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Case report

Afatinib use in recurrent epithelial ovarian carcinoma

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1. Patient case

41 year old germline and somatic BRCA negative Caucasian female underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for a pelvic mass at the age of 34. Pathology revealed a serous borderline tumor. The patient presented two years later with nausea, abdominal pain, and bloating. CT scan revealed a 3 cm mass on the anterior abdominal wall and a 2 cm mass at the vaginal cuff. She underwent a secondary optimal tumor debulking with implants removed from the anterior abdominal wall, rectum, sigmoid colon, vaginal cuff, and stomach. Pathology showed high grade serous carcinoma in all tumor implants. She received carboplatin (AUC 6) and nab-paclitaxel (260 mg/m^2) every 3 weeks for a total of 6 cycles. Nab-paclitaxel was given after the patient had an allergic reaction to her first dose of paclitaxel. A year after completing chemotherapy, an increasing CA-125 and CT scan revealed intra-abdominal tumor recurrence. She underwent 3 cycles of carboplatin (AUC 6) and liposomal doxorubicin (50 mg/m^2) with persistently elevated CA-125 levels. Her regimen was changed to 6 cycles of nab-paclitaxel (260 mg/m^2) and bevacizumab (15 mg/m^2) with normalization of her CA-125 level and no residual tumor. Nine months later, the patient presented with intra-abdominal recurrence. She was given 4 cycles of carboplatin (AUC 6) and gemcitabine (1000 mg/m^2) and maintenance q3week topotecan (1.5 mg/m^2). After a year, CA-125 levels started to rise and single agent liposomal doxorubicin was started with subsequent maintenance aromatase inhibitor, Letrozole. Patient was ineligible for clinical trials due to recurrence in the colon. She developed vaginal bleeding and had biopsy-confirmed recurrent high grade serous carcinoma at the vaginal cuff and sigmoid colon. Biopsies were sent for genetic sequencing which showed an activating HER2/*neu* alteration (ERBB2 G776_V777). Genomic results were discussed at a multi-disciplinary molecular tumor board and afatinib was recommended. The patient started on afatinib (40 mg PO daily) and had a significant decrease in her CA-125, decrease in the size of her vaginal tumor, and resolution of her bleeding. The patient experienced Grade 1 nausea and a Grade 2 dermatologic rash but was able to continue on afatinib. The patient had a progression free interval of ten months on afatinib. The decision was made to restart nab-paclitaxel (100 mg/m^2) and bevacizumab (15 mg/m^2) after an increase in CA-125. The patient has continued on maintenance nab-paclitaxel for the past six months and has had stable CA-125 levels.

2. Discussion

Great efforts are being made to advance the treatment of ovarian cancer but this malignancy is still the 5th leading cause of cancer-related death among women in the United States (La Vecchia et al., 2017). Serous ovarian carcinomas (SOC) comprise 40% of ovarian neoplasms and are the most common form of this malignancy (La Vecchia et al., 2017). The lack of obvious symptoms until advanced stages and the high rate of recurrence greatly contribute to the low (36%) 5-year survival rate of patients with SOC (La Vecchia et al., 2017). In light of this data, new approaches to ovarian cancer treatment

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are necessary.

Primary surgical resection is considered the standard treatment for SOC, with adjuvant chemotherapy offered to patients with Stage 1C disease or greater (Kampan et al., 2015). The current standard chemotherapy regimen consists of intravenously administered paclitaxel (175 mg/m^2) and carboplatin (AUC 5–7.5) q3 weeks for 6 cycles (Kampan et al., 2015). Approximately 60% of ovarian cancer patients will respond to initial treatment with combined paclitaxel-carboplatin, yet the median progression-free survival (PFS) is only 15 months (Kampan et al., 2015). The efficacy of platinum regimens is dependent on the treatment-free interval. Patients develop greater platinum resistance, and therefore lower response rates (RR), with shorter intervals between primary therapy and recurrence (Kampan et al., 2015).

The field of targeted therapies for the treatment of EOC has grown significantly in the last ten years. Anti-angiogenic agents are a large part of this expanding field, with bevacizumab being the most well studied.

The human epidermal growth factor receptor-2 gene (HER-2/ERBB2) represents another possible target for ovarian cancer based on its successful use in other malignancies. It encodes tyrosine kinase and is member of the ERBB receptor family. Dimerization of HER-2 and any of the ERBB receptors activates a series of signal transduction pathways involved in cellular proliferation, differentiation, and migration (Yan et al., 2014). Due to the nature of this receptor, protein overexpression, gene amplification, and gene mutations induce rapid tumor growth (Yan et al., 2014).

