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SGO Journal Club Commentary

Cervical cancer – times… they are a changing: A report from the Society of Gynecologic Oncology journal club

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ABSTRACT

In January 2021, the Society of Gynecologic Oncology (SGO) Clinical Practice and Education Committees launched a "Journal Club" webinar series to invite national experts to discuss literature pertaining to common clinical scenarios encountered by the members of SGO. On December 13, 2021, SGO hosted its third journal club focused on the use of immunotherapy in cervical cancer. Charles A. Leath, III from the O'Neal Comprehensive Cancer at the University of Alabama and Leslie M. Randall from Massey Cancer Center at Virginia Commonwealth University discussed the recently published KEYNOTE-826 trial (Colombo et al., 2021) and Jyoti Mayadev from the University of California, San Diego Moores Cancer Center discussed GOG-9929 (Mayadev et al., 2020). Renata Urban from the University of Washington and Christine S. Walsh from the University of Colorado served as moderators. The following is a report of the journal club presentation.

1. Current state of cervical cancer therapy

Over the past two decades, the systemic treatment regimens for metastatic and recurrent cervical cancer have evolved from the doublet chemotherapy regimens of cisplatin/topotecan (GOG-179) (Long et al., 2005) and cisplatin/paclitaxel (GOG-204) (Monk et al., 2009) to the current standard of the three-drug combination of cisplatin, paclitaxel, and bevacizumab (GOG-240) (Tewari et al., 2017). Despite incremental improvements in overall survival from 9.4 months in GOG-179 to 12.9 months in GOG-204, and to 17.0 months in GOG-240, the treatment of persistent locally advanced, metastatic, and recurrent cervical cancer continues to represent a high unmet clinical need. Data from the Surveillance, Epidemiology and End Results (SEER) program demonstrates that despite a decline in the rate of new cervical cancer cases, the decline in deaths due to cervical cancer is not nearly as steep, reflecting a lack of effective salvage therapies [https://seer.cancer.gov/statfacts/html/cervix.html]. There are several options for second line and later treatments listed by the National Comprehensive Cancer Network (NCCN), but survival with these regimens range from 6.5 to 8.0 months and efficacy is limited (Yu and Garcia, 2015).

It is in the context of this high unmet clinical need that the Food and Drug Administration (FDA) recently granted accelerated approval to two new drugs for the treatment of cervical cancer. On June 12, 2018, the FDA approved pembrolizumab as single agent therapy for patients with recurrent or metastatic cervical cancer whose cancers have progressed on or after chemotherapy and express PD-L1, defined as a combined positive score (CPS) $\geq$ 1, determined by an FDA-approved test. Pembrolizumab is a humanized monoclonal IgG4 antibody directed against the PD-1 receptor and is classified as an immune checkpoint inhibitor. Its approval was based on the KEYNOTE-158 study (NCT02628067) that evaluated pembrolizumab 200 mg administered IV every 21 days in 98 patients with recurrent or metastatic cervical cancer. Among the 77 patients (79%) whose tumors expressed PD-L1, the objective response rate (ORR) was 14.3% (95% CI: 7%, 24%) and 91% had a response duration that exceeded 6 months. There were no responses observed among the 21 patients whose tumors did not express PD-L1.

The 2018 FDA approval of pembrolizumab was contingent upon verification of clinical benefit in confirmatory trials. On October 13, 2021, the FDA expanded the pembrolizumab indication based on the confirmatory KEYNOTE-826 trial (NCT03635567) (Colombo et al., 2021). Pembrolizumab is now approved for use in combination with

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chemotherapy with or without bevacizumab for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS $\geq$ 1) determined by an FDA-approved test. This new approval effectively moves an immuno-oncology agent into first-line therapy.

The second FDA accelerated approval was for tisotumab vedotin, approved on September 20, 2021, for the treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Tisotumab vedotin is a tissue factor-directed antibody-drug conjugate linked to a microtubule inhibitor. InnovaTV 204 (NCT03438396) (Coleman et al., 2021) was a phase 2 study of 101 patients with recurrent or metastatic cervical cancer who had progressed on or after doublet chemotherapy with bevacizumab and who had received two or fewer prior systemic regimens for recurrent or metastatic disease. Patients were treated with tisotumab vedotin-tftv 2 mg/kg (to a maximum of 200 mg for patients $>$ 100 kg) every 3 weeks until disease progression or unacceptable toxicity. At a median follow-up time of 10 months, the ORR was 24% (95% CI: 16%, 33%) and the duration of response was 8.3 months (95% CI: 4.2, not reached). The most common adverse reactions included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (26%), and dry eye (23%). The most common laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, and increased creatinine. Serious treatment-related adverse events were uncommon but included peripheral sensorimotor neuropathy (2%) and pyrexia (2%). The approval of tisotumab vedotin provides a PD-L1 agnostic, second-line therapeutic option that provides additional and novel treatment options for patients with recurrent or progressive cervical cancer.

