Gynecologic Oncology Reports 33 (2020) 100581

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Long-term durable responses after pembrolizumab immunotherapy for recurrent, resistant endometrial cancer

John K. Chan[a,*], David S. Lakomy[b], Yassmina McDonald[a], Daniel S Kapp[c]

[a] Division of Gynecologic Oncology, Palo Alto Medical Foundation / California Pacific / Sutter Research Institute, Palo Alto, CA, USA
[b] Dartmouth Geisel School of Medicine, Dartmouth College, Hanover, NH, USA
[c] Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, USA

1. Introduction

Uterine cancer remains the most common and second most deadly gynecological cancer in the United States, with an estimated 61,880 new cases and 12,160 deaths per year (Siegel et al., 2019). Those with early stage disease have a good prognosis of a 95% 5-year survival rate compared to only 17% of women with advanced staged disease (Makker et al., 2017). Furthermore, there has been a significant increase in the number of endometrial cancer-associated deaths over the past 20 years (Makker et al., 2017). Recently, novel treatments such as immunotherapies directed by biomarkers have received significant attention in gynecologic oncology (Garcia and Ring, 2018). Pembrolizumab, a programmed cell death protein-1 (PD-1) signal pathway inhibitor, was approved by the FDA in May 2017 for malignancies characterized by microsatellite instability (MSI) or mismatch repair (MMR) deficiency, agnostic of tissue type ("Pembrolizumab Prescribing Information," 2019). Given its recent approval, there have been few reports that have described the long-term response to pembrolizumab in endometrial cancer (Le et al., 2017; Ott et al., 2017; Marabelle et al., 2020). Here, we present two cases with metastatic, chemotherapy-resistant endometrial cancers treated with pembrolizumab who have achieved long-term durable responses.

Informed consent from each patient and IRB approval from Palo Alto Medical Foundation Research Institute was obtained.

2. Cases

2.1. Patient one

A 67-year-old patient with a past medical history of type 1 diabetes and celiac disease presented with vaginal bleeding in October 2015. Endometrial biopsy indicated complex atypical hyperplasia, borderline for adenocarcinoma. She underwent a laparoscopic total hysterectomy, bilateral salpingo-oophorectomy, pelvic *peri*-aortic lymph node dissection, and peritoneal washing in October 2015. Pathology indicated stage 1A, grade 2 endometrioid adenocarcinoma with no evidence of lymphovascular invasion or peritoneal metastases. Immunohistochemistry (IHC) showed loss of expression of MLH1 and PMS2 and intact expression of MSH2 and MSH6. Given her early stage, no adjuvant therapy was indicated. Patient was given genetic counseling and tested negative for Lynch syndrome.

She remained in remission for approximately 1.5 years, but then again presented with vaginal bleeding as well as a palpable mass at the vaginal cuff in March 2017. Biopsy and IHC of the mass indicated metastatic endometrioid adenocarcinoma with an identical IHC expression pattern found in the initial specimen. Additionally, CT scan of the chest revealed two lung nodules, the largest measuring 1.7 × 2.3 cm. In March, the patient received external beam radiation therapy and brachytherapy to the pelvis and vagina, followed by five cycles of carboplatin AUC 6 and docetaxel 75 mg/m^2 completed in August 2017. The sixth cycle was not given due to severe pain, nausea, and neutropenia requiring hospitalization. Two months later in September 2017, CT scan revealed progressive disease with enlarging tumors and new pulmonary nodules. Due to her treatment-related symptoms from chemotherapy, she refused additional chemotherapy for four months. In December 2017, the largest pulmonary nodule measured 4.5 × 4.3 cm (Fig. 1A).

Given her tumor profile and progression of disease while on chemotherapy, she was started on pembrolizumab (200 mg IV every 21 days) in December 2017. In February 2018, CT images showed that the majority of her pulmonary nodules were stable; only one lesion displayed slight interval enlargement, possibly due to pseudoprogression. By April 2018, after six completed cycles of pembrolizumab, CT scan of her thoracic metastases showed regression of all lesions. By May 2019, the lung nodule decreased to a size of 0.9 × 0.9 cm (Fig. 1B) from 4.5 × 4.3 cm, with no new metastases. At the time of this report (April 2020) she remains on pembrolizumab having completed 40 cycles with continued partial response, per iRECIST criteria (Seymour et al., 2017).

