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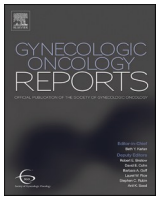

Response of low HER2-expressing ovarian carcinosarcoma to trastuzumab deruxtecan, a case report

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1. Introduction

Ovarian carcinosarcoma (OCS) is a rare histologic type of epithelial ovarian cancer comprising 1 to 4 % of ovarian cancers (Mano et al., 2007). OCS has a much poorer prognosis than high-grade serous ovarian carcinoma (HGSOC). Rauh-Hain et al, utilizing the National Cancer Data Base, reported women with all stages of OCS had a worse five-year survival rate, 26.63 % [95 % Confidence Interval (CI) = 24.86 %–28.53 %] vs. 43.61 % (95 % CI = 43.07 %–44.17 %) for women with HGSOC (Rauh-Hain et al., 2016). Among patients with stage III disease the 5 year overall survival (OS) for OCS was 20.14 % (17.60 %–23.05 %) vs 40.42 % (39.68 %–41.18 %) for women with HGSOC.

Because of the rarity of ovarian carcinosarcoma and aggressive biology most ovarian clinical trials exclude ovarian carcinosarcoma. A recent cooperative group trial studying uterine carcinosarcoma included ovarian carcinosarcomas which were analyzed separately (Powell et al., 2022). In this study, the combination of paclitaxel and carboplatin (PC) was compared to standard therapy with paclitaxel and ifosfamide (PI). Among 90 eligible patients with OCS, those in the PC arm had longer median OS (30 v 25 months) and median progression-free survival (15 v 10 months) than those in the PI arm, but these differences were not statistically significant due to the small sample size.

There is limited specific response data for second and subsequent lines of therapy for OCS. Recent molecular testing has identified pathogenic germ line mutations in patients with gynecologic carcinosarcomas. (Sia et al., 2023) BRCA and non-BRCA mutations in homologous recombinant repair genes have been identified which could lead to therapy with PARP inhibition. Powell et al suggested a potentially important target in UCS is HER2 overexpression. (Powell et al., 2022) Rottman et al utilizing by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) found that 16 % of 80 gynecologic carcinosarcoma specimens were HER2-positive but only 1 of 15 (6.7 %) ovarian/tubal carcinosarcomas was HER-2 positive. (Rottmann et al., 2020) Crane et al reported 9 % of 168 uterine carcinosarcomas from Caris Life Sciences utilizing Next Generation Sequencing were HER2/neu amplified. (Crane et al., 2020).

In vitro trastuzumab deruxtecan has been demonstrated activity in both uterine and ovarian carcinosarcomas (Mauricio et al., 2023). Trastuzumab deruxtecan has been studied in HER2-expressing uterine carcinosarcomas based on the ASCO/CAP HER2 testing guideline for gastroesophageal adenocarcinoma, and demonstrated a 55 % (12 of 22) response rate (Nishikawa et al., 2023). The response rate for tumors that were IHC 1 + versus 2 + -3 + were similar, 70 % and 68 %, respectively. This confirmed activity of Trastuzumab deruxtecan in low HER2/neu expressing tumors as reported by Modi previously in breast cancer (Modi et al., 2022). Therefore, after genomic tumor board approval, extensive counseling, and informed consent, we offered to treat a heavily treated patient with low HER2-expressing ovarian carcinosarcoma with trastuzumab deruxtecan.

2. Methods

This is an institutional review board–approved retrospective study of a patient with HER2/neu-expressing ovarian carcinosarcoma who received trastuzumab deruxtecan 5.4 mg/kg intravenously once every 3 weeks. The patient was monitored for response with cancer antigen (CA)-125 with each cycle and with periodic computed tomography (CT) scans. Radiologic review was conducted utilizing RECIST criteria. The patient was monitored for toxicity in each visit before therapy with symptom and laboratory evaluation and periodic echocardiogram. Objectives included evaluation of response rate and duration of response to treatment with trastuzumab deruxtecan. The patient gave consent for her medical history to be published.

3. Case report

A 75 yo G0 Caucasian female with scoliosis, and prior history of polio underwent a CT scan was demonstrated carcinomatosis with a left ovarian neoplasm and enlarged periportal lymph nodes (05/07/2021). An interventional radiology biopsy demonstrated high grade serous carcinoma of gynecologic origin. A plan for neoadjuvant chemotherapy with carboplatin AUC 5 and paclitaxel 60 mg/m2 day 1 and 8 was made. Prechemotherapy CA-125 was elevated to 641 u/ml. After 4 cycles of chemotherapy her CA-125 normalized and CT demonstrated decreased carcinomatosis. Genetic testing demonstrated a pathogenic CHEK2 mutation. At interval debulking surgery, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, sigmoid resection with primary side to side functional end to end re-anastomosis, and

