cancer antigen 125 (CA-125) was 329 U/Ml. She underwent surgical staging at an outside hospital with robotic-assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pelvic sentinel lymph node dissection. Notably, an enlarged, necrotic lymph node measuring 3 × 2 cm was found extending from the right common iliac artery to the right para-aortic region, densely adherent to the vein and extending posterior to it, which was deemed unsafe for resection. Final pathology showed an International Federation of Gynecology and Obstetrics (FIGO) stage IIIC2 USC with > 50% myometrial invasion (MMI), extensive lymphovascular space invasion (LVSI), and extensive cervical stromal invasion with < 0.1 mm margin to the paracervix. Right common iliac and para-aortic lymph nodes were positive. Peritoneal washings were negative for malignant cells. Immunohistochemical stains demonstrated a mutant-type p53. Tumor molecular testing showed positive HER2 expression and proficient mismatch repair (MMR) status. She transferred care to our institution and was initiated on carboplatin, paclitaxel, and trastuzumab for 9 cycles followed by trastuzumab monotherapy as maintenance therapy. She underwent a transthoracic echocardiogram (TTE) for cardiac monitoring with the left ventricular ejection fraction (LVEF) estimated at 70%. Normal left ventricular size, wall thickness, and systolic function were also noted. The seven-month postoperative restaging CT showed persistent retroperitoneal lymphadenopathy (1.3 cm retrocaval node, 1.2 cm left para-aortic node, 1.3 cm right proximal iliac node, 1 cm proximal left iliac node, 1.1 cm right pelvic sidewall node) that is unchanged post-operatively. To address her treatment-refractory disease, she underwent consolidative extended field pelvic proton radiation therapy to the residual nodal disease to a total dose of 54 Gray (cGe) in 30 fractions with concurrent trastuzumab followed by a vaginal multichannel cylinder brachytherapy boost of 18 Gy in 3 fractions to the vaginal cuff. While on treatment with pelvic external beam radiation therapy (EBRT) and trastuzumab, the patient reported Grade 1 nausea. At her 3 month follow up post-radiation, she reported a good recovery with residual fatigue, decreased appetite, and constipation. She resumed vaginal intercourse without pain or post-coital vaginal bleeding. She experienced no trastuzumab-related toxicities during this period. She was found to have radiographic progression of disease in the lungs five days after completing radiation therapy and trastuzumab was discontinued. Recovery from radiation-related bowel changes was noted at her 12-month follow up. She is now 2 years post-treatment and undergoing systemic therapy due to progression of distant metastases.

2.2. Case 2

This is a 73-year-old G3P3 woman who presented with intermittent post-menopausal bleeding for one year and was found to have carcinosarcoma of the uterus on EMB. She subsequently underwent robotic-assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic and periaortic lymph node dissection. Final pathology revealed a FIGO stage IA serous carcinoma with carcinosarcoma features involving < 50% MMI without cervical stromal involvement or LVSI. Post-operatively, she received adjuvant platinum-based chemotherapy for six cycles. After a six-year disease-free interval, she developed persistent vaginal spotting. On pelvic exam, she had a large fleshy vascular mass at the vaginal cuff. Biopsy of the vaginal mass confirmed the recurrence of her high-grade uterine serous carcinoma which was equivocal for HER2 on IHC and positive on fluorescence in situ hybridization (FISH) (Fig. 1). Staging positron emission tomography (PET) with CT confirmed an isolated vaginal recurrence in the vagina. Initial cardiac evaluation with TTE estimated LVEF at 60–65%. Left ventricular size and systolic function was normal. She was treated with carboplatin, paclitaxel and trastuzumab for six cycles followed by EBRT to the pelvis with concurrent trastuzumab and brachytherapy. At this time, she has completed the six cycles of systemic therapy and EBRT (45 Gy in 25 fractions) and interstitial brachytherapy to the vaginal cuff to a total dose of 24 Gy in 4 fractions with concurrent trastuzumab followed by maintenance trastuzumab. Her course was notable for grade 2 anemia, grade 2 vomiting, grade 1 nausea, and peripheral neuropathy. At her most recent three-month follow up, she continues to experience grade 1 fatigue but has otherwise recovered fully from other cancer-related toxicities. Her restaging PET/CT 4-months post treatment showed a complete response and no evidence of disease recurrence or distant metastases (Fig. 2) and remained recurrence free at her most recent follow up. TTE was repeated every three months while she was on trastuzumab maintenance therapy with findings similar to her initial evaluation.