The patient reports manageable symptoms of mild fatigue, nausea,

* Corresponding author at: Division of Gynecologic Oncology, Palo Alto Medical Foundation / California Pacific / Sutter Research Institute, 1100 Van Ness Avenue, Floor 4, San Francisco, CA 94109, USA.
E-mail address: chanjohn@sutterhealth.org (J.K. Chan).

https://doi.org/10.1016/j.gore.2020.100581
Received 21 February 2020; Received in revised form 29 April 2020; Accepted 1 May 2020
Available online 26 May 2020

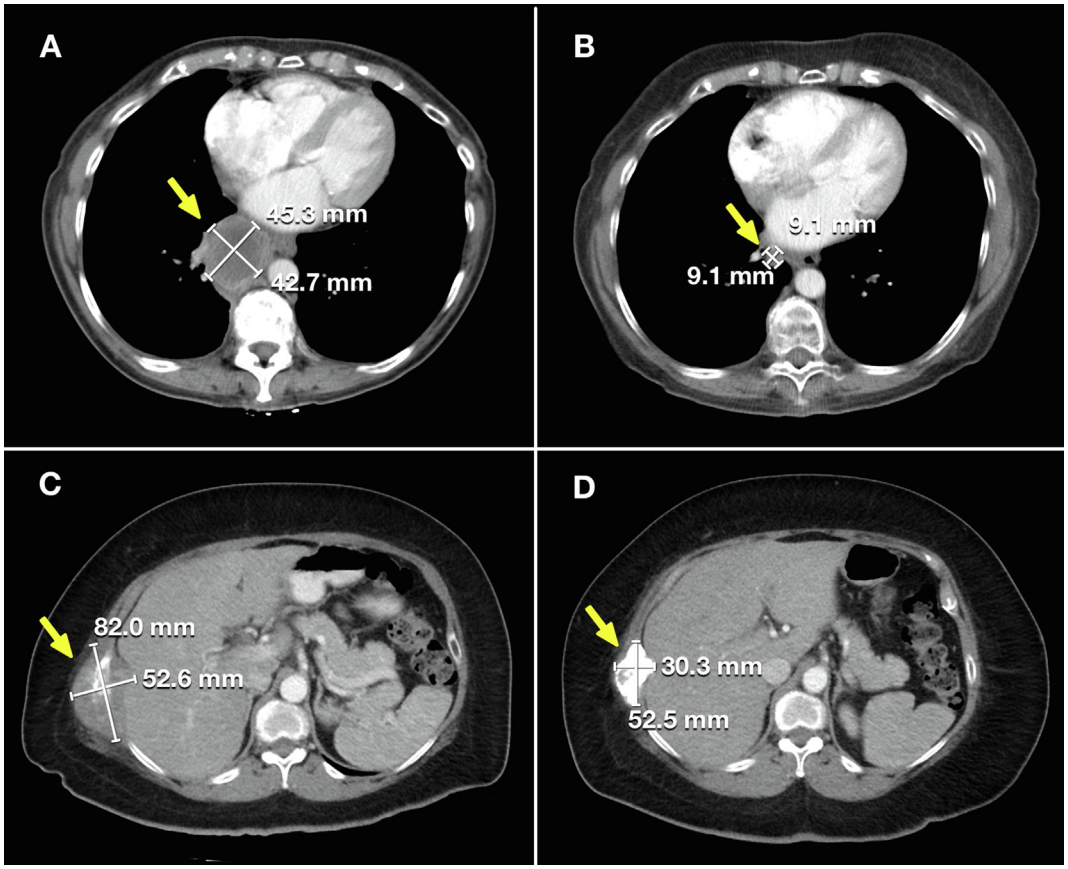

Fig. 1. Patient 1 (A) December 2017 CT of right pulmonary nodule, (B) December 2018 CT of drastic decrease in right pulmonary nodule size following pembrolizumab therapy. Patient 2 (C) March 2018 CT showing sclerotic rib lesion, (D) April 2019 CT showing decrease in its size following radiation therapy and pembrolizumab therapy.

and diarrhea, as well as more labile blood glucose readings, which have required consistent monitoring by her endocrinologist. Thyroid function was monitored prior to and after initiation of pembrolizumab therapy with no clinically significant changes noted.

2.2. Patient two

A 57-year-old woman presented in August 2017 with an enlarged uterus and a heterogeneously enhancing, pedunculated mass (16.8 × 12.4 × 17.1 cm) off the inferior portion, with concomitant extensive pelvic lymphadenopathy. In October 2017, she underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic node dissection. Pathology showed a grade 2 endometrioid carcinoma with lymph node involvement, stage IIIC2 disease. IHC identified loss of expression of MLH1 and PMS2 and intact MHS2 and MSH6 expression. Patient was given genetic counseling and tested negative for Lynch syndrome.

