Gynecologic Oncology Reports 31 (2020) 100520

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Case report

HER2-positive metastatic cervical cancer responsive to first and second-line treatment: A case report

Dylan Fortman[a,*], Rochell Issa[a], Laura Stanbery[a], Mary Albrethsen[a], John Nemunaitis[a], Timothy Kasunic[b]

[a] College of Medicine and Life Sciences, University of Toledo, Toledo, OH, United States
[b] Hematology and Oncology, Toledo Clinic Cancer Center, Toledo, OH, United States

ARTICLE INFO

Keywords:
Cervical cancer
Precision Medicine
Cisplatin
Trastuzumab
HER2
Immunotherapy

ABSTRACT

Cervical cancer is the fourth most common malignant disease among women, with metastatic disease having a dismal survival rate compared to localized disease when using standard combination chemotherapy. Next-generation sequencing (NGS) of tumors has allowed for targeted treatments of cancers in patients who have progressed on first-line therapy. We present a case of a 46 year-old female with advanced cervical adenocarcinoma and metastatic recurrence in the lungs found to have HER2 mutation who underwent first and second-line HER2-targeted therapy with sustained disease response. We review the standard of care for advanced cervical cancer, toxicity profiles of chemotherapy and immunotherapy that were employed, the economics of NGS and targeted treatment, and future directions for HER2-targeted therapy. This case report highlights a patient with metastatic cervical cancer responsive to first and second-line HER2-targeted therapy.

1. Background

Cervical cancer is the fourth most common malignant disease among women, with advanced stages being found in 13% of cases (Boussios et al., 2016; Li et al., 2016). Metastatic cervical cancer has been shown to have a 5-year survival rate of 16.5% compared to 91.5% in localized disease with the use of standard cisplatin-based combination chemotherapy; therefore, there is increasing need for targeted, novel therapies to serve as monotherapy or adjuvant therapy for these cases (Li et al., 2016; Oh et al., 2015). With the advent of genetic profiling of a patient's tumor, clinicians can enroll patients into clinical trials using precision-based medicine. For example, HER2 gene amplification and the use of trastuzumab has been well-documented to be active in metastatic breast cancers that had received extensive prior therapy; more recently, the approval of other HER2-active agents including the combinations of trastuzumab-pertuzumab and ado-trastuzumab-emtansine (T-DM1) have demonstrated efficacy in metastatic breast cancer (Hernández-Blanquisett et al., 2016). Overexpression of HER2 has also been identified in gastric and esophageal carcinomas, with the addition of trastuzumab to other cytotoxic agents being the standard of care in treatment (El Dika and Ilson, 2018). Here we present a patient with HER2-positive cervical cancer with distant metastasis to the lungs whom responded to first and second-line HER2 therapy.

2. Patient presentation

A 46 year-old female patient presented to an University of Toledo Gynecologist for a routine pap smear with complaints of persistent postmenopausal spotting on 8/3/2011. Physical examination revealed no abnormal cervical or axillary lymph nodes, and a pelvic exam was notable for slight expansion of the lower uterine segment; subsequent colposcopic examination was unremarkable. A thin prep pap smear demonstrated adenocarcinoma, favoring endocervical origin, with a subsequent pelvic ultrasound demonstrating a thickened stripe at 8 mm. Cervical biopsies demonstrated endocervical type adenocarcinoma and features concerning for possible invasion. The patient's preoperative diagnosis was determined to be stage IA cervical cancer, and she underwent radical hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and a partial vaginectomy on 8/19/2011. The specimen showed endocervical adenocarcinoma with extensive involvement of the cervix and uterus, including deep myometrial and stromal invasion. Regional lymph node biopsies revealed metastatic adenocarcinoma in one of four left pelvic lymph nodes and in one of five right pelvic lymph nodes; however, there was no tumor seen in the sole paraaortic lymph node sampled. Histologically, it was deemed as grade 2 endocervical mucinous adenocarcinoma, stage IIIB, pT3, pN1, M0. The patient underwent computed tomography (CT)

