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ABSTRACT

Cervical cancer continues to be a common cancer in women worldwide, especially in less developed regions where advanced stage presentations are common. Addition of bevacizumab to cytotoxic chemotherapy has been the only notable recent advance in the treatment of recurrent and metastatic cervical cancer. Outcomes in patients with locally advanced disease have also plateaued after meaningful gains were achieved with concomitant chemoradiation treatment. Recently, progress has been made in understanding the molecular aberrations in cervical cancer and new therapeutic modalities are emerging, including immune checkpoint inhibitors, therapeutic vaccines, antibody-drug conjugates, and others. In this review we will discuss the data and potential utility of these approaches.

INTRODUCTION

Cervical cancer is the fourth most common cancer affecting women worldwide. With an estimated 570 000 cases and 311 000 deaths in 2018, this disease accounts for 3.3% of all cancer-related deaths.¹ There is wide variation in incidence and mortality in various regions. The age-adjusted incidence and mortality rates per 100 000 are, respectively, 26.8–43.1 and 19.0–30.0 in Africa, 4.1–17.2 and 2.1–10 in Asia, 6.8–16.0 and 2.1–6.1 in Europe, 13.0–15.2 and 7.0–7.1 in Central and South America, and 6.0 and 1.7 in North America. In India, cervical cancer ranks as the second most common cancer among women, with approximately 122 844 annual diagnoses and 67 477 reported deaths.² Although uncommon at initial diagnosis, metastatic disease develops in 15% to 61% of women with cervical cancer, usually within the first 2 years of completing treatment.³ More specifically, patients with International Federation of Obstetrics and Gynaecology (FIGO) stage IB–IIA disease have a recurrence risk ranging from 10% to 20% despite primary chemoradiation, while those with FIGO stage IIB–IVA have a 30% to 70% chance of disease recurrence.^{4–6}

Histopathologically, squamous cell carcinoma, adenocarcinoma and adenosquamous carcinomas account for approximately 70%, 25% and 3% of all cervical cancers, respectively. Rarer histologies include neuroendocrine or small cell carcinomas.⁷ Ninety-five per cent of cases are caused by persistent

infections with carcinogenic human papilloma virus (HPV).⁸

OUTCOMES WITH CURRENT STANDARD OF CARE TREATMENT IN STAGE IVB DISEASE

The current standard treatment for various stages of cervical cancer is shown in [table 1](#). Over the past three decades, the median overall survival (OS) of patients with stage IVB or recurrent disease had not vastly improved despite multiple studies with single agent or combination chemotherapy. Paclitaxel plus cisplatin is the standard of care for this subgroup of patients. The results of GOG 240 study where the addition of bevacizumab increased median survival by 3.7 months to extend it to 17 months was the first advance in this scenario for a long time.⁹ Given the current paradigm of rational targeted and immunotherapeutic approaches in a variety of cancers, there is a need to better understand the molecular pathogenesis of various subtypes of cervical cancer.

BIOLOGICAL CLASSIFICATION: INTEGRATED GENOMIC AND MOLECULAR CHARACTERISATION OF CERVICAL CANCER

A comprehensive study of invasive cervical cancer was conducted as part of The Cancer Genome Atlas (TCGA) project, with a focus on identifying novel clinical and molecular associations as well as functionally altered signalling pathways that may drive tumorigenesis and serve as prognostic or therapeutic markers. Through comprehensive molecular and integrative profiling, novel genomic and proteomic characteristics that subclassify cervical cancers were identified. Three clusters were proposed: keratin-low squamous cluster, keratin-high squamous cluster and adenocarcinoma-rich cluster. These clusters are defined by different HPV subtype associations and molecular features.¹⁰

A more clinically relevant outcome of the TCGA and similar molecular profiling projects has been the identification of genetic aberrations that may be exploited therapeutically. A list of selected targets and

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Table 1 Current standard-of-care treatment⁴⁰