In November 2017, the patient started paclitaxel 175 mg/m^2 and carboplatin AUC 6 every 21 days. Treatment was initially well-tolerated aside from grade 1 peripheral neuropathy. However, after cycle three of treatment she began to feel right-sided rib pain, with imaging showing a 5.0 × 2.5 × 3.1 cm expansile lytic mass involving her tenth rib and surrounding soft tissue. A biopsy of this mass showed metastatic carcinoma consistent with her primary endometrioid carcinoma. A CT scan in March 2018 indicated that her rib mass expanded to a size of 8.2 × 5.3 cm (Fig. 1C), and the patient was subsequently treated with radiation therapy.

Given her tumor profile and progressive disease, she started pembrolizumab (200 mg IV every 21 days) in April 2018. A CT scan two months later showed stabilization of the previously growing lesion. One month later in August, the tumor was observed to have decreased in size. The rib lesion has continued to decrease to 5.3 × 3.0 cm (Fig. 1D) as of April 2019. As of the time of this report (April 2020) the patient remains on pembrolizumab having completed 35 cycles with continued partial response without any new metastases per iRECIST criteria (Seymour et al., 2017). The patient remains on this regimen with no major adverse effects, except lingering peripheral neuropathy, a possible sequelae of prior paclitaxel treatment. Thyroid function was monitored with no pathologic change or clinical intervention needed.

3. Discussion

Pembrolizumab is an IgG4 isotype antibody that binds and blocks PD-1 receptors to regulate T-cell differentiation and apoptosis (Garcia and Ring, 2018). It has significant activity in the treatment of multiple cancers with 19 current FDA-approved indications ("Pembrolizumab Prescribing Information," 2019). In particular, given the recent approval of pembrolizumab for cancer characterized by MSI or MMR deficiency, treatment for cancers with these characteristics may prove to be particularly effective due to their augmented somatic hypermutation and enhanced neoepitope formation. These serve to enhance susceptibility to immune targeting, especially when given with concurrent immune checkpoint blockade (Dudley et al., 2016). Both patients presented are classified as MSI-H/dMMR as IHC profile showed loss of expression of DNA-MMR enzymes MLH1 and PMS2, per KEYNOTE-158 criteria (Marabelle et al., 2020).

In the KEYNOTE-028 study, three out of the 24 endometrial cancer patients treated with pembrolizumab achieved partial response, with duration of response reported to be 63.7 + and 64.7 + weeks; three had stable disease with a median duration of 24.6 weeks (Ott et al.,

2017). In another phase II study on pembrolizumab in MMR-deficient solid tumors, 73% of endometrial cancer patients achieved disease control; however, the duration of response was not reported (Le et al., 2017). In KEYNOTE-158, 49 unresectable or metastatic endometrial cancer patients with confirmed MSI-H/dMMR saw an objective response rate of 57.1% and a duration of response of 2.9–27.0 + months (Marabelle et al., 2020). Our report reinforces these previous findings by presenting additional cases of chemotherapy-resistant endometrial cancer with a durable response to pembrolizumab of over 112 and 96 weeks, respectively.

Overall, therapies for recurrent and metastatic endometrial cancer remain limited. Chemotherapy regimens which include doxorubicin, topotecan, gemcitabine, and dactinomycin have response rates ranging from 4 to 22% (Bestvina and Fleming, 2016). Hormonal therapies including megestrol acetate, medroxyprogesterone acetate, and tamoxifen also have limited benefit with response rates of 10–27% (Bestvina and Fleming, 2016). Recent studies on biologic or targeted agents including bevacizumab, lapatinib, and temsirolimus, among others, have reported response rates of approximately 4–20%. (Morice et al., 2016). KEYNOTE-158 observed an objective response rate of 34.4% for pembrolizumab (Marabelle et al., 2020). In our case report, patient one had recurrent disease one month after systemic chemotherapy and patient two had refractory and progressive disease while on chemotherapy.

Our case report was limited by the small number of patients who had a favorable response to pembrolizumab treatment. We were unable to identify additional demographic or clinico-pathologic characteristics of patients who could attain extraordinary responses. Full tumor mutation panels could not be acquired due to insurance coverage denial, based on FDA indications restricted to IHC, and limited patient income and resources. Future studies are warranted to determine potential biomarkers associated with durable response, including those involved with DNA repair and homologous recombination mechanisms. Furthermore, research regarding the use of PD-1 inhibitors in combination with chemotherapy for primary advanced endometrial cancers is currently ongoing.

