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Review

The current status of immunotherapy for cervical cancer

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ABSTRACT

Background: Immunotherapy has been proven effective in several tumours, hence diverse immune checkpoint inhibitors are currently licensed for the treatment of melanoma, kidney cancer, lung cancer and most recently, tumours with microsatellite instability. There is much enthusiasm for investigating this approach in gynaecological cancers and the possibility that immunotherapy might become part of the therapeutic landscape for gynaecological malignancies.

Cervical cancer is the fourth most frequent cancer in women worldwide and represents 7.9% of all female cancers with a higher burden of the disease and mortality in low- and middle-income countries. Cervical cancer is largely a preventable disease, since the introduction of screening tests, the recognition of the human papillomavirus (HPV) as an etiological agent, and the subsequent development of primary prophylaxis against high risk HPV subtypes. Treatment for relapsed/advanced disease has improved over the last 5 years, since the introduction of antiangiogenic therapy. However, despite advances, the median overall survival for advanced cervical cancer is 16.8 months and the 5-year overall survival for all stages is 68%. There is a need to improve outcomes and immunotherapy could offer this possibility. Clinical trials aim to understand the best timing for immunotherapy, either in the adjuvant setting or recurrent disease and whether immunotherapy, alone or in combination with other agents, improves outcomes.

Abbreviations: APC, antigen-presenting cell; CAR, chimeric antigen receptor; CD4, -8, -80, cluster of differentiation 4, -8, -80; CTL, cytotoxic-T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; DFS, disease free survival; DNA, deoxyribonucleic acid; FIGO, International Federation of Gynecology and Obstetrics; HLA, human leucocyte antigen; HPV, human papilloma virus; IL-2, interleukin 2; LLO, listerolysin O; ILT's, Ig-like transcripts; Lm, *Listeria monocytogenes*; MAGE-A3, melanoma-associated antigen 3; MCH, major histocompatibility complex; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression free survival; RNA, ribonucleic acid; SLP, synthetic long-peptide; TCR, T-cell receptor; TGF_{β}, transforming growth factor beta; TILs, tumor-infiltrating lymphocytes; TRAEs, treatment related adverse events.

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1. Background

Cervical cancer is the fourth most frequent cancer in women with an estimated 530,000 new cases representing 7.9% of all female cancers.[1] 85% of the global burden occurs in low- and middle-income economies, where it accounts for almost 12% of all female cancers.[2] Cervical cancer is rare before age 20, however it affects a younger population of women with a median age at diagnosis of 49 years.[3] Cervical cancer causes 270,000 deaths annually and mortality varies 18-fold between different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to more than 20 per 100,000 in Melanesia, Middle and Eastern Africa.[1]

Although significant progress has been achieved in the screening and prevention of cervical cancer, five-year overall survival remains around 60% and treatment for relapsed disease is still challenging. For women diagnosed at an early stage, the likelihood of recurrence is 10–20% following primary surgery or radiotherapy, and for those with more advanced disease, recurrence rate is up to 70% depending on the stage.[4] Median overall survival (OS) for patients with recurrent disease has improved since the introduction of bevacizumab (antiangiogenic agent) in combination with chemotherapy[5] increasing the median OS to above the one year mark. There is no specific standard of care option beyond the first line systemic therapy, the most commonly used regimens include weekly paclitaxel, carboplatin-based, docetaxel-based chemotherapy, topotecan, gemcitabine and targeted therapy within clinical trials.[6] In this setting, a retrospective series reported a response rate of 13.2%, median progression-free survival (PFS) is 3.2 months with a median overall survival (OS) of only 9.3 months.[6] There is an urgent need for better therapies.