FIGO stage	Recommended treatment
IA1 and IA2	Type II radical hysterectomy+pelvic lymph node dissection
IB1 and IIA1	Type III radical hysterectomy+pelvic lymph node dissection
IB2 and IIA2	Pelvic EBRT+brachytherapy+cisplatin-based concurrent chemotherapy
IIIB to IVA	Pelvic EBRT+brachytherapy+cisplatin-based concurrent chemotherapy±EBRT to para-aortic nodes
IVB or recurrent disease not amenable to local therapy	Paclitaxel+cisplatin+bevacizumab Paclitaxel+cisplatin Paclitaxel+topotecan+bevacizumab Paclitaxel+topotecan Paclitaxel+carboplatin

EBRT, External Beam Radiation Therapy; FIGO, International Federation of Obstetrics and Gynaecology.

corresponding agents that could be of potential therapeutic value is shown in [table 2](#).

We will review here the targeted therapies which are in clinical use or in phase II/III studies in cervical cancer. A summary of selected studies of targeted therapy in cervical cancer is shown in [table 3](#).

Table 2 Potential targets and corresponding agents in cervical cancer

Pathway/target	Agents approved or in trials
VEGF/VEGFR	Bevacizumab, pazopanib, sunitinib, nintedanib, brivanib, cediranib
CD274 (also known as PD-L1) amplification	Immune checkpoint inhibitors
PDCD1LG2 (also known as PD-L2) amplification	Immune checkpoint inhibitors
BCAR4 amplification/HER2	Lapatinib
EGFR	Cetuximab, gefitinib, erlotinib
mTOR	Temsirolimus
HDAC	Valproic acid
PARP	Olaparib, veliparib

BCAR4, breast cancer anti-estrogen resistance 4; CD274, cluster of differentiation 274; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; PARP, poly ADP ribose polymerase; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin.

TARGETED THERAPY IN METASTATIC AND/OR RECURRENT CERVICAL CANCER

Cell surface receptors

VEGF/VEGFR-directed therapy

Antiangiogenic therapy targeting the vascular endothelial growth factor (VEGF) and other pathways has improved outcomes in multiple solid tumours. Poor prognosis and early recurrence in cervical cancer has been associated with VEGF expression.¹¹ Bevacizumab is a recombinant humanised monoclonal immunoglobulin (Ig)-G1 antibody directed against VEGF-A. By inactivating VEGF-A, it blocks signal transduction through VEGFR-1-associated and VEGFR-2-associated pathways. Data from a phase II study showed that single agent bevacizumab in metastatic cervical cancer was relatively well tolerated and its use resulted in 3.4-month progression-free survival (PFS) and 7.29-month OS.¹² GOG 240 compared the use of cisplatin/paclitaxel and topotecan/paclitaxel with or without bevacizumab. The study suggested a significant improvement in PFS (8.2 months vs 5.9 months; HR 0.67; 95% CI 0.54 to 0.82) and OS (17.0 months vs 13.3 months; HR 0.71; 98% CI 0.54 to 0.95) when bevacizumab was added to cytotoxic chemotherapy in patients with recurrent or persistent disease.⁹ Tumour-related angiogenesis leads to a more disorganised vasculature, which limits the delivery of drugs to tumour cells. Antiangiogenic agents have been shown to 'normalise' tumour vasculature, resulting in enhanced delivery of oxygen and drugs into the tumour microenvironment.¹³ This at least partly explains the higher responses with combination of bevacizumab and chemotherapy. The results of GOG 240 led to US FDA approval of bevacizumab in first-line management of advanced cervical cancer in the year 2014.

Although the overall health-related quality-of-life analysis in the GOG 240 showed no significant difference between the no-bevacizumab and bevacizumab arms, three adverse effects were significantly more frequent with addition of bevacizumab: hypertension (chemotherapy alone 0.5% vs chemotherapy plus bevacizumab 11.4%), gastrointestinal perforations (chemotherapy alone 0.5% vs chemotherapy plus bevacizumab 10.1%) and venous thrombotic events (chemotherapy alone 3.2% vs chemotherapy plus bevacizumab 8.3%).

A very important aspect when deciding the treatment in real world is the cost-benefit analysis. The estimated total cost of therapy with bevacizumab is approximately 13.2 times that for chemotherapy alone,¹⁴ and this treatment is inaccessible to most patients with cervical cancer in developing countries where the majority of these patients reside.