* Corresponding author at: Toledo Clinic Cancer Center, 4126 N Holland Sylvania Rd #105, Toledo, Ohio 43623, United States.
E-mail address: dylan.fortman@rockets.utoledo.edu (D. Fortman).

https://doi.org/10.1016/j.gore.2019.100520
Received 30 August 2019; Received in revised form 9 November 2019; Accepted 18 November 2019
Available online 21 November 2019

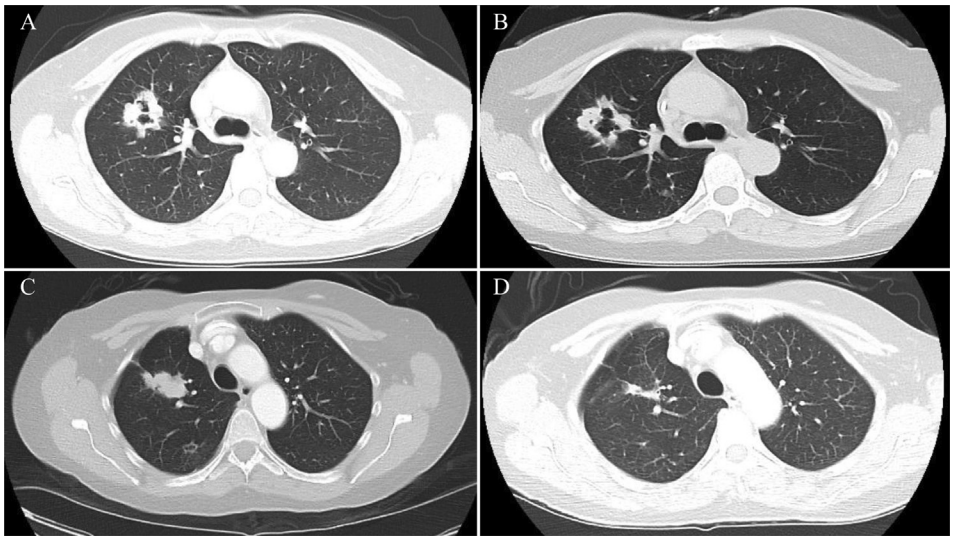

Fig. 1. A–D. Patient's CT scan of the chest with contrast depicting the right upper lung (RUL) nodule at its largest size in different levels of the thoracic cavity throughout the course of treatment. A. CT scan on 10/8/2014 depicting initial RUL nodule measuring 2.8 cm × 3.4 cm. B. Repeat scan on 2/18/2015 during topotecan chemotherapy demonstrating enlargement of RUL nodule, measuring 3.7 cm × 3.9 cm. C. Repeat scan on 11/14/2017 during trastuzumab-pertuzumab immunotherapy demonstrating progression of RUL nodule, measuring 3.7 cm × 2 cm. D. Repeat scan on 3/1/2018 during TDM-1 immunotherapy demonstrating decrease in size of RUL nodule, measuring 1.9 cm × 0.7 cm.

imaging of her chest, abdomen, and pelvis which showed no evidence of metastatic disease but did reveal an atrophic right kidney. The patient subsequently began adjuvant chemoradiation therapy post-operatively. The radiation dose was 4660 cGy to the pelvis with 1200 cGy to the vaginal cuff with high-dose rate brachytherapy which was completed in 11/2011 with concurrent chemotherapy treatment of cisplatin completed in 1/2012. She tolerated this course of treatment reasonably well despite its high toxicity, although she remained concerned for her functional left kidney and the associated nephrotoxicity of cisplatin.