The recognition of the human papilloma virus as etiological cause of the disease has been an important milestone in the understanding of the disease, helping to develop new preventive strategies and improve screening.[7] HPV infections are common and the life-time risk of infection is approximately 80% for productive women, HPV life cycle is related with their host cell biology[8] and wide majority of HPV infections are cleared within 6–12 months, a minor percentage (10–12%) remains uncleared and produced oncogenic changes in the epithelium[9] leading to pre-malignant lesions and cancer years after the first infection.[10,11]

Ninety-five percent of cases of cervical cancer are caused by persistent infections with carcinogenic human papillomaviruses.[7] Persistent infections express viral oncogenes E6 and E7 that inactivate p53 and retinoblastoma protein, respectively, leading to increased genomic instability, accumulation of somatic mutations, and in some cases, integration of HPV into the host genome.[8] There are more than 150 HPV types identified, approximately 40 can infect the cervix and amongst all the HPV types, twelve are classified as high risk, these include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[12] HPV16 is the most carcinogenic in terms of cervical cancer incidence and cervical intraepithelial neoplasia grade 3,[13,14] HPV18 is second in terms of etiologic importance; however, it is the most important etiological agent amongst adenocarcinomas.[13]

Prophylactic vaccines will not be discussed in this review; however, it is important to mention that they provide a protective immunity against most HPV high risk subtypes, but do not offer universal protection against HPV infection nor are they as effective as treatment for existing HPV infection.[9] The reason for this is that prophylactic vaccines target capsid antigens and HPV-infected basal epithelial cells do not express detectable levels of capsid antigen; hence, they are unlikely to be effective in the elimination of established HPV infections and HPV associated diseases.[9]

2. Immunotherapy for cervical cancer

The immune system plays a key role in the control of HPV infection. The changes in the microenvironment and the interplay between virally-infected keratinocytes and the local immune microenvironment will determine the course of disease in HPV-induced carcinogenesis.[15] This raises the possibility that immunotherapy strategies could rebalance the local immune factors to release existing, or generate new and effective, antitumour immunity.[16] The immune system can be used to erradicate cancer by selective recognition of virus-associated tumour cells[17] or by releasing the negative feedback on the cytotoxic T lymphocytes (CTLs) allowing them to target neoplasic cells.[18]

2.1. *Therapeutic vaccines (Table 1)*

Therapeutic vaccines induce the activation and proliferation of T cells which specifically recognize and kill cancer cells by making use of constitutively expressed tumour-specific antigens E6 and E7.[19] For vaccines to work, the antigen needs to be recognized by the antigen presenting cell (APC) and then induce specific CTLs against the antigen. Different types of vaccines have been designed for the treatment of HPV-related cervical cancer, with varying strengths and weaknesses, immunogenicity and efficacy.

Live-vector vaccines are highly immunogenic and can induce strong cellular and humoral immune responses. These vaccines deliver E6 and E7 antigens to APCs to stimulate antigen presentation through the major histocompatibility complex (MHC) class I and II.[19] Limitations to this approach are the potential safety risk, particularly in immunocompromised individuals and the limited immune response efficacy after repeated immunization with the same vector.[20]

ADXS11–001 also known as AXAL™ (Advaxis) is a therapeutic vaccine that uses *Listeria monocytogenes* (Lm) as a bacterial vector. Lm is a gram-positive intracellular bacterium capable of escaping the host phagosomes and, in consequence, infecting the host cells; it can activate both innate and adaptive immune responses.[21] ADXS11-001 is a live-attenuated *L. monocytogenes* vaccine that secretes the HPV-16 E7 antigen fused to a non-hemolytic fragment of the Lm protein listeriolysin O (LLO).[19] Lm-LLO immunotherapies do not induce neutralizing antibodies and have the capacity to

Table 1 – HPV therapeutic vaccines, phase I and II clinical trials.