The tyrosine kinase inhibitors sunitinib (inhibits VEGFR, PDGFR, c-KIT, FLT-3) and pazopanib (inhibits VEGFR, PDGFR, c-KIT) have not shown significant benefits in response rates, PFS or OS in advanced cervical cancer.^{15 16} Brivanib, an inhibitor of VEGFR and FGFR, is currently under evaluation for its role in advanced cervical cancer.

Table 3 Selected studies of targeted therapy in cervical cancer

Author/study design/ year/reference	Drug	Patient population/n	Results/conclusions	Grade 3 or 4 toxicities
VEGF-targeted therapies				
Tewari <i>et al</i> (2014) Randomised controlled study ⁹	Bevacizumab (chemotherapy vs chemotherapy +bevacizumab)	Metastatic, recurrent or unresectable disease as first-line therapy (n=452)	Median OS: 13.3 vs 17 months HR: 0.71 (97% CI 0.54 to 0.94) P=0.0035 Median PFS: 5.9 vs 8.2 months HR: 0.67 (95% CI 0.54 to 0.82) P=0.002 RR: 36% vs 48% P=0.008	(chemotherapy+ bevacizumab arm): hypertension (11.4%), gastrointestinal perforations (10.1%), venous thrombotic events (8.3%)
Mackay <i>et al</i> (2010) Single arm, phase II ¹⁵	Sunitinib	Metastatic or unresectable persistent progressed on one line of therapy (n=19)	Median TTP: 3.5 months SD: 84% RR: 0%	Fatigue (15.8%), diarrhoea (15.8%), hypertension (10.3%), HFS (10.3%), anaemia (23.5%)
Monk <i>et al</i> (2010) Phase II randomised controlled study, open label ¹⁶	Pazopanib	Metastatic disease progressed on one or more lines of therapy (n=74)	Median OS: 12.4 months TTP: 4.5 months SD: 43% RR: 9%	Diarrhoea (11%)
EGFR-targeted therapies				
Goncalves <i>et al</i> (2008) Phase II single-arm study, open label ¹⁹	Gefitinib	Metastatic, recurrent or unresectable disease progressed on one or more line of therapy (n=30)	Median OS: 3.7 months Median TTP: 1.23 months SD: 20% RR: 0%	Diarrhoea (13.3%) Anorexia (6.7%)
Schilder <i>et al</i> (2009) Phase II single-arm, open-label study ¹⁸	Erlotinib	Metastatic, recurrent or unresectable disease progressed on one or more line of therapy (n=28)	Median OS: 4.96 months Median TTP: 1.87 months SD: 16% RR: 0%	Diarrhoea (12%) Rash (8%) Anaemia (16%) Fatigue (8%) Nausea (8%) Emesis (8%)
Kurtz <i>et al</i> (2009) Phase II single arm study ²²	Cetuximab (combination with cisplatin and topotecan)	Metastatic, recurrent or unresectable disease as first-line therapy (n=19)	Median OS: 7.33 months Median TTP: 5.73 months SD: 32% RR: 32%	Febrile neutropenia (22%) Haemorrhage (11%) CINV (22.5%) Skin reaction (22%) Pulmonary embolism (5%) Death due to toxicity (10.5%)
HER2 and EGFR-targeted therapy				
Monk <i>et al</i> (2010) Phase II, randomised controlled study, open label ¹⁶	Lapatinib	Metastatic disease progressed on one or more lines of therapy (n=78)	Median OS: 11 months TTP: 4.27 months SD: 44% RR: 5%	Diarrhoea (13%) Fatigue (5%) Anaemia (5%) Dyspnoea (6%)
Immune checkpoint inhibitor				