Disclosures: Dr. Chan, Consultant or Speaker bureau: AbbVie, Acerta, Aravive, AstraZeneca, Clovis, Eisai, Glaxosmithkline, Merck, Roche,

Acknowledgments

This research was supported by the Denise Cobb Hale and Fisher Family Fund. We wish to thank Dr. Roy E. Abendroth for his care of patient two during radiation therapy.

References

Bestvina, C.M., Fleming, G.F., 2016. Chemotherapy for endometrial cancer in adjuvant and advanced disease settings. Oncologist 21, 1250–1259. https://doi.org/10.1634/theoncologist.2016-0062.

Dudley, J.C., Lin, M.-T., Le, D.T., Eshleman, J.R., 2016. Microsatellite instability as a biomarker for PD-1 blockade. Clin. Can. Res. 22, 813–820. https://doi.org/10.1158/1078-0432.CCR-15-1678.

Garcia, C., Ring, K.L., 2018. The role of PD-1 checkpoint inhibition in gynecologic malignancies. Curr. Treat. Options in Oncol. 19, 70. https://doi.org/10.1007/s11864-018-0593-2.

Le, D.T., Durham, J.N., Smith, K.N., Wang, H., Bartlett, B.R., Aulakh, L.K., Lu, S., Kemberling, H., Wilt, C., Luber, B.S., Wong, F., Azad, N.S., Rucki, A.A., Laheru, D., Donehower, R., Zaheer, A., Fisher, G.A., Crocenzi, T.S., Lee, J.J., Greten, T.F., Duffy, A.G., Ciombor, K.K., Eyring, A.D., Lam, B.H., Joe, A., Kang, S.P., Holdhoff, M., Danilova, L., Cope, L., Meyer, C., Zhou, S., Goldberg, R.M., Armstrong, D.K., Bever, K.M., Fader, A.N., Taube, J., Housseau, F., Spetzler, D., Xiao, N., Pardoll, D.M., Papadopoulos, N., Kinzler, K.W., Eshleman, J.R., Vogelstein, B., Anders, R.A., Diaz, L.A., 2017. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357, 409–413. https://doi.org/10.1126/science.aan6733.

Makker, Vicky, Green, Angela K., Wenham, Robert M., Mutch, David, Davidson, Brittany, Miller, David Scott, 2017. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynaecol. Oncol. Res. Pract. 4 (1). https://doi.org/10.1186/s40661-017-0056-7.

Marabelle, A., Le, D.T., Ascierto, P.A., Di Giacomo, A.M., De Jesus-Acosta, A., Delord, J.-P., Geva, R., Gottfried, M., Penel, N., Hansen, A.R., Piha-Paul, S.A., Doi, T., Gao, B., Chung, H.C., Lopez-Martin, J., Bang, Y.-J., Frommer, R.S., Shah, M., Ghori, R., Joe, A.K., Pruitt, S.K., Diaz, L.A., 2020. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J. Clin. Oncol. 38, 1–10. https://doi.org/10.1200/JCO.19.02105.

Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., Darai, E., 2016. Endometrial cancer. The Lancet 387, 1094–1108. https://doi.org/10.1016/S0140-6736(15)00130-0.

Ott, P.A., Bang, Y.-J., Berton-Rigaud, D., Elez, E., Pishvaian, M.J., Rugo, H.S., Puzanov, I., Mehnert, J.M., Aung, K.L., Lopez, J., Carrigan, M., Saraf, S., Chen, M., Soria, J.-C., 2017. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1–positive endometrial cancer: results from the KEYNOTE-028 study. JCO 35, 2535–2541. https://doi.org/10.1200/JCO.2017.72.5952.

Pembrolizumab Prescribing Information, 2019.

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L.H., Mandrekar, S., Lin, N.U., Litière, S., Dancey, J., Chen, A., Hodi, F.S., Therasse, P., Hoekstra, O.S., Shankar, L.K., Wolchok, J.D., Ballinger, M., Caramella, C., de Vries, E.G.E., 2017. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 18, e143–e152. https://doi.org/10.1016/S1470-2045(17)30074-8.

Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019: Cancer Statistics, 2019. CA A Cancer J Clin 69, 7–34. 10.3322/caac.21551.