The patient was seen by radiation oncology on 10/8/2014 and was noted to have worsening fatigue, skin pallor, and shortness of breath requiring more frequent use of her inhaler. In addition, there was concern for the patient's 20-pack-year smoking history. She underwent a screening chest CT at that time (Fig. 1A) which revealed an interval development of bilateral spiculated pulmonary masses, the largest measuring 2.8 cm × 3.4 cm within the right upper lobe (RUL), concerning for primary lung malignancy versus metastatic cervical cancer. Biopsies and pathology of this mass confirmed cervical adenocarcinoma. The patient preferred to avoid further use of agents associated with a high risk of nephrotoxicity; thus, she was placed on topotecan, paclitaxel, and bevacizumab, and she received 7 cycles of chemotherapy from 10/10/2014 to 2/3/2015. Repeat chest CT performed on 2/18/2015 (Fig. 1B) demonstrated that the pulmonary masses were increasing in size, with the previously mentioned RUL mass measuring approximately 3.7 cm × 3.9 cm. On 3/5/2015, the decision was made to re-biopsy this lesion in the RUL to send for HPV and next-generation sequencing (NGS) and perform radiofrequency ablation before this lesion grew too large for adequate, successful future ablation; this re-biopsied tissue ultimately exhibited an ERBB2 (HER2) amplification. Treatment with topotecan, paclitaxel, and bevacizumab ceased and the patient began a clinical trial with trastuzumab-pertuzumab. Scans performed on 5/26/2015 indicated that the patient had disease progression with an increase in size of the RUL lesion, and the patient was removed from the study. However, a positron emission tomography (PET) scan was performed which showed no abnormal tracer uptake (SUV 1.2) in the RUL lesion. Although the PET scan suggested SUV below cancer level activity, study guidelines did not allow for continuation of treatment. Following approval with the insurer, the patient started back on trastuzumab-pertuzumab, outside of the clinical study, on 7/8/2015.

On 12/14/2015, the patient underwent a PET-CT which revealed an elongated soft-tissue mass off the anterior aspect of the cavitary RUL lesion (Fig. 2). The decision was made to continue on trastuzumab-pertuzumab, and follow-up CT scans were continued which demonstrated a decrease in size of the RUL nodule and anterior mass with residual opacity thought to be linear scarring from radiofrequency ablation. In addition, concerning satellite pulmonary lesions inferior to the RUL lesion (Fig. 3) had resolved with continued therapy. There was no evidence for other new masses or other sites of disease. An interval decrease in the RUL lesion size to 1.4 cm × 0.7 cm was seen on 6/7/2017, until progression was noted on 9/25/2017. CT of the chest/abdomen/pelvis performed in 11/14/2017 (Fig. 1C) showed the previously seen RUL mass increased to 3.7xm × 2 cm from 3.4 cm × 1.4 cm on 09/25/2017. The patient underwent CT-guided biopsy, confirming metastatic endocervical carcinoma. At that point she had completed 40 cycles of trastuzumab-pertuzumab, and this treatment was discontinued.

The patient's treatment course was then changed again, subsequently receiving stereotactic radiation therapy (SBRT) to the RUL lesion in 1/18/2018 and starting on TDM-1 in 1/29/2018. A repeat chest CT scan on 3/1/2018 (Fig. 1D) demonstrated a decrease in size of the RUL pulmonary mass to 1.9 cm × 0.7 cm, and there was no other measurable disease. However, it is important to note that this interval decrease in the RUL lung mass cannot be solely explained by TDM-1 and/or SBRT. Since that time, a CT of the chest on 1/2/2019 (Fig. 4) showed no evidence of residual or recurrent disease. Post-radiation changes in the right upper lung have shown improvement since 9/2018. She continues on TDM-1, having completed 27 cycles.

3. Discussion

In recent years, the use of NGS to identify targetable mutations has been valuable for patients with progression on first-line treatment. A benefit of targeted therapies is that they often result in improved overall survival, improved response rate, and improved time to progression (Chawla et al., 2018). In regards to toxicity, platinum agents have been known to have many adverse side effects, including nephrotoxicity, neurotoxicity, and ototoxicity (Astolfi et al., 2013). Comparatively, the predominant side effects of trastuzumab include gastrointestinal disturbances, hematologic deficiencies, pulmonary symptoms, and cardiotoxicity (Ross et al., 2009).