Continued

Table 3 Continued

Author/study design/ year/reference	Drug	Patient population/n	Results/conclusions	Grade 3 or 4 toxicities
Frenel <i>et al</i> (2016) Phase Ib multicohort open-label study ²⁷	Pembrolizumab	Metastatic, recurrent or unresectable disease progressed on one or more line of therapy (n=24)	Median OS: 9 months RR: 17%	Rash (9%) Proteinuria (4%) Colitis (4%) Guillain-Barre syndrome (4%)
Therapeutic vaccine				
Basu <i>et al</i> (2018) Phase II ³²	Axalimogene filolisbac (ADXS11-001) (ADXS11-001 with cisplatin vs ADXS11- 001 alone)	Metastatic, recurrent or unresectable disease progressed on one or more line of therapy (n=109)	Median OS: 8.78 vs 8.28 months Median PFS: 6.10 vs 6.08 months RR: 17.1% vs 14.7%	Overall grade 3 or 4 toxicities (19.7%)
PARP Inhibitor				
Thaker <i>et al</i> (2015) Limited access phase I trial ³⁶	Veliparib (with paclitaxel and cisplatin)	Advanced, persistent or recurrent (n=37)	SD: 41% RR: 34%	NA
Antibody–drug conjugate				
Vergote <i>et al</i> (2017) Multicohort phase IIA study ³⁷	Tisotumab–vedotin	Metastatic disease progressed on one or more lines of therapy (n=34)	SD: 18% RR: 32%	Conjunctivitis (3%) Neuropathy (6%)
Immune checkpoint Inhibitor in adjuvant treatment				
Mayadev <i>et al</i> (2017) Phase I study ³⁸	Ipilimumab	Node-positive disease post-CTRT for sequential therapy with ipilimumab as adjuvant therapy (n=34)	1-year DFS: 74%	Neutropenia (5.3%) Rash (5.3%) Lipase (5.3%)

Only grade 3 or 4 toxicities which were seen in more than 3% patients have been documented in this table.

CINV, chemotherapy-induced nausea vomiting; DFS, disease-free survival; NA, not available; OS, overall survival; RR, response rate; SD, stable disease; TTP, time to progression.

EGFR/HER2

Cervical cancer has moderate to high levels of epidermal growth factor receptor (EGFR) protein expression.¹⁷ Unfortunately, studies with gefitinib and erlotinib as single agents in the treatment of recurrent cervical cancer have shown minimal activity.^{18–19} Cetuximab, a monoclonal antibody against EGFR, was also evaluated in this setting, but multiple studies with or without cytotoxic chemotherapy have shown no meaningful benefit with this drug.^{20–22} Lapatinib, a HER2 inhibitor, as a single agent failed to show benefit in a phase II study where it was compared with pazopanib.¹⁶ The combination of lapatinib and pazopanib (combination of HER2 inhibitor with VEGFR inhibitor) caused excessive toxicity and hence the recruitment to this arm of the same study was closed prematurely.¹⁶

A recent study of molecular profiling of cervical cancer samples and testing in patient-derived xenograft (PDX) models has shown that co-administration of trastuzumab and lapatinib in the HER2-overexpressed PDX significantly inhibited tumour growth compared with the control.²³ However, only one out of nine patients had a

HER2-amplified tumour and further larger studies are needed for validation of these findings.

Immune-directed therapy

Immune checkpoint inhibitors

PD-1 (programmed cell death 1) and PD-L1 expression on cervical cancer infiltrating T cells and dendritic cells, respectively, has been reported to be associated with high-risk HPV positivity and increasing cervical intraepithelial neoplasia grade. PD-1 is expressed by a high fraction of infiltrating CD8 T cells in cervical cancer, suggesting that blocking of PD-1 could have therapeutic potential.^{24–25}

A phase II single-arm study (ClinicalTrials.gov identifier: NCT02257528) is evaluating the safety and efficacy of nivolumab, a fully human antibody against PD-1, as a second-line treatment of persistent or recurrent cervical cancer after progression or intolerance to cytotoxic chemotherapy. In this study, patients are receiving nivolumab at a dose of 3 mg/kg every 2 weeks for a maximum of 46 doses over 92 weeks in the absence of disease progression or unacceptable toxicity. The results of this study are expected by the end of 2018.