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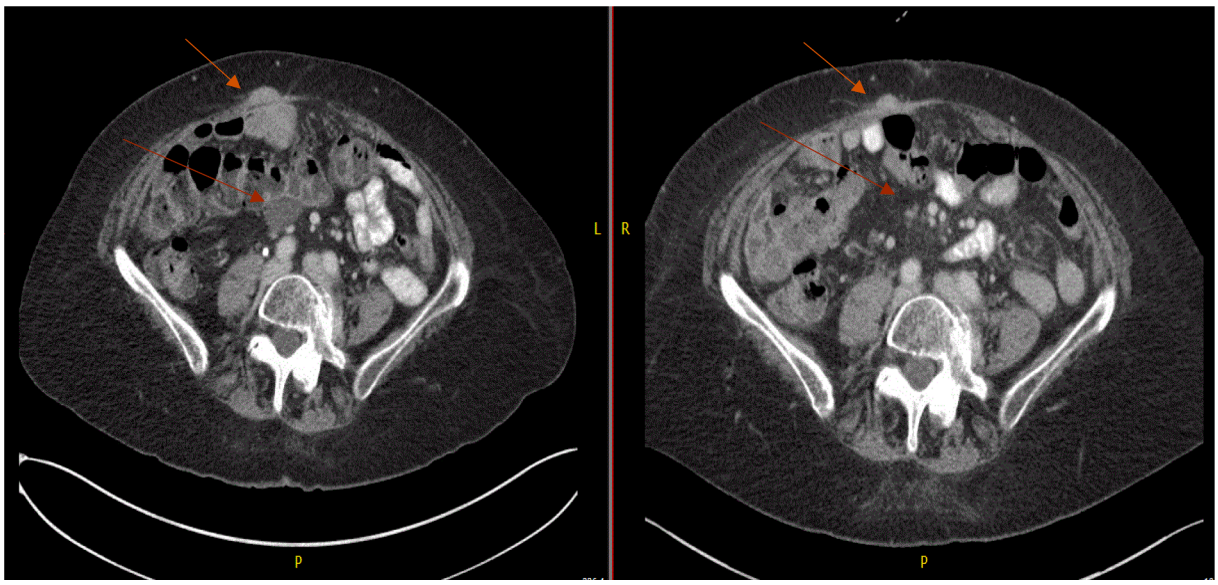

Fig. 1. CT scans before and 9 weeks after initiating therapy.

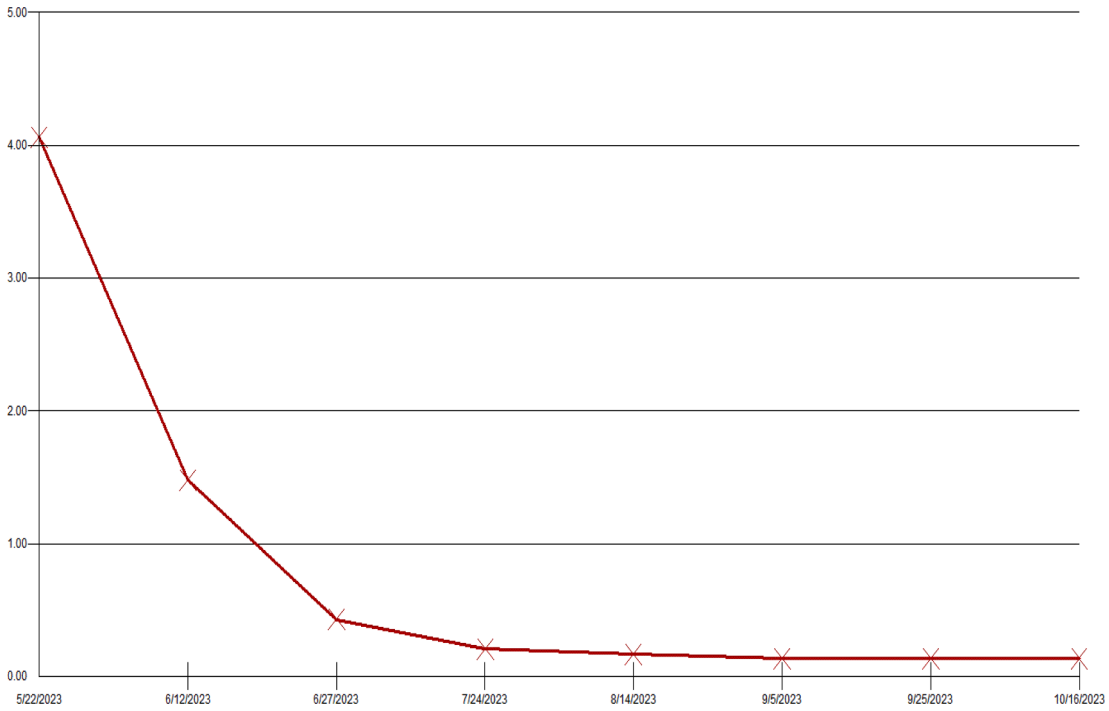

Fig. 2. Curve of CA 125 values after initiating therapy.