The overall positive side-effect profile of utilizing targeted treatment, however, leaves room for a potential increase in financial burden. The cost of receiving cancer treatment, maintenance lab testing, and diagnostic imaging is arguably one of the biggest economic challenges for patients. However, if FoundationOne CDx testing is performed in metastatic non-small cell lung cancer one time prior to initial treatment, the number of patients needed to screen to prevent one death is only five patients; in addition, the cost is low at $0.018 per member per

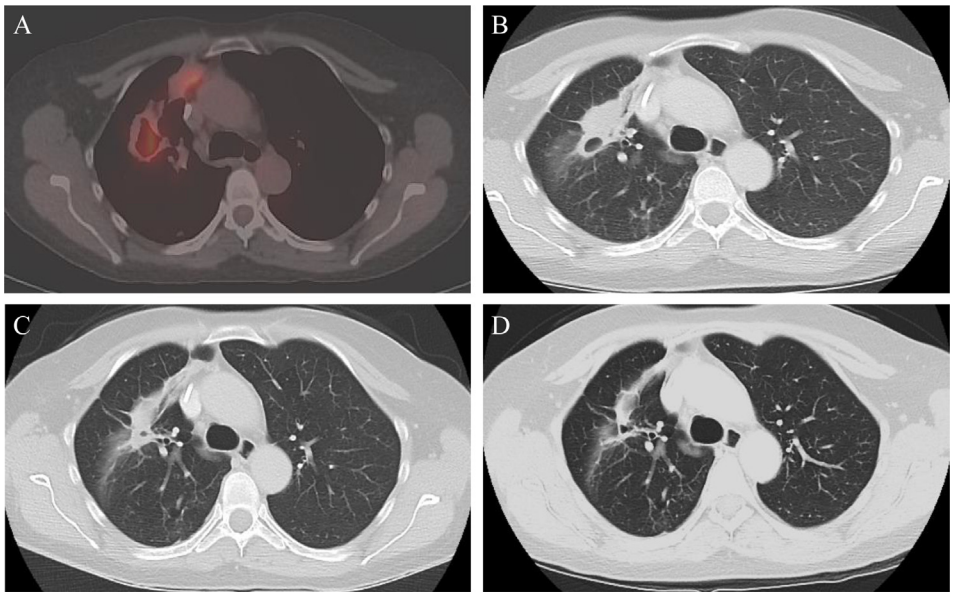

Fig. 2. A–D. Patient's imaging revealing an anterior, elongated mass off the right upper lung (RUL) nodule lesion that was responsive to trastuzumab-pertuzumab. A. PET-CT scan of the chest on 12/14/2015 depicting the right upper lung (RUL) nodule and an anterior, elongating soft tissue mass off the RUL nodule. B–D. Chest CT with contrast demonstrating improvement of the RUL nodule and anterior soft tissue mass on 4/4/2016, 7/7/2016, and 12/30/2016 respectively.