Another phase II study (ClinicalTrials.gov identifier: NCT01693783) is evaluating the role of ipilimumab in the same setting. The study recruited a total of 42 patients with a median age of 49 years. Of these, 29 patients had squamous and 13 patients had adenocarcinoma, 35 patients had received prior radiation therapy and 21 patients had received two to three prior regimens of chemotherapy. Toxicities were manageable and grade 3 toxicities included diarrhoea (four patients) and colitis (three patients). The best attained response in 34 evaluable patients was as follows: 3 partial response, 8 stable disease and 23 disease progression. The median PFS was 2.5 months (95% CI 2.3 to 3.2). The final results are expected by the end of 2018.²⁶

Preliminary results from the phase Ib KEYNOTE-028 study evaluating the safety and efficacy of pembrolizumab in patients with advanced solid tumours were presented at the American Society of Clinical Oncology Meeting in 2016.²⁷ This phase I trial included an expansion cohort of patients with advanced squamous cervical cancer who had unresectable or metastatic cervical cancer, failed prior systemic therapy and a PD-L1 expression in $\geq 1\%$ of tumour or stroma cells by immunohistochemistry (IHC). Pembrolizumab was given at a dose of 10 mg/kg every 2 weeks for up to 24 months or until confirmed progression, intolerable toxicity or death. The primary endpoint was the overall response rate. A total of 24 patients with median age of 41.5 years were enrolled, of whom 15 (63%) patients had distant metastases. Most patients (96%) had received prior radiotherapy, 63% had received two or more prior lines of chemotherapy, and 42% had previously received bevacizumab. Five patients (21%) had a grade 3 adverse event related to treatment, including two rashes, one neutropenia, one proteinuria and two of whom discontinued pembrolizumab; one for a colitis and the other for a Guillain-Barre syndrome. At a median follow-up of 48.9 weeks, the overall response rate was 17%, including long-lasting responses (mean duration of response, 26 weeks). Although median PFS was modest, median OS reached 9 months, which is substantial in a heavily pretreated population.

The clinical benefit of pembrolizumab in advanced cervical cancer is being further investigated in the phase II KEYNOTE-158 trial (ClinicalTrials.gov identifier: NCT02628067). Based on the tumour response results of this study,²⁸ in June 2018 the US FDA accorded accelerated approval for pembrolizumab in metastatic or recurrent cervical cancer patients progressing on or after chemotherapy, whose tumours expressed PD-L1 with a combined positive score (CPS) ≥ 1 , as determined by an approved companion diagnostic test using the PD-L1 IHC 22C3 pharmDxKit. KEYNOTE-158 was a multicentre, non-randomised, open-label study where patients were treated with pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or disease progression. Of the 98 patients in cohort E (cervical cancer cohort), 77 (79%) had tumours that expressed PD-L1. In these 77 patients, Eastern Cooperative Oncology Group

performance status was 0 (32%) or 1 (68%), median age was 45 years, the overwhelming majority (92%) had squamous carcinoma, 95% had M1 disease while 5% had recurrent disease, and 35% had received 1% and 65% had received two or more prior lines of therapy in the recurrent or metastatic setting. At a median follow-up of 11.7 months, the response rate was 14.3% (95% CI 7.4 to 24.1), with a complete response rate of 2.6% and partial response rate of 11.7%. In the 11 responding patients, median duration of response was not yet reached and 91% experienced durations of response of 6 months or longer. There were no responses in patients whose tumours did not have PD-L1 expression (CPS < 1). Of patients with cervical cancer receiving pembrolizumab, 39% experienced a serious adverse event and 8% had to discontinue this drug because of drug-related toxicity.

The immune checkpoint inhibitor approach is likely to provide higher benefit in earlier lines of treatment and perhaps in combination with other strategies such as chemotherapy and/or radiotherapy.