HER-2 aberrations are common to many tumor types including breast, colon, endometrium, and lung. Observed frequency of HER-2 positivity in ovarian cancer varies with a range of 1.8–76% (Serrano-Olvera et al., 2006). Review of molecular tumor data from GOG-111 and GOG-9404 showed HER-2 overexpression in approximately 7% of EOC cases (Farley et al., 2009) and as high as 12% in serous histologies (Farley et al., 2009). In these clinical study populations, regardless of copy number, ERBB2 amplification was not correlated with tumor stage, tumor histology, overall survival (OS), or sensitivity to platinum-based chemotherapy (Farley et al., 2009).

HER-2 overexpressing tumors are targetable using a variety of anti-ERBB2 drugs which are currently approved for breast, stomach, and lung cancers. Non-small cell lung cancer (NSCLC) is now treatable using afatinib. This ATP-competitive, aniline-quinazoline derivative binds and irreversibly inhibits signaling from EGFR, HER-2, and HER-4. Downregulating HER-2 and EGFR phosphorylation inhibits downstream signaling cascades and induces anti-proliferative effects through cell cycle G1 arrest and apoptotic cell death. Afatinib is approved as monotherapy for treatment of locally advanced or metastatic NSCLC having non-resistant EGFR mutations (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/201292s014lbl.pdf, n.d.). As shown in the LUX-LUNG 3 trial, continuous daily dosing of afatinib, at 40–50 mg/day in the aforementioned NSCLC patient groups with EGFR mutation-positive Del19, was found to significantly increase RR and PFS in comparison to the standard six cycle cisplatin-pemetrexed chemotherapy regimen (Sequist et al., 2013).

With the impressive efficacy of HER-2 targeting therapies in breast, gastric, and lung cancers, attempts are being made to achieve similar efficacy for ovarian cancer. Trastuzumab, a HER-2 monoclonal antibody that binds the extracellular domain of EGFR, showed success in the treatment of HER-2 positive breast cancer. Due to its efficacy, the Gynecologic Oncology Group initiated a phase II trial of single agent trastuzumab for patients with recurrent or refractory ovarian carcinoma. Unfortunately, the low response rate of 7.3% limits the utility of this agent as a monotherapy (Bookman et al., 2003). Similarly, pertuzumab, another HER-2 antibody used in the treatment of breast cancers, was found to significantly increase RR and PFS when combined with gemcitabine in platinum-resistant ovarian cancers (Makhija et al., 2010).

The effectiveness of afatinib likely depends on a number of different clinical and molecular factors that have yet to be identified. As an example, the Carvajal-Hausdorf study identified cases of HER2 amplification showing differing levels of intracellular (ICD) and extracellular domains (ECD) (Carvajal-Hausdorf et al., 2017). Because HER2 targeted agents are directed against the HER2 ICD or ECD, these findings suggest that targeted HER2 agents may need to be tailored to the specific domain levels present.

For the patient in this case, afatinib was chosen as treatment due to the presence of an activating mutation in HER2. This use is an extrapolation of the results from the LUX-Lung trial in NSCLC. We have presented this case to demonstrate anecdotal effectiveness of targeting HER2/*neu* activation in patients with ovarian cancer and a HER2 activating tumor mutation.

3. Conclusion

Commercially available genomic sequencing can be used to guide individual treatment plans for primary or recurrent malignancies and should be based on the activating mutations present in the tumor. Her2/*neu* mutations are an effective target in lung cancers and afatinib is an effective targeting agent. Larger clinical trials are needed to assess the effectiveness of afatinib in ovarian cancer patients and to identify the specific sub-populations in which it may be most effective. Due to the rarity of this mutation in ovarian cancer, this may require a basket trial study that would assess use of afatinib or other HER2 targeting small molecule inhibitors in tumor types with activating HER2 mutation.

Declaration of Competing Interests

Dr. Amanda Shepherd-Littlejohn, Wyatt Hanft, Dr. Vanessa Kennedy, and Dr. Edwin Alvarez have no financial or personal conflicts of interest in producing this manuscript. Dr. Shepherd-Littlejohn, Wyatt Hanft, Dr. Kennedy, and Dr. Alvarez have nothing to disclose.

Author contributions

Wyatt Hanft, MPH, conceived the idea, collected patient data, and wrote the first draft of the paper.

Dr. Amanda Shepherd-Littlejohn collected patient data, developed the discussion and contribution section of the paper, and edited the paper after the first draft. Dr. Shepherd-Littlejohn is also responsible for submission and is the corresponding author.

Dr. Vanessa Kennedy and Dr. Edwin Alvarez conceived the idea, were the final editors of the paper, and acted as mentors during the production of the manuscript.

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