1.1. Immunotherapy in cervical cancer

Immunotherapies have been increasingly studied in the treatment of cervical cancer and provocative data have been reported with the use of T-cell based therapies and vaccine strategies (Ferrall et al., 2021). The current journal club evaluates two studies that utilize immune checkpoint inhibition strategies. KEYNOTE-826 explores the use of pembrolizumab, which blocks the PD-1/PD-L1 interaction that regulates CD8 + T cell function and builds upon the experience learned in KEYNOTE-028 (Frenel et al., 2017) and KEYNOTE-158 (Chung et al., 2019). GOG-9929 investigates the use of ipilimumab, a monoclonal antibody that targets CTLA-4, another important immune checkpoint that directs the immune response (Okazaki et al., 2013).

1.2. Keynote-826

KEYNOTE-826 was a multi-center, randomized, double-blind, phase 3 trial that evaluated the addition of pembrolizumab to paclitaxel/cisplatin or carboplatin with or without bevacizumab (Colombo et al., 2021). Key eligibility criteria were persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment; no prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy were permitted); and performance status of 0 or 1. Patients were stratified by presence or absence of metastatic disease at diagnosis, PD-L1 combined positive score (CPS) ($<$1 versus 1 to $<$ 10 versus $\geq$ 10), and planned use of bevacizumab. Patients were randomized to pembrolizumab 200 mg administered IV every 21 days versus placebo. All patients received chemotherapy and approximately 63% of all patients received bevacizumab. Pembrolizumab was continued for 24 months or until disease progression or unacceptable toxicity. Dual primary endpoints were overall survival and progression-free survival. Secondary endpoints were ORR, duration of response, 12-month progression-free survival, and safety. Exploratory endpoints included patient reported outcomes assessed by EuroQol EQ-5D-5L VAS.

The statistical design of this trial utilized a hierarchical modeling strategy described by Maurer and Bretz (Maurer and Bretz, 2013) to test across six primary hypotheses of overall survival and progression-free survival in three populations, including patients with PD-L1 CPS $\geq$ 1, intention-to-treat, and patients with PD-L1 CPS $\geq$ 10. This hierarchical design allows for the testing of multiple hypotheses without diminishing statistical power and has been found be useful when investigating agents whose benefit is associated with a biomarker.

617 participants were randomly allocated between November 20, 2018 and January 31, 2020. 308 participants received pembrolizumab and 309 received placebo. Patient characteristics were matched between the two groups (table 1 of manuscript) with similar age, race, ECOG performance status, stage at initial diagnosis, disease status at trial entry, and histology. Approximately 89% of patients had tumors with PD-L1 expression (CPS $\geq$ 10, 51% vs 51%; CPS 1 to $<$ 10, 27% vs 37%; CPS $<$ 1, 11% vs 11%).

In all efficacy analyses using the hierarchical statistical testing strategy, the use of pembrolizumab was associated with improved outcomes. Focusing on overall survival (Figure 3 of manuscript), the hazard ratio favored pembrolizumab use in patients with a CPS $\geq$ 1 (HR 0.64, 95% CI: 0.50, 0.81), in the intention-to-treat population (HR 0.67, 95% CI: 0.54, 0.84), and in patients with a CPS $\geq$ 10 (HR 0.61, 95% CI: 0.44, 0.84). Similar benefits to pembrolizumab use were seen in the progression-free survival analyses (figure 2 of manuscript). In patients with a CPS score greater than 1, median PFS was 10.4 months versus 8.2 months and overall survival at 24 months was 53% versus 41.7%.

In both groups, the most common adverse events were anemia, alopecia, and nausea, and the most common grade 3 to 5 adverse events were anemia, neutropenia, and hypertension (table 2 of manuscript). Adverse events deemed potentially immune-mediated occurred in 33.9% versus 15.2% of participants receiving pembrolizumab versus placebo. Discontinuation of any trial agent due to adverse events occurred in 37.5% with pembrolizumab versus 26.5% with placebo. Time to deterioration of quality of life as measured by the EQ-5D-5L questionnaire was longer with pembrolizumab than with placebo (58.2% versus 44.8% free from deterioration at 12-months). The improved quality of life with immune checkpoint inhibition is noteworthy since it is consistent with the improvement observed in the cemiplimab arm of EMPOWER-Cervical 1/GOG-3016;ENGOT-cx9 trial for second or third line systemic treatment (Tewari, et al., 2021) and most of our therapeutic trials have reported no detriment in quality of life with investigational therapy (Friedlander et al., 2021; Ray-Coquard et al., 2019; Pothuri et al., 2020).