Therapeutic vaccines

Cervical cancer therapeutic vaccines aim to eradicate HPV-infected cells by stimulating cytotoxic T cells against the viral/tumour antigens. The HPV E6 and E7 oncoproteins are expressed in HPV-associated cancers and are ideal targets for a therapeutic vaccine.²⁹ Many live bacterial vectors have been explored in HPV therapeutic vaccines including *Listeria monocytogenes*, *Lactobacillus lactis*, *Lactobacillus plantarum*, *Salmonella enterica* and BCG.³⁰ *Listeria monocytogenes* has the ability to replicate in the cytosol of antigen-presenting cells and infects monocytes and macrophages, allowing bacterial peptide antigens to be processed and presented via both Major Histocompatibility Complex class I and II pathways, generating potent CD8 and CD4 T cell-mediated immune responses. The sensitivity of *Listeria* to antibiotics allows the vector to be killed in vivo as required. The *Listeria*-based vaccine potency is further enhanced by encoding recombinant proteins composed of HPV E6 and E7 antigens fused to immunostimulatory molecules.³¹

Axalimogene filolisbac (ADXS11-001), a live, attenuated *Listeria monocytogenes* bacterial vector secreting HPV-16 E7 fused to listeriolysin O (LLO), is under investigation for treatment of HPV-associated malignancies including cervical cancer. A phase II study evaluated the safety and efficacy of ADXS11-001, administered with or without cisplatin, in patients with recurrent/refractory cervical cancer following prior chemotherapy and/or radiotherapy.³² A total of 109 patients were treated, of whom 69 were evaluable for tumour response. Median OS was comparable between treatment groups (ADXS11-001, 8.28 months, 95% CI 5.85 to 10.5 months; ADXS11-001 plus cisplatin, 8.78 months, 95% CI 7.4 to 13.3 months). In ADXS11-001 versus ADXS11-001 plus cisplatin groups, the 12-month and 18-month milestone OS rates were 30.9% versus 38.9%, and 23.6% versus 25.9%, respectively. The median PFS (6.10 vs 6.08 months) and the

overall response rate (17.1% vs 14.7%) were similar in both groups. ADXS11-001 was generally well tolerated and adverse events were predominantly mild to moderate in severity and not related to treatment. More adverse events were reported in the combination group.

The results of this initial study of ADXS11-001 in a recurrent/refractory population indicated that there was no added benefit in survival with the addition of cisplatin in this setting. These results formed the basis for the phase II GOG/NRG 0265 monotherapy trial in a similar population, in which the 12-month OS rate was 38%.³³

A combination of therapeutic vaccines and immune checkpoint inhibition is being explored to overcome immune tolerance. ADXS11-0011 is being evaluated in combination with durvalumab, a PD-L1 inhibitor (ClinicalTrials.gov identifier: NCT02291055). This study is currently suspended after a patient died due to respiratory failure in February 2018 after sixth combination cycle.^{34 35}

PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) is a constitutively expressed enzyme that is involved in base excision DNA repair as well as cell replication, transcription, differentiation and gene regulation, and its inhibition has been shown to be synthetic lethal with homologous recombination DNA repair defects.

The PARP inhibitor veliparib was studied in combination with cytotoxic therapy in women with recurrent or persistent cervical cancer after receiving pelvic radiation (with or without cisplatin).³⁶ The study regimen consisted of cisplatin and paclitaxel on day 1 with dose escalation of veliparib twice daily dosing for 7 days. The maximum dosage level of 400 mg twice daily veliparib was achieved. Of the 29 patients with measurable disease, 2 patients (6.9%) had a complete response and 8 patients (27.6%) had a partial response. Additionally, 12 patients (41.4%) had stable disease.

Although phase I studies have reported potential activity, further studies need to be performed to determine the true role of this class of drugs, including the dosage and schedule.

Antibody–drug conjugate

Cytotoxic drugs, usually highly toxic by themselves, have been conjugated to antibodies which are targeted to specific receptors on cancer cells in many cancers. One such antibody–drug conjugate, tisotumab–vedotin, has been studied in patients with recurrent and relapsed cervical cancer. This conjugate combines a human antibody to tissue factor, which is overexpressed in a number of cancers including cervical cancer, with a microtubule-disrupting agent, MMAE, using a linker. A phase II study was reported in an expansion cohort of 34 patients with cervical cancer with advanced or metastatic disease who had failed standard treatment.³⁷ The response rate in this resistant group of patients was 32% with a median duration of response of 8.3 months in confirmed responders.