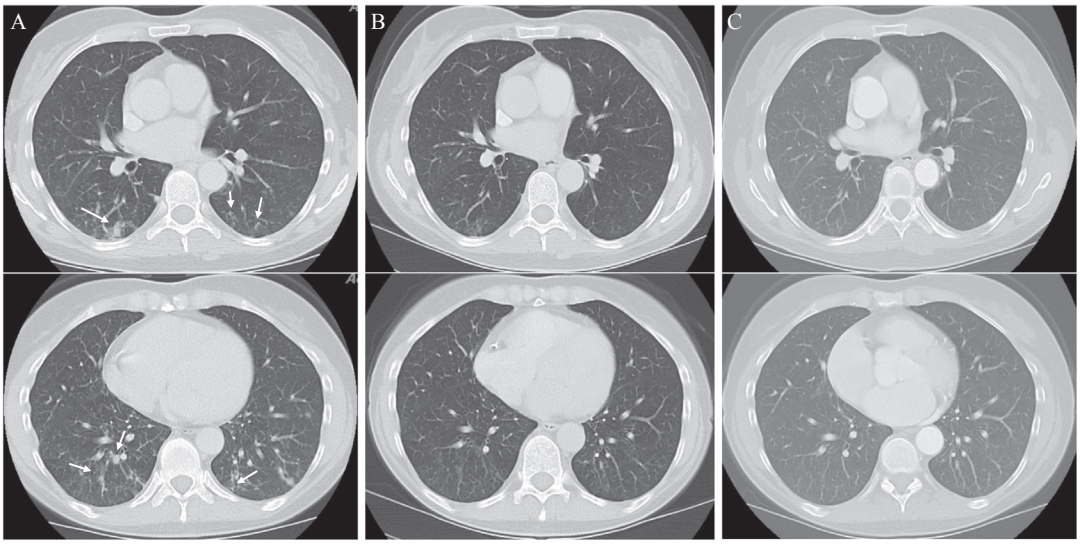

Fig. 3. A–C. Patient's CT scan of the chest with contrast depicting satellite, interstitial lung nodules inferior to the right upper lung (RUL) nodule concerning for malignancy and the progressive resolution of these lesions while on trastuzumab-pertuzumab. A (top, bottom). CT scan on 4/4/2016 depicting satellite lung lesions (arrows) inferior to the RUL lesion. B (top, bottom). CT scan on 7/7/2016 depicting improvement of satellite lung lesions previously seen. C (top, bottom). CT scan on 12/30/2016 demonstrating resolution of satellite lung lesions.

month (PMPM) and $0.216 per member per year (PMPY) (Signorovitch et al., 2019). Comprehensive genomic profiling is performed far less frequently, has a lower number of patients needed to treat, and has a low cost to the payer.

In this case, a HER2 mutation was found through NGS. The HER2 gene is a growth-factor receptor that is overexpressed in nearly 10–34% of breast cancer cases (Signorovitch et al., 2019). In contrast, HER2 gene amplification or protein expression in cervical cancer ranges from 1 to 2%, and its expression has been shown to have a poor prognosis for locally advanced, recurrent tumors (Oh et al., 2015). Although HER2-directed therapy in combination with chemotherapy is a standard of care for advanced breast and upper gastrointestinal cancers, its success has not been demonstrated in all HER2-amplified cancer types. However, there has been recent data supporting the use of HER2-directed therapy in patients with somatic HER2-mutant cervical cancer as part of the ongoing phase II SUMMIT 'basket' trial; one group has demonstrated that treatment with neratinib led to a clinical benefit rate of 54.5% in these types of patients and a durable response and disease control in patients with metastatic HER2-mutant cervical cancer (D'Souza et al., 2019).

In summary, this case demonstrates the combination of trastuzumab-pertuzumab, and the single-agent TDM-1, being effective in treatment of cervical cancer with HER2 amplification; in our patient, the total duration of treatment with these two agents has been four years, and she continues to respond despite her advanced illness. This case also highlights the importance of continued research of targeted therapy, as it allows an avenue for patients with disease progression on first-line therapy to receive other treatment options within clinical trials.

CRediT authorship contribution statement

Dylan Fortman: Conceptualization, Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing. **Rochell Issa:** Conceptualization, Data curation, Investigation, Resources, Writing - original draft. **Laura Stanbery:** Writing - review & editing.