There are several open questions that are not answered by KEYNOTE-826. One pertains to the role of bevacizumab in combination with chemotherapy and pembrolizumab. Our speakers were asked to debate whether to include bevacizumab when using the KEYNOTE-826 regimen. Both speakers felt data from GOG-240 support bevacizumab use if there are no contraindications to its use. The forest plot in the KEYNOTE-826 manuscript demonstrates HR $<$ 1.0 whether concomitant bevacizumab is used or not. When bevacizumab is not used, the 95% confidence interval for disease progression and death crosses 1 (figures 2 and 3 in manuscript). Other open questions pertain to which agents should follow the use of pembrolizumab in the primary setting, and the ideal treatment of patients with PD-L1 negative cervical cancers.

1.3. GOG-9929

Approximately 40% of patients present with locally advanced cervical cancer at the time of diagnosis. Node-positive disease is typically treated with chemotherapy and extended-field radiation, but recurrence risks remain high in the range of 60–70%. Radiation therapy is known to impact the tumor microenvironment and has been found to induce an abscopal response, or induction of an antitumor response throughout the body, not only at the site of the targeted radiation therapy (Dyer et al., 2019; Topalian et al., 2012; Herrera et al., 2017). GOG-9929 was designed to evaluate the addition of the immunotherapeutic agent ipilimumab to standard therapy.

GOG-9929 was a phase I trial of sequential ipilimumab after chemoradiation for the primary treatment of patients with locally advanced cervical cancer stages IB2 to IIA with positive para-aortic lymph nodes and stage IIB, IIIB, IVA with positive pelvic lymph nodes (Mayadev et al., 2020). 34 patients were enrolled and following the conclusion of chemoradiation and brachytherapy, and the recovery of counts, treated with four doses of ipilimumab 3 mg/kg administered IV every 3 weeks. The treatment was generally well tolerated with 2 of 19 evaluable patients (9.5%) experiencing an acute grade 3 toxicity (elevated lipase, dermatitis), both of which self-resolved. At 1-year, the overall survival was 90% and progression-free survival was 81%.

Cervical swabs, DNA, plasma, and white blood cells were collected for translational studies. Neither human papillomavirus genotype nor HLA subtype were associated with outcomes. Flow cytometry was performed to assess the differential expression of immune markers on peripheral blood lymphocytes, including CD4, CD25, FoxP3, CD8, CTLA4, PD-1, HLA-DR, CD27, CD137, CD45RA/RO, and ICOS1. ICOS is an inducible T-cell co-stimulator that is structurally and functionally related to CD28. Chemoradiation treatment increased ICOS and PD-1 expression in both CD4 and CD8 T cell compartments and levels were sustained through treatment with ipilimumab. These data suggest that chemoradiation causes T cell activation but the role that ipilimumab plays in sustaining this response cannot be concluded from this data (Da Silva et al., 2020).

1.4. On the horizon

In patients with node positive locally advanced cervical cancer (stage IB2, II, IIIB, IVA with spread to lymph nodes), NRG GY017 (NCT03738228) is a phase I study is designed to determine whether differences in the sequencing of atezolizumab (anti PD-L1 monoclonal antibody) and standard of care chemoradiation have an impact on immune activation as determined by the translational evaluation of clonal T cell receptor beta repertoires in peripheral blood.

The CALLA study (NCT03830866) is a randomized phase III study determining the efficacy and safety of durvalumab (anti-PD-L1 monoclonal antibody) with chemoradiotherapy in patients with locally advanced cervical cancer (stage IB2 to IIB with spread to lymph nodes, stage IIIA to IVA with any nodal status).

GOG-3047/KEYNOTE-A18/ENGOT-cx11 (NCT04221945) is a randomized phase III, double-blind study of chemoradiotherapy with or without pembrolizumab for the treatment of high-risk, locally advanced cervical cancer (stage IB2 to IIB with spread to lymph nodes, stage IIA to IVA with any nodal status).

2. Conclusions

Recent FDA approvals for pembrolizumab and tisotumab vedotin have changed the landscape for the treatment of metastatic and recurrent cervical cancer. Immunotherapy is a treatment modality that holds great promise in the treatment of cervical cancer. Times… they are a changing.

Author contributions

Drs. Walsh and Urban developed the clinical commentary. Drs. Leath, Mayadev and Randall reviewed and provided edits.

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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