Author/year/*n*	Treatment schedule	Response	Toxicity
Maciag et al., 2009[22] Phase I trial recurrent or metastatic disease *n* = 15	DL1: ADXS11-001 1×10^9 two doses every 21 days DL2: ADXS11-001 3.3×10^9 two doses every 21 days DL3: ADXS11-001 1×10^{10} two doses every 21 days	7pts SD 1pts PR	Pyrexia (100%), vomiting 60%, pain (57%), chills, anaemia (53%) Grade 3: 40% (6pts)
Ghamande et al., 2016[23] Phase I recurrent or metastatic disease *n* = 9	DL1: ADXS11-001 5×10^9 three weekly during 12 wks DL2: ADXS11-001 1×10^{10} three weekly during 12 wks	Not informed	TRAE: 75% AE: 99% grade 1–2 Grade 3: Chills, vomit, hypotension, tachycardia, fever and nausea.
Huh et al., 2013 (GOG 0265)[24] Phase II recurrent or metastatic disease *n* = 26	ADXS11-001 1×10^9 every 28 days for 3 doses	Mean 12mo survival: 38.5% Median OS: 6.2 mo	AE: 91% grade 1–2 TRAE: 38%: nausea, vomiting, chills, fatigue, and fever. Grade 3 TRAE: 15% (4pts) hypotension, cytokine release syndrome. Grade 4 AE: 1 pt lung infection and sepsis.
Petit et al., 2014[26] Phase II recurrent or metastatic disease *n* = 109	Arm A: ADXS11-001 1×10^9 for 3 doses Arm B: ADXS11-001 1×10^9 for 4 doses plus cisplatin 50 mg/m^2 during 5 wks	ORR 11% (5CR/6PR). DCR: 38% OS: 8.4 mo Arm A and 8.77 mo Arm B. 12 mo survival 32% and 24 mo survival 18%	AE: 79% grade 1–2, mainly flu-like symptoms 2 pts grade 3 AE
Welters et al., 2008[32] Phase II adjuvant stage IB1 and HPV16+ *n* = 6	HPV16 E6 E7 SLP vaccine	Vaccine enhanced number and activity of HPV16 specific CD4+ and CD8+ cells	Grade 1–2: local pain, fever, flu-like symptoms, swelling, itching, burning eyes.
Poelgeest et al., 2013[33] Phase II recurrent or metastatic disease *n* = 31	HPV16 E6-E7 SLP vaccine 300 μg for 4 doses every 21 days	Median OS: 12.6 mo No tumour regression or delay of progression	Grade 1–2: fever, fatigue, headache, flu-like symptoms, chills, nausea, swelling extremities, rash, vomiting, tingling extremities, and injection site pain.
Ramanathan et al., 2014[38] Phase I recurrent or metastatic disease *n* = 14	Arm 1: placebo 3 doses every 14 days Arm 2: unprimed DC 3 doses 1×10^6 cells every 14 days Arm 3: primed DC 3 doses 1×10^6 cells every 14	SD on Arm 3	Grade 1–2: itching at injection site, fever, chills, abdominal discomfort, vomit, ALP increased.
Ferrara et al., 2003[39] Phase I recurrent or metastatic disease *n* = 15	Analogous dentritic cells pulsed with HPV E7 protein	Serological response in 3 pts Cellular response in 4 pts No objective clinical response	
Santin et al., 2008[40] Phase I. Stage IB or IIA *n* = 10	DL1: HPV16/18 E7 antigen pulsed DC 5×10^6 for 5 doses every 21 days DL2: HPV16/18 E7 antigen pulsed DC 10×10^6 for 5 doses every 21 days DL3: HPV16/18 E7 antigen pulsed DC 15×10^6 for 5 doses every 21 days	CD4+ T cell response in all patients	Mild swelling and erythema at the injection site.

DL: dose level; pts/pt: patients, wks: weeks; TRAE: treatment related adverse events; AE: adverse events; mo: month; OS: overall survival; ORR: objective response rate; CR: complete response; PR: partial response; SD: stable disease; DCR: disease control rate; DC: dendritic cells.

facilitate chemotaxis of activated immune cells as well as to stimulate robust immune memory responses.[19]

Results from phase I trials[22,23] have shown a safety toxicity profile and treatment related adverse events (TRAEs) including pyrexia, vomiting, flu-like symptoms, muscular pain, and hypotension. Two phase II trials with promising results have been reported. GOG-0265[24] studied patients with persistent/recurrent or metastatic squamous or non-squamous cervical cancer. Twenty-six patients were enrolled; the mean 12-month survival was 38.5% with a median OS of 6.2 months.[25] Another trial evaluated the efficacy and safety of ADXS11-001 administered with or without cisplatin, this phase II trial enrolled 110 patients with recurrent or progressive invasive cervical cancer.[26] Patients were randomized to either 3 doses of ADXS11-001 or 4 doses of ADXS11-001 with cisplatin. 109 patients received treatment with majority of adverse events (AE) reported as mild or moderate. In terms of efficacy, 12-month survival was 32%, 18-month survival was 22% and 24-month survival was 18%. The response rate was 11% and the average duration of response in both treatment groups was 9.5 months. Overall survival was 8.4 months for ADXS11-001 and 8.77 months for ADXS11-001 with cisplatin. No significant differences between the response rates, disease control rates, duration of response, or PFS were observed with the addition of cisplatin.