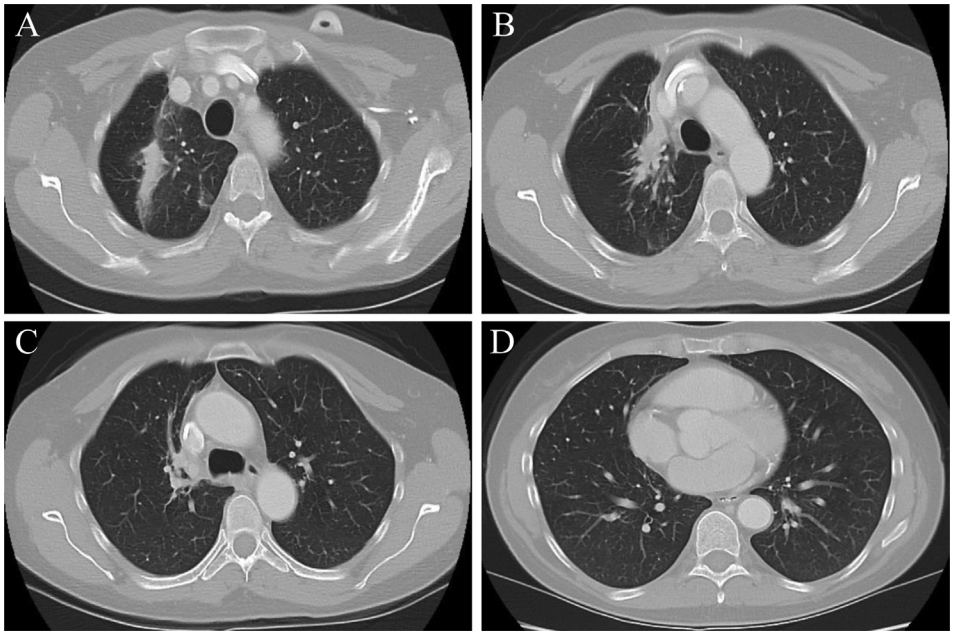

Fig. 4. A–D. Patient's CT scan of the chest with contrast on 1/2/2019 depicting stable scarring and volume loss in right upper lobe thought to represent post-radiation changes and no evidence for residual or recurrent tumor.

Mary Albrethsen: Writing - review & editing. **John Nemunaitis:** Writing - review & editing. **Timothy Kasunic:** Conceptualization, Formal analysis, Project administration, Supervision, Validation, Writing - review & editing.

Acknowledgements

The authors would like to thank Cheryl Sanders, Training and Development Specialist, at the Toledo Clinic Cancer Center for her help in acquiring the images used in the figures of this manuscript.

Declaration of Conflicts of Interests

The authors declare there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2019.100520.

References

Astolfi, L., et al., 2013. Correlation of adverse effects of cisplatin administration in patients affected by solid tumours: a retrospective evaluation. Oncol. Rep. 29 (4), 1285–1292. https://doi.org/10.3892/or.2013.2279.

Boussios, S., et al., 2016. Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: Where do we stand? A literature review. Crit. Rev. Oncol./Hematol. 108, 164–174. https://doi.org/10.1016/j.critrevonc.2016.11.006.

Chawla, A., et al., 2018. Estimated cost of anticancer therapy directed by comprehensive genomic profiling in a single-center study. JCO Precis. Oncol. 2, 1–11.

D'Souza, et al., 2019. Neratinib in patients with HER2-mutant, metastatic cervical cancer: findings from the phase 2 SUMMIT 'basket' trial. 2019 SGO Annual Meeting. March 16–19, 2019; Honolulu, HI. Abstract 18.

El Dika, I., Ilson, D., 2018. Current and future therapies for targeting HER2 mutations in gastrointestinal cancer. Expert Rev. Anticancer Ther. 18 (11), 1085–1092. https://doi.org/10.1080/14737140.2018.1510324.

Hernández-Blanquisett, A., et al., 2016. Current and emerging therapies of HER2-positive metastatic breast cancer. Breast 29, 170–177. https://doi.org/10.1016/j.breast.2016.07.026.

Li, H., Wu, X., Cheng, X., 2016. Advances in diagnosis and treatment of metastatic cervical cancer. J. Gynecol. Oncol. 27 (4). https://doi.org/10.3802/jgo.2016.27.e43.

Oh, D., et al., 2015. HER2 as a novel therapeutic target for cervical cancer. Oncotarget 6 (34). https://doi.org/10.18632/oncotarget.5283.

Ross, J.S., et al., 2009. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 14 (4), 320–368.

Signorovitch, J., et al., 2019. Budget impact analysis of comprehensive genomic profiling in patients with advanced non-small cell lung cancer. J. Med. Econ. 22 (2), 140–150.