ghost ileostomy was performed. There was no gross residual disease. HIPEC chemotherapy with cisplatin 75 mg/m2 and paclitaxel 135 mg/m2 was perfused for 90 min. Pathology demonstrated carcinosarcoma with heterologous (chondroid) differentiation involving the left ovary and tube sigmoid colon and omentum. We planned 4 cycles of adjuvant chemotherapy but administered a 5th cycle while awaiting maintenance niraparib approval. Despite dose initiation of niraparib at 200 mg daily, for low body weight, therapy was held after 3 weeks for thrombocytopenia and then restarted at 100 mg/daily. After 4 months there was mild disease progression on CT and confirmed on PET/CT. The patient received ifosfamide for 2 cycles with further disease progression. Because initial thrombocytopenia resulted in therapy interruption and incomplete treatment, it was elected to restart maintenance niraparib 100 mg/daily and disease was relatively stable over 6 months until there was radiologic and symptomatic disease progression. In an effort to determine treatment options at recurrence, a variety of genomic tests were performed. Next generation sequencing demonstrated no actionable mutations. Tumor FOLR1 expression was low, eliminating mirvetuximab as a treatment option. Immunohistochemistry (IHC) for HER2 was 1 + and and florescent in-situ hybridization (FISH) was negative. She presented to the emergency room with flank pain and SOB. Workup and Cardiology consultation led to the diagnosis of a type I NSTEMI. Her cardiac echo demonstrated an ejection fraction of 52 %. She was presented to genomic tumor board who expressed concern over famtrastuzumab deruxtecan in a patient with a recent NSTEMI and low ejection fraction. However, in view of limited treatment options, fam-

trastuzumab deruxtecan therapy 5.4 mg/kg every three weeks was initiated. The patient received 6 cycles of trastuzumab deruxtecan with 50 % decrease in her measurable disease (Fig. 1) and CA-125 (Fig. 2).

4. Discussion

Human epidermal growth factor receptor plays a central role in the pathogenesis of several human cancers and is associated with poorer outcome. Slamon et al originally reported HER2/neu-overexpression in breast and ovarian cancer is associated with poorer survival (Slamon et al., 1989). Limiting their study to epithelial ovarian cancer, Berchuck et al reported high levels of HER2/neu-overexpression in 1/3rd of ovarian cancers and this was associated with a poorer survival (Berchuck et al., 1990). Santin et al reported HER2/neu-overexpression is also associated with a poorer prognosis in patients with serous endometrial cancer. (Santin et al., 2005) Despite the poorer prognosis of HER2/neu expressing cancers this oncogene is a potential anticancer therapy target.

Distinct expression and staining patterns of HER2/neu by IHC or FISH varies across tumor types with separate accepted distinct definitions of HER2/neu positivity for breast, gastroesophageal and colorectal cancer (Buza, 2021). In the breast cancer HER2/neu is considered positive for 3 + IHC. While HER2/neu 2 + expression is considered equivocal and must be confirmed by FISH testing. In the updated ASCO-College of American Pathologists guideline although no changes are made over prior recommendations for HER2/neu testing in breast cancer but the authors state "an IHC 1 + or 2 + result may make patients eligible for treatment targeting nonamplified/nonoverexpressed levels of HER2 expression" (Wolff et al., 2023).

Trastuzumab deruxtecan is a HER2-directed antibody and topoisomerase inhibitor conjugate used for the treatment of HER2-positive breast cancer, HER2-low breast cancer, HER2-mutant non-small cell lung cancer, and HER2-positive gastric or gastroesophageal junction adenocarcinoma. The management of gynecologic carcinosarcoma is often based on uterine carcinosarcoma as this is the most common gynecologic site for this histology. The favorable response of uterine carcinosarcoma to trastuzumab deruxtecan and the presence of HER2 expression in this patient's tumor led us to want to treat our patient with OCS with trastuzumab deruxtecan (Nishikawa et al., 2023). Basket oncology trials accrue patients who share a common biomarker. This patient responded to treatment with low IHC positivity and negative FISH, implying activity of trastuzumab deruxtecan in the setting of HER2 expression but not amplification. At ASCO 2023, the results of DESTINY-PanTumor02 Phase II trial was reported and there was a response rate of 45 % among 40 HER2-expressing ovarian cancers (Meric-Bernstam et al., 2023). The data regarding the specific histologies of these patients has not been made public.

CRediT authorship contribution statement

Peter G. Rose: Conceptualization, Data curation, Project administration, Visualization, Writing – original draft, 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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