Combination approaches with checkpoint inhibitors are currently under evaluation for patients with recurrent or metastatic HPV-related cancers, including cervical cancer (NCT02291055).[27] In the adjuvant setting, AIM2CERV (NCT02853604)[28] a randomized phase III placebo control study, in patients with high-risk locally advanced cervical cancer (FIGO stage Ib2 and II with pelvic nodal involvement, FIGO stage III and IV and any stage with para-aortic involvement), will evaluate adjuvant ADXS11-001 following chemoradiation.

Peptide-based vaccines involve the direct administration of peptides derived from HPV antigens for uptake by dendritic cells (DCs), to be presented in association with MHC class I/II molecules.[29] Peptide-based vaccines are safe, stable, and relatively easy to produce. However, they have relatively poor immunogenicity and require lipids or other adjuvants, to enhance vaccine potency.[29] Phase I trials of HPV16 synthetic long-peptide (HPV16-SLP) vaccine have demonstrated[30–32] an immune response either by itself or in combination with chemotherapy. Toxicities did not exceed grade 2 and included injection site pain, fever, and flu-like symptoms. The phase II trial enrolled 21 patients with advanced or recurrent gynaecological cancer[33]; adverse events were similar to those observed in the phase I trials. Median overall survival was 12.6 months (range 4–26 months) and median OS was 8.8 months. HPV16-SLP vaccines are under study in combination with chemotherapy (NCT02128126),[34] and check-point inhibitors (NCT02426892).[35]

Dendritic based-vaccines, DCs are leukocytes with the ability to present antigens to T cells. Isolated DCs loaded with tumour antigen *ex vivo* and administered as a cellular vaccine have been found to induce protective and therapeutic anti-tumour immunity.[36] A number of tumour-associated antigens have been identified as potential immunogens in DC-based vaccination strategies, including peptides that are presented in a human leucocyte antigen (HLA) restricted fashion, therefore available only to patients with specific HLA haplotypes. Other tumour-associated antigens have been studied, including tumour-derived RNA, tumour-derived apoptotic bodies, and tumour lysates. In this case, as tumour cells serve as a source of antigen, such vaccines are available to all patients, irrespective of HLA type.[37] Phase I trial data[38–40] showed that generating loaded DCs *in vitro* is feasible and this strategy is able to generate specific serologic responses with mild toxicity. Therapeutic vaccination, including dendritic based-vaccines, aims to expand high-avidity CD8+ T cells that can differentiate into CTLs able to kill cancer cells and can generate long-lived memory CD8+T cells.[41] Dendritic cell-based vaccines have the potential to induce both tumour-specific effector and memory T cells, yet there is a need to improve their efficacy and the next generation of DC vaccines is expected to generate large numbers of high-avidity effector CD8(+) T cells and to overcome regulatory T cells[41] as well as intrinsic regulators such as CD28-CTLA-4, PD1-PDL1, and ILTs. New strategies might include the combination of DC vaccine with agents that target different pathways, these polyvalent vaccines targeting distinct yet specific DC subsets are expected to trigger a more comprehensive anti-cancer response.[41]

2.2. *Checkpoint inhibitors (Table 2)*

Checkpoint inhibitors block inhibitory receptors of immune system elements leading to the activation of immune cells against the tumour.[42] Virus-induced cancers present a specific immunologic profile and their response to immune checkpoint inhibitors is expected to be different than other cancers.[42] This eventual differential tumour response is a consequence of a higher mutational load[43] possibly leading to a better response.[42] Another possible explanation is a higher expression of PD-L1 in virus-induced cancers;[42] PD-L1 expression as a biomarker of response is controversial due in part to the lack of clarity regarding the appropriate cut-off values quantifying clinically meaningful PD-L1 expression[44] and paucity of data showing correlation with treatment outcomes in those with cervical cancer. Nonetheless, increased expression of PD-1 in infiltrating TILs suggests that the blockade of PD-1/PD-L1 may have a therapeutic potential in cervical cancer patients.[45]