However, there was ocular toxicity, including conjunctivitis and keratitis in 53% of patients. This was mitigated after the first 15 patients by additional measures such as strict dose adjustment, lubricating eye drops, eye cooling and steroid drops. The results have been updated, and this is a promising avenue of treatment in these patients.

TARGETED THERAPY IN LOCALLY ADVANCED CERVICAL CANCER

Adjuvant immune checkpoint inhibitors

A phase I trial studied the effect of ipilimumab after chemoradiation in patients with stages IB2–IIB disease with para-aortic nodes or stages IIIB–IVA with any positive nodes. In this study, patients received standard cisplatin-based chemoradiation (CRT) followed by brachytherapy and intravenous ipilimumab once every 3 weeks for 12 weeks within 2 weeks of finishing brachytherapy. All 34 patients completed CRT, 90% completed four cycles of ipilimumab while the other 10% completed two cycles. The ipilimumab maximum tolerated dose was 10 mg/kg. There were three patients (16%) with acute grade 3 toxicity (elevated lipase, neutropenia, rash) which self-resolved. With a median follow-up of 12 months, there were no major late toxicities reported and a 1-year DFS of 74%.³⁸ Translational endpoints of this study included the effect of chemoradiation on enumeration and subsets of T cells, and CTLA4, PD-1 and inducible co-stimulator (ICOS) expression. There was no difference in CD4⁺ and CD8⁺ T-cell levels or CTLA-4 expression with sequential ipilimumab. Chemoradiation itself increased ICOS and PD-1 expression. This paves the path for further studies using immunotherapy in locally advanced cervical cancer.³⁸

An ongoing phase II study (ClinicalTrials.gov identifier: NCT02635360) is assessing the role of pembrolizumab, a humanised monoclonal antibody of IgG4 kappa class directed against PD-1, in a randomised fashion in patients on CRT. Patients will receive pembrolizumab 3 mg/kg q 21 days for 3 months starting with CRT or after completion of CRT. The study is at present recruiting patients at five centres across the USA.

Adjuvant therapeutic vaccine

A double-blind, placebo-controlled randomised study of ADXS11-001 administered in the adjuvant setting after completion of cisplatin-based CRT in subjects with locally advanced cervical cancer at higher risk for recurrence or death has started recruiting patients since August 2016 (ClinicalTrials.gov identifier: NCT02853604). The primary and secondary outcomes of the study are DFS and OS and safety of the vaccine, respectively.

NEED FOR COST-EFFECTIVE TREATMENTS

Cervical cancer ranks second in incidence and mortality behind breast cancer in lower Human Development Index (HDI) settings; however, it is the most commonly diagnosed cancer in 28 countries and the leading cause of cancer death in 42 countries, the vast majority of which

are in Sub-Saharan Africa and South-East Asia. In relative terms, the regional incidence and mortality rates are 7 to 10 times lower in North America and Australia/New Zealand as compared with those in the low-HDI regions.¹ It is obvious that cervical cancer is a disease of low-income regions.

As mentioned earlier, the cost of adding bevacizumab to cytotoxic chemotherapy is 13 times that of cytotoxic chemotherapy alone.¹⁴ Although a cost-benefit analysis of immune-directed therapies in cervical cancer has not been done yet, it is evident that these options will not be feasible for a significant portion of this population. Hence, there is a pressing need for cost-effective treatment options which should bring better outcomes in these patients.

GLIMPSE INTO THE FUTURE

A number of biological agents modulating different signal transduction pathways are currently in clinical development. To name a few, these are arresting cell cycle, histone deacetylases, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), heat shock protein (HSP), WEE1, NOTCH signalling and others.³⁹ With a better understanding of the central role of HPV infection in tumourigenesis of cervical cancer, more studies are evaluating the role of immune-directed therapies in cervical cancer, in adjuvant as well as metastatic settings.

Soon, we may be able to achieve success with these therapies in cervical cancer just as we have achieved with HER2-targeted therapies in HER2-positive breast cancer and immune checkpoint inhibitors in melanoma. However, the larger context is the declining incidence of cervical cancer in most parts of the world, including less developed ones, due to a variety of reasons which will result in lesser number of women requiring treatment for advanced or metastatic disease in the future.

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