3. Discussion

We present two cases of patients with persistent or recurrent USC after primary surgery and adjuvant therapy who underwent systemic chemotherapy and trastuzumab followed by pelvic radiation therapy with concurrent trastuzumab. Both patients tolerated this multimodal treatment without significant or persistent moderate or severe adverse events. These two cases provide insight into the safety and feasibility of administering radiation therapy with trastuzumab in endometrial cancer in the maintenance phase.

Trastuzumab is a humanized monoclonal antibody against HER2/neu that is currently the first-line treatment for patients with metastatic breast cancer with HER2/neu overexpression. While trastuzumab has been extensively studied in breast cancer, there is more limited data on its use in USC. A prospective trial examined the efficacy of adding trastuzumab to carboplatin and paclitaxel in USC (Fader et al., 2018). This trial, which included patients with stage III, IV, or recurrent HER2/neu-positive USC, demonstrated an improvement median progression-free survival (PFS) 4.6 months in the trastuzumab arm (8 months vs 12.6 months) with a 56% decrease in the risk of recurrence compared to chemotherapy alone. Patients in the intervention arm continued to receive trastuzumab as maintenance monotherapy until disease progression or prohibitive toxicity. Notably, there was no difference in the toxicity profile between the two arms. Secondary analysis continued to favor the trastuzumab arm by demonstrating significantly higher PFS and overall survival (OS) as compared to the chemotherapy-only arm (Fader et al., 2020). The median overall survival was 29.6 months in the trastuzumab arm versus 24.4 months in the control arm. The significant benefit in overall survival was more pronounced in patients with stage III to IV disease. However, the role of adjuvant radiation in this patient population on maintenance therapy has not been studied.

With the emergence of molecular tumor classifications and systemic therapies (chemotherapy, immunotherapy, and target therapies), the landscape of adjuvant multi-modality therapy is ever changing and increasingly individualized. Preclinical studies have suggested that trastuzumab and other HER2-targeted agents may enhance the radiosensitivity of HER2-overexpressing cancer cells, making it a potentially promising agent in combination with radiation therapy (Liang et al., 2003; Huang et al., 2020). Currently, there is a paucity of data and no prospective evidence for the combined use of trastuzumab and radiation therapy in endometrial cancer. However, a growing body of evidence has demonstrated the safety and tolerability of radiation therapy with concurrent trastuzumab in the treatment of HER2-positive breast cancer, gastrointestinal tumors, and head and neck cancers. In a systematic