PD-1 and PD-L1 inhibitors. Programmed cell death protein-1/programmed death ligand-1 immune regulatory axis is a promising target for cervical cancer treatment.[44] Pembrolizumab (Merck Sharp & Dohme) is a humanised monoclonal immunoglobulin G4 (IgG4) kappa isotype antibody targeting PD-1. Preliminary results from the expansion cohort of the phase Ib KEYNOTE 028 study in patients with PD-L1-positive (≥1%) advanced solid tumours including cervical cancer[46] reported 24 patients with metastatic or unresectable cervical squamous cell carcinoma who had failed a prior systemic therapy. Seventy-five percent of the patients experienced a TRAE and 20.8% experienced a grade 3 TRAE. In terms of efficacy, ORR was 12.5% and the median duration of response was 19.3 weeks; 6-month PFS rate was 13.0% and 6-month OS rate was 66.7%. Preliminary results from the phase II KEYNOTE 158 trial[47] included 47 recurrent/metastatic squamous cervical cancer patients; ORR was 17% and authors suggested that response was independent of PD-L1 status.

Table 2 – Immune checkpoint inhibitors, phase I clinical trials.

Author/year/*n*	Treatment schedule	Response	Toxicity
Frenel et al., 2016[46] Phase I expansion cohort, metastatic disease *n* = 24 PD-L1 IHC ≥ 1%	Pembrolizumab 10 mg/kg every 2 weeks up to 2 years	ORR: 17% Median duration of response: 19.3 wks 6 month PFS: 13% and OS: 66.7%	75% TRAE: pyrexia, rash in more than 10 pts 20.8% grade 3 TRAEs, 2 discontinued pembrolizumab due to colitis and Guillain–Barre syndrome
Schellens et al., 2017[47] Phase II, metastatic disease *n* = 46	Pembrolizumab 200 mg 3weekly to 2 years	ORR 17% (87% PD-L1+) 15 pts had ≥27 wks follow-up: ORR 27%.	Not reported
Hollebecque et al., 2017[52] Phase I/II recurrent or metastatic disease *n* = 24 (19 pts cervical cancer)	Nivolumab 240 mg every 2 weeks	ORR 26.3% DCR 70.8% Median PFS 5.5mo, OR NR	70.8% TRAEs 12.5% grade 3–4
Lheureux et al., 2015[59] Phase I/II recurrent or metastatic disease *n* = 42	Phase I: Ipilimumab 3 mg/kg every 21 days for 4 doses. Phase II: Ipilimumab 10 mg/kg every 21 days for 4 doses and 4 cycles (same dose) every 12 weeks.	Median PFS 2.5 mo	Grade 3: diarrhoea, colitis
Mayadev et al., 2017[60] Phase I, FIGO IB2/IIA or IIB/IIIB/IVA, positive nodes *n* = 34	Weekly cisplatin 40 mg/m^2 during 6 weeks and extended field radiotherapy. If no progression 2–6 wks after: DL:1 Ipilimumab 3 mg/kg for 4 doses every 21 days DL2: Ipilimumab 10 mg/kg for 4 doses every 21 days DL3: Ipilimumab 10 mg/kg for 4 doses every 21 days	1-year DFS: 74%	Grade 1–2: rash, endocrinopaties, gastrointestinal toxicity. Grade 3: 16% including lipase increased, neutropaenia and rash.

IHC: immunohistochemistry; ORR: objective response rate; PFS: progression free survival; OS: overall survival; TRAE: treatment related adverse events; DCR: disease control rate; NR: not reached; DFS: disease free survival.

KEYNOTE 158 (NCT02628067) is currently recruiting patients across different solid tumours.[48]

The use of pembrolizumab in first line treatment is under evaluation in the PAPAYA trial (NCT03144466).[49] This phase I study includes patients with FIGO stage IB to IVA cervical cancer. Intravenous pembrolizumab will be followed by radical cisplatin-based chemoradiotherapy and subsequent brachytherapy after which patients will receive additional doses of pembrolizumab. A phase II study of pembrolizumab in combination with chemoradiation and brachytherapy in women with locally advanced cervical cancer is also open for recruitment (NCT02635360).[50] These studies will help assess whether cell death from ionizing radiation and the release of tumour antigens can initiate an immunogenic response in both the irradiated tumour and, potentially, in distant metastases through the abscopal effect.[18]

Nivolumab (Bristol-Myers Squibb) is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response.[51] Checkmate 358 (NCT02488759)[52] is an ongoing phase I/II in virus-associated tumours including cervical cancer. Preliminary data of efficacy and toxicity in patients with recurrent or metastatic cervical, vaginal, and vulvar cancer (total 24 patients, 19 of whom had cervical cancer) have been reported. ORR was 20.8% and disease control rate was 70.8%. Responses were observed regardless of PD-L1 expression, HPV status, and number of prior therapies. Median PFS was 5.5 mo; median OS has not yet been reached (median follow-up 31 weeks). Nivolumab has also been studied in the NRG-GY002, a phase II study for patients with persistent or recurrent cervical cancer (NCT02257528).[53] A trial of the combination of nivolumab with HPV-16 SLP vaccine (ISA 101) in HPV-16 positive tumours is also recruiting patients (NCT02426892).[35]

Other checkpoint inhibitors are also under investigation for cervical cancer treatment. Atezolizumab (Roche) a fully humanized, engineered monoclonal antibody of IgG1 isotype PD-L1, is currently under evaluation through the Phase Ib PROLOG study (NCT02914470).[54] This study assesses the safety and tolerability of the combination of atezolizumab with carboplatin/cyclophosphamide in both advanced breast cancer and gynaecological cancer patients including cervical cancer. A phase II trial of atezolizumab in combination with Vigil™ (Gradalis) is currently recruiting patients with gynaecological malignancies, including cervical cancer (NCT03073525).[55] Atezolizumab in combination with bevacizumab is under evaluation in a phase II study with dedicated enrolment of women with metastatic, recurrent or persistent cervical

cancer (NCT02921269).[56] It is thought that anti-angiogenic therapy may potentially enhance immunotherapy efficacy due to the increase in intratumoural T-cell infiltration.[57]

Another checkpoint inhibitor, durvalumab (Medimmune/AstraZeneca), a human IgG1 kappa monoclonal antibody that blocks the interaction of PD-L1 with the PD-1 and CD80 molecules, is under evaluation in a phase I trial in combination with Tremelimumab (AstraZeneca) a fully human monoclonal antibody against CTLA-4 (NCT01975831). This trial will include patients with cervical cancer that have failed to respond to or relapsed following standard treatment.[58]

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) was the first immune-checkpoint receptor to be therapeutically targeted. It is expressed exclusively on T cells and capable of down-regulating T-cell function to prevent over-activation of the immune system.[18] Ipilimumab (Bristol-Myers Squibb), was studied in a phase I/II trial in patients with metastatic or recurrent cervical cancer.[59] Forty-two patients were enrolled; toxicities were manageable and grade 3 toxicities included diarrhoea and colitis; median PFS was 2.5 months (95% CI: 2.3–3.2). GOG 9929[60] is a phase I clinical trial investigating the role of ipilimumab after chemoradiation in patients with node positive cervical cancer. The trial included 34 patients with FIGO stage IB2/IIA or IIB/IIIB/IVA cervical cancer and positive nodes. 19 of the 34 patients were evaluable, all patients completed chemo-radiotherapy; 90% had 4 cycles of ipilimumab and the maximum tolerated dose was ipilimumab 10 mg/kg. In terms of toxicity, majority of the adverse events were grade 1–2 and 16% of the patients experienced grade 3 toxicity including lipase increased, neutropenia and rash. 1-year disease free survival (DFS) was 74%.

2.3. *Adoptive cell transfer therapy*

Adoptive transfer of tumour-antigen targeting T cells into a cancer patient, after *ex vivo* amplification, with or without genetic modification is a promising treatment strategy. However, limitations include its technological complexity, labour-intensity and high cost.

Adoptive T-cell therapy involves the *ex vivo* culture of tumour specimens and expansion of tumour infiltrating lymphocytes (TILs). T cells of a preferred antigen-specificity and phenotype can be identified *in vitro* and proliferated. These T cells are infused into autologous tumour-bearing patients after receiving lymphodepleting chemotherapy agents. The number of antigen-specific T cells in peripheral blood after this method usually exceeds by far that