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Advances in Immunotherapy for Cervical Cancer

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Abstract

PURPOSE: Novel therapies are needed for the treatment of recurrent cervical cancer. The best chemotherapy regimen to date has a response rate of 48% with an overall survival of 17 months, with limited options for second-line chemotherapy. Immunotherapy can induce a strong immune response in cervical cancer due to retained viral antigens and is reviewed in this article.

RECENT FINDINGS: Current clinical trials include treatment with Listeria that elicits an immune response against the E7 oncoprotein and active vaccines against the E7 oncoprotein. While the response rates to PD-1 inhibition alone have been modest, the landmark survival reported in these trials suggests the activity of these agents may not be measured by RECIST criteria. The KEYNOTE-158 trial has led to the approval of pembrolizumab in recurrent PD-L1 positive cervical cancer. Combinations of PD-1 and anti-CTLA-4 have shown promising and durable activity. There is active research with new combinations of checkpoint inhibitors, as well as combinations of these drugs with chemotherapy and radiation, and other novel approaches.

SUMMARY: Immune therapy has broad activity in cervical cancer. Responses to immunotherapy can be dramatic and durable. Continued work to find the optimal combination and setting for immunotherapy is ongoing.

Keywords

Cervical cancer; Immunotherapy; Checkpoint inhibitors

INTRODUCTION

Chemotherapy options for recurrent cervical cancer are limited and are considered non-curative. As evaluated by the Gynecologic Oncology Group (GOG), the best regimen in recurrent or metastatic cervical cancer is the combination of cisplatin, paclitaxel, and bevacizumab with an overall response rate of 48% and a median survival of 17 months[1]. However, there is no consensus on the benefit of second line chemotherapy in recurrent cervical cancer due to the poor prognosis in this group of patients. Immunotherapy represents a new method to treat cancers dependent on the natural ability of the immune system to recognize and kill tumor cells directly. The original observation that a malignant

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tumor of the neck could respond dramatically after an infection first suggested the power of immunotherapy in the treatment of cancer [2]. Since that time therapies have been developed to increase the immune response to cancers and are now approved for the treatment of many cancers.

Almost all cervical cancer is a result of Human Papilloma Virus (HPV) infection[3]. After epithelial damage, HPV can infect the basal cell layer of keratinocytes [4, 5]. In most individuals this infection is cleared. However, high risk HPV types such as 16 and 18 are more likely to persist and integrate into the host genome such that there is excess expression of the oncoproteins E6 and E7. These oncoproteins interfere with natural immune response by down regulating critical pathways such as interferon production, the STING pathway, and inhibit the expression of HPV antigens by the class I MHC molecules[6]. HPV infection can also impair Langerhans cell function which is critical to the immune response. However, the retained viral antigens in cervical cancer makes immunotherapy an attractive treatment option since the antigens could be recognized as foreign. While checkpoint inhibition with blockade of the of PD-1 receptor has been the dominate class of drugs tested in cervical cancer, several other immunotherapy strategies are currently under development which are reviewed (Table 1).

Active Vaccines

Prophylactic HPV vaccines are currently approved and are highly effective in preventing HPV infections, but appear to be ineffective in clearing established HPV infection[7, 8]. Investigations of novel therapeutic vaccines targeting both cervical dysplasia and cervical cancer are ongoing. A preclinical trial utilizing Pseudomonas Exotoxin-HPV16 E70KDEL3 fusion protein or TVGV-1 combined with one of two different adjuvants showed promising results in a mouse model and was associated with longer survival and greater production of HPV16 E7 specific CD8+ T-cells.[9]. Results of the therapeutic vaccine pNGVL4a-CRT/E7(detox) have been reported in 32 women with CIN2/3 secondary to HPV16[10]. This vaccine consists of a DNA plasmid (pNGVL4a-A) that encodes calreticulin linked to a detox form of HPV type 16 E7 antigen. This vaccine was designed to increase cytotoxic T-cells in the hopes of clearing established HPV 16 infections. In this first-in-human clinical trial, 27 women were vaccinated and the resolution rate to CIN 1 or less was 30%. An increase in cytotoxic T-cells compared to matched controls was noted.

There is an interest regarding the role of combining vaccines with other immunotherapy approaches. One such novel strategy is the proposed VolATIL trial (NCT03946358) which combines the UCPVax vaccine with atezolizumab, a PD-L1 inhibitor, and has been developed for a group of 47 planned participants with HPV positive human cancers including cancers of the head and neck, anus and cervix. As designed, patients will receive both atezolizumab as well as the UCPVax for induction[11]. The primary endpoint is the objective response rate at 4 months with secondary endpoints to include OS, PFS, and health related QOL.

Listeria Based Treatments

Listeria monocytogenes is a gram-positive bacterium that stimulates cell mediated immunity[12, 13]. *L monocytogenes* has unique properties making this organism a reasonable choice for vector development including cytoplasmic replication and the lack of an endotoxin. Axalimogene filolisbac or ADXS11-001 was developed as a therapeutic agent via bioengineering and secretes a fusion protein that includes a truncated fragment of listeriolysin O (tLLO) which is fused to human HPV-16 E7[14]. Following administration, antigen presenting cells take up the agent by phagocytosis and the tLLO-HPV-16 E7 fusion protein activates the MHC class I pathway. In addition, following uptake via phagocytosis, antigens that are secreted by *L monocytogenes* can also be presented in the MHC class II pathway[15, 16]. ADXS11-001 may also alter the tumor microenvironment to facilitate T-cell infiltration and reduce immune suppression by immune regulatory cells[17, 18].

In a phase I trial, 15 patients with metastatic cervical cancer were treated with ADXS11-001 (*Lm*-LLO-E7). Treatment consisted of two vaccinations three weeks apart at one of three different dose levels (1×10^9 CFU/ml, 3.3×10^9 CFU/ml or 1×10^{10} CFU/ml) in conjunction with post treatment ampicillin[19]. Objectively, seven of 13 (54%) evaluable patients had stable disease and one patient had an unconfirmed partial response to therapy. A randomized phase 2 trial of ADXS11-001 was conducted in 25 centers within India[14]. This trial compared the dose of 1×10^9 CFU/ml either alone in combination with five weekly doses of cisplatin 40mg/m2 starting on day 29. The primary endpoint of the trial was OS. A total of 110 women were randomized in the study and median OS was similar for both groups of patients with a median OS of 8.3 months (95% CI, 5.9-10.5) for ADXS11-001 alone as compared to 8.8 months (95% CI, 7.4-13.3) for the combination. The landmark 12-month survival for this trial was 35% (38/109). The GOG also conducted (GOG-0265) a two stage, phase 2 trial of single agent ADXS11 in 50 patients[20]. The median OS was 6.2 months (95% CI, 4.4-12.3) and 12-month OS was 38% (range 12.0-40.1), which was found to be a 52% improvement from the expected survival. The treatment was well tolerated with anemia the only grade 3+ TRAE.

Pembrolizumab

Expression of PD-L1 by tumors allows the tumor to escape cell destruction by CD8+ killer T-cells. Significant expression of PD-L1 is more common in squamous cancer than in adenocarcinoma[21]. A meta-analysis has suggested that PD-L1 expression is associated with a worse prognosis independent of other risk factors such as stage, tumor size, depth of invasion, LVSI, or lymph node metastasis.

Pembrolizumab is a humanized antibody to PD-1. When bound to the PD-1 receptor it blocks the interaction of this receptor with the ligand (PD-L1). The KEYNOTE-028 included 24 patients with stage IVB or recurrent cervical cancer and were treated with the PD-1 antibody pembrolizumab at 10 mg/kg every two weeks for 24 months[22]. All patients had received prior systemic chemotherapy with 63% treated with two or more regimens and 42% had previously been treated with bevacizumab. There were 4 responses (4 PR) for a response rate of 16.7%. The PFS was 2 months and the median overall survival was 11 months.

The KEYNOTE-158 trial (NCT02628067) included 98 patients with recurrent or metastatic cancer[23]. The trial utilized 200 mg of IV pembrolizumab every 3 weeks for 24 months. Similar to the Keynote-028 trial, 65% patients had been treated with 2 or more prior lines of systemic chemotherapy. The overall RR was 12% (3 CR, 9 PR). However, 84% of patients were PD-L1 positive and all of the responses were limited to the PD-L1 positive group for a 14.6% RR in this cohort. The median PFS was 2.1 months with an overall survival of 9.4 months, but in the PD-L1 positive group the overall survival was 11 months. The landmark survival in the PD-L1 positive group was 80% at 6 months and 47% at 12 months. As with other trials of immunotherapy, responses tended to be durable. The median duration of response was not reached in the study (95%tile 4.1-18.6+) but 91% of responders were noted to have a duration of response greater than 6 months. Because of this trial and the high unmet need, the FDA granted accelerated approval of pembrolizumab in patients with previously treated recurrent cervical cancer who were PD-L1 positive with the companion diagnostic PD-L1 IHC 22C3 pharmDx assay with a CPS ≥ 1 (Dako North America, Carpinteria, CA)[24].

A phase III trial comparing the PD-1 inhibitor cemiplimab to investigator's choice of chemotherapy is ongoing[25]. Preliminary results are not yet available and are expected to be mature in June of 2023.

Nivolumab

Similar to pembrolizumab, nivolumab is an antibody to PD-1. Nivolumab in cervical cancer was first evaluated in the phase II study NRG-GY002 (NCT022257528). Patients with metastatic or recurrent cervical cancer with one prior systemic chemotherapy were given nivolumab at 3 mg/kg every 2 weeks.[26]. The primary endpoint was PFS by RECIST 1.1. All patients had received one prior chemotherapy in the recurrent setting and PD-L1 was expressed in 77% of patients. Of the 25 patients evaluable for response, there was only 1 partial response noted for a RR of 4% (95% CI 0.4-22.9). Despite the minimal response rate, the median survival in this group was 14.5 months (95% CI 8.3-26.8). The survival was 78% at the 6 month landmark and 56% at the 12-month landmark. The grade 3+ treatment-related adverse event rate was 24%.

Checkmate 358 included a single agent nivolumab arm with nivolumab administered at 240 mg IV q 2 wk. All patients in this trial had received prior systemic chemotherapy with 58% receiving 2 or more prior therapies and 32% receiving prior bevacizumab. Patients were enrolled without respect to PD-L1 expression. The overall response rate was 26% (95% CI 9.1 – 52.2)[27]. In this trial 38% of patients were PD-L1 negative and 84% had two or more lines of therapy. Median PFS was 5.1 months and OS was 21.9 months. The landmark survival was 78% at 12 months and 50% at 24 months. Responses were seen in both PD-L1 positive and PD-L1 negative tumors suggesting this marker may not be necessary for PD-1 checkpoint inhibition in cervical cancer[27].

It is unclear why there is a discordance between GY002 and the single arm nivolumab arm of Checkmate 358. However, it should be noted that in GY002 there were 4 patients with an unconfirmed response. These patients were taken off study because of new lesions despite regression of target lesions and may have represented a significant response[26]. The median

overall survival of 14.3 months for treatment in the recurrent second line metastatic setting in this trial does suggest activity that is not accurately measured by RECIST criteria.

CTLA4 antibodies

Blockade of the CTLA4 antigen increases antigen presentation to the immune system resulting in an expanded killer T-cell response to antigens. Anti-CTLA4 therapy is theoretically attractive in cervical cancer due to down regulation of antigen presentation by the viral oncoproteins[6]. A phase II trial of the anti-CTLA4 antibody ipilimumab 10 mg/kg every 3 weeks x 4 then every 12 weeks in 42 patients with recurrent squamous or adenocarcinoma has been reported[28]. The response rate in this trial was only 3% in the 34 evaluable patients with a PFS of 2.5 months (95% CI, 2.1-3.2) and an OS of 8.5 months (95% CI, 3.6-not reached).

Combination of Checkpoint Inhibitors and Radiation

The combination of immunotherapy and radiation is theoretically attractive as radiation may induce an immune response to the tumor due to tumor death[29]. There are multiple ongoing trials looking at adding checkpoint inhibitors either during radiation or following radiation to improve outcomes[30–40]. These trials are listed in Table 2.

PD-1 and Chemotherapy Combinations

Taking a lead from other cancers where the addition of chemotherapy to checkpoint inhibition has improved outcomes, this approach is being evaluated in cervical cancer. Several trials of chemotherapy with PD-1 inhibitors are ongoing and listed in Table 2.

PD-1/ CTLA4 Checkpoint Inhibitor Combinations

The preliminary report on the combination arms of Checkmate 358 that included both nivolumab and ipilimumab at two different dosing schedules has been presented[41]. This combination of an anti-PD-1 and an anti-CTLA-4 agent demonstrated significant activity in treatment of metastatic cervical cancer for both first-line and second-line therapy in the metastatic setting. The first combination arm (Combo A, n=45) included nivolumab at 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 6 weeks for up to 2 years. The second combination (Combo B, n = 46) was nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 240 mg every 2 weeks for up to 2 years. The study included patients with squamous cell cervical cancers regardless of PD-L1 expression. The overall response rate was 26.7% for Comb A and 41.3% for Combo B. When broken down by prior therapy, the Combo B arm demonstrated a 45.8% (95%CI: 25.6-67.2) response rate in patients without prior systemic therapy and a 36.4% (17.2-59.3) response rate in those previously treated with one or two prior lines of systemic chemotherapy. In patients on Combo B without prior systemic therapy, the PFS was 8.5 months with an OS that was not reached (95% CI: 13.9 - NR). In patients with prior therapy the PFS was 5.8 months with an OS of 25.4 months (95% CI: 17.5-NR). The 12 month OS in combo B was 78% without prior therapy and 85% with prior systemic chemotherapy. No new safety signals were noted in this trial. The treatment related grade 3/4 events were 29%

in the Combo A and 37% in the Combo B arm. The discontinuation rate due to treatment related adverse events was 13% and 20% respectively.

Another combination of the PD-1 inhibitor AGEN2034 and the anti-CTLA 4 antibody AGEN1884 has been tested in combination in a phase I trial [42]. Two large phase II trials with this combination are ongoing and listed in Table 2[39, 40].

Other Checkpoint Inhibitors

Several other checkpoint inhibitors are currently under development. Targets of these antibodies include TIM-3, LAG-3, VISTA, and TIGIT[43]. Currently these agents are being tested as single agents or in combination with other checkpoint inhibitors. It is to be determined if they are more active than the currently available agents in cervical cancer.

Tumor Infiltrating Lymphocytes

It has been demonstrated that tumor infiltrating lymphocytes (TILs) are associated with a better clinical outcome in cervical cancer[44]. LN-145 is an ongoing clinical trial (NCT03108495) of a product derived from tumor infiltrating lymphocytes that are extracted and expanded in the laboratory. These TILs are then re-infused after marrow ablative chemotherapy. Complete and durable responses have been observed with this type of therapy[45]. In 18 evaluable patients with cervical cancer, responses were in 5 patients, including two with a complete response[46].

T-cells with genetically engineered T-cell receptors (TCR) that recognize HLA-A*02:01-restricted, HPV-16-oncoprotein have been developed. These T-cells have the ability to kill cells in vitro[47]. A phase I clinical trial (NCT02280811) using this therapy has shown a response in HPV16 positive anal cancer, demonstrating proof of principle[48].

CONCLUSIONS

There is tremendous interest in immunotherapy for cervical cancer with multiple ongoing trials. Although many of these approaches have demonstrated a low overall response rate, the prolonged response for some patients appears to be durable. Dramatic responses can seen with checkpoint combination checkpoint therapy as note in Figure 1. Given the limited options for patients with recurrent cervical cancer, it is likely that these agents will be the treatment of choice for first line metastatic disease or even as sensitizing agents with primary therapy to prevent recurrence. The optimal combination and regimen will need to be refined and balanced against the potential toxicity of these agents.

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KEYPOINTS

- Immunotherapy is a promising treatment for cervical cancer
- Active vaccination may also induce immune response and is being investigated
- Checkpoint inhibitors are now approved in the treatment of recurrent cervical cancer and combination checkpoint inhibition have demonstrated responses that are better than current chemotherapy options

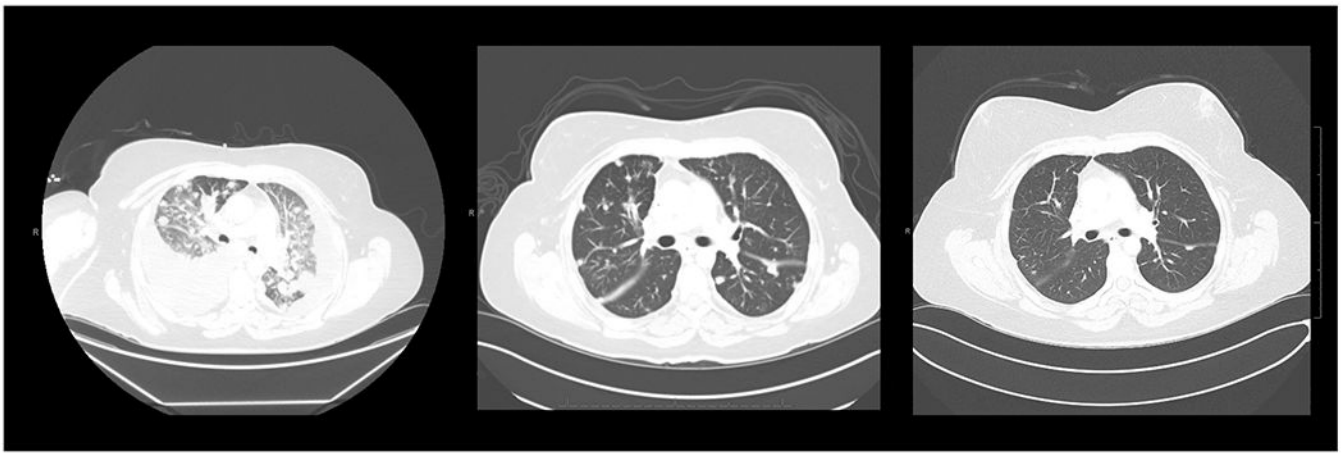

Figure 1.

Dramatic response to therapy with the combination of ipilimumab and nivolumab on CHECKMATE 358. CT scans at baseline, 2 months, and 1 year of therapy. The patient remains without disease >12 months after completing two years of immunotherapy. Images © per the authors.

TABLE 1.

Reported Trials of Immunotherapy in Cervical Cancer (Original table)

	Author/yr	Regimen	Prior Systemic Therapy	n	PD-L1	ORR% (CI) (95%tile CI)	PFS months (95%tile CI)	OS months (95%tile CI)
ADXS11	Basu [14]	ADXS11-001	0	56	NA	17.1% (8.1-32.7)	6.1 (5.9-9.4)	8.3 (5.8-10.5)
		ADXS11-001 + cisplatin		54	NA	14.7% (6.4-30.1)	6.4 (4.2-8.9)	8.8 (7.4-13.3)
GOG-0265	Huh [20]	ADXS11-001	1-3	50	NA	3.7% (0.1-18.3)	3.1 (2.8-3.7)	6.2 (4.4-12.3)
KEYNOTE-028	Frenel [22]	Pembrolizumab 10 mg/kg	1-3	24	+	17% (5-37)	2.0 (2.0-3.0)	11.0 (4-15)
KEYNOTE-158	Chung [23]	Pembrolizumab 200 mg	0-5	98	+/−	12.2% (6.5-20.4)	2.1 (2.0-2.1)	9.4 (7.7-13.1)
				84	+	14.6% (7.8-24.2)	2.1 (2.1-2.3)	11.0 (9.1-14.1)
GY002	Santin [26]	Nivolumab 3 mg/kg	1+	25	+/−	4.0% (0.4-22.9)	3.5 (1.9-5.1)	14.5 (8.3-26.8)
Ipilimumab	Lheureux [28]	Ipilimumab 10mg/kg	1-3	42	+/−	2.7% (0.5-14.9)	2.5 (2.1-3.2)	8.5 (3.6-NR)
CheckMate 358	Naumann [27]	Nivo Only	1-2		+/−	26.3% (9.1-51.2)	5.1mo (1.9-9.1)	21.9 (15.1-NR)
	Naumann [41]	Ipi 1 + Nivo 3	0	19	+/−	31.6% (12.6-56.6)	13.8 (2.1-NR)	NR (17.4-NR)
			1-2	26	+/−	23.1% (9.0-43.6)	3.6 (1.9-5.1)	10.3 (7.9-15.2)
		Ipi 3 + Nivo 1	0	24	+/−	45.8% (25.6-67.2)	8.5 (3.7-NR)	NR (13.9-NR)
			1-2	22	+/−	36% (17.2-59.3)	5.8 (3.5-17.2)	25.4 (17.5-NR)

NR- Not Reached

Ipi = Ipilimumab

Nivo = Nivolumab

TABLE 2.

Ongoing Trials of Immunotherapy in Cervical Cancer (Original table)

	NTC	Setting	Phase	Agents	n	Estimated Completion Date
CHECKPOINT INHIBITORS						
GOG 3016/ENGOT-cx9	NTC03257267	Second-line metastatic	Phase III	Cemiplimab Chemotherapy (Investigator's choice)	534	June 2023
CHECKPOINT INHIBITORS + RADIATION						
NiCOL	NCT03298893	Locally advanced untreated cervical cancer	Phase I	Cisplatin + WPRT + Nivolumab	21	May, 2022
UVA-LACC-PD201	NCT02635360	Locally advanced untreated cervical cancer	Randomized phase I	Cisplatin + WPRT + Pembrolizumab Cisplatin + WPRT followed by Pembrolizumab	88	May, 2021
GOG-9929	NCT01711515	Node (+) cervical cancer	Phase I	Cisplatin + WPRT + Ipiilimumab	34	June, 2017
NRG GY017/ NCI-2018-02791	NCT03738228	Locally advanced cervical cancer	Randomized Phase I	Cisplatin + WPRT + atezolizumab Atezolizumab followed by WPRT + cisplatin	40	November, 2021
CALLA	NCT03830866	Locally advanced untreated cervical cancer	Phase III	Cisplatin + WPRT + durvalumab cisplatin + WPRT + placebo	714	April, 2024
ATEZOLACC	NCT03612791	Locally advanced untreated cervical cancer	Randomized Phase II	Cisplatin + WPRT Cisplatin + WPRT + atzezolizumab	190	July, 2022
KEYNOTE-826/ MK-3475-826	NCT03635567	First-line metastatic	Randomized Phase III	Paclitaxel + platinum ± bevacizumab followed by Pembrolizumab Paclitaxel + platinum ± bevacizumab followed by placebo	600	November, 2022
BEATcc/GOG-3030/ ENGOT Cx10/JGOG 1084/GEICO 68-C	NCT03556839	Recurrent/ Metastatic		Paclitaxel + cisplatin + bevacizumab followed by atezolizumab Paclitaxel + cisplatin + bevacizumab followed by placebo	404	July, 2023
MCC-19662/ML40521	NCT03614949	First-line metastatic	Phase II	Radiation + atezolizumab	26	December, 2022
PD-1 and CTLA-4 COMBINATIONS						
C-550-01	NCT03495882	Second-line metastatic	Phase I/II	AGEN0234 + AGEN1884	150	March 2023
RaPiDS/GOG-3028/ C-750-01	NCT03894215	Second-line metastatic	Randomized Phase II	AGEN0234 ± AGEN 1884	200	August, 2023

WPRT - whole pelvic radiation therapy