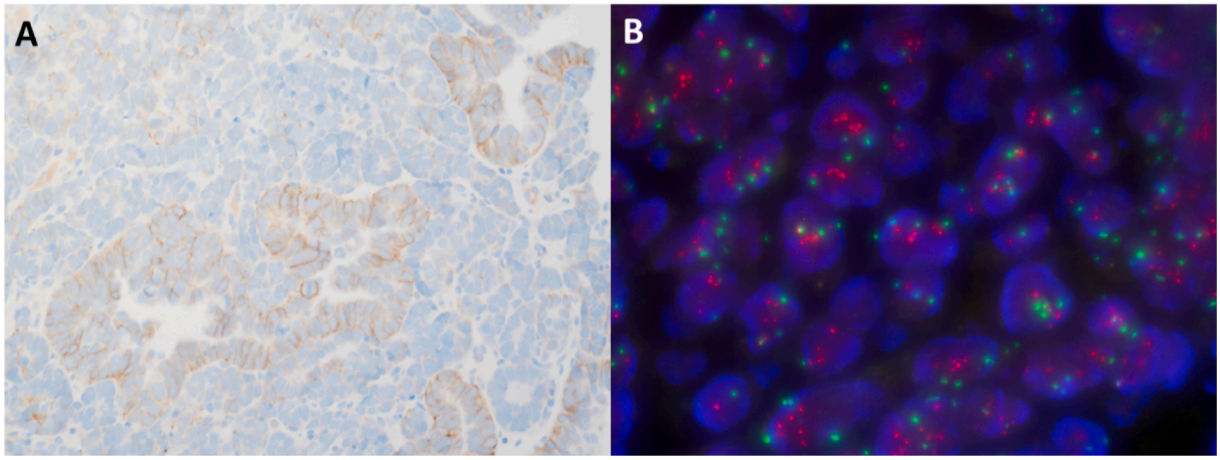

Fig. 1. HER2 expression in vaginal tumor biopsy. (A)HER2 expression analysis by IHC showed equivocal (2 +) expression that was confirmed positive by (B) FISH.

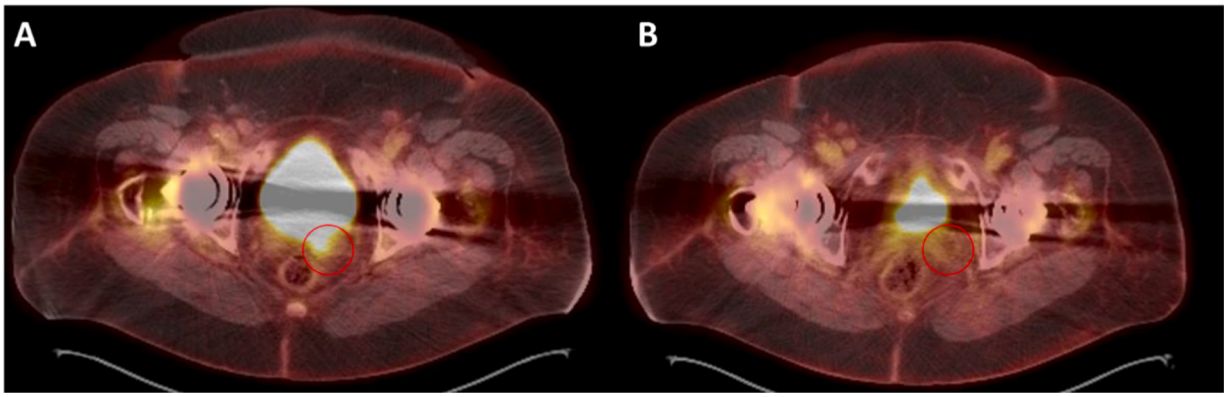

Fig. 2. Complete radiographic response on PET/CT. (A) Initial staging PET/CT demonstrates a hypermetabolic soft tissue thickening at the left aspect of the vaginal cuff. (B) Resolution of the asymmetric radiotracer activity in the left aspect of the vaginal cuff one year later.

review, concomitant administration of radiation and anti-HER2 therapy, including trastuzumab, in these disease sites had acceptable toxicity profiles (Mignot et al., 2017). Likewise, a prospective phase III clinical trial comparing radiation treatment with and without trastuzumab in HER2-positive ductal carcinoma in situ further reinforced the safety and tolerability in this combination therapy (Cobleigh et al., 2021). In this study, acute toxicity was low in both groups and grade 3 adverse events were 3.9% and 4.9% in the radiation-only and radiation plus trastuzumab arms, respectively. In a contemporary review of the safety of metastasis-directed radiation therapy combined with systemic therapies, HER2-targeted therapies including trastuzumab has been determined to be safe to use concurrently with radiation therapy (Guimond et al., 2022).

In our case report, there were no adverse outcomes from the administration of pelvic radiation therapy concomitantly with trastuzumab. In conclusion, our report suggests that trastuzumab-based therapy may be a promising treatment option for HER2-positive endometrial cancer patients who receive concurrent or adjuvant chemotherapy and radiation therapy. Larger prospective studies are needed to confirm these findings and further evaluate the safety and efficacy of this treatment approach.

CRediT authorship contribution statement

Serena Mao: Writing – original draft, Data curation. **Nerlyne Desravines:** Writing – original draft. **Shabnam Zarei:** Data curation. **Akila Viswanathan:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Amanda Fader:** Conceptualization, Data curation, Supervision, Writing – review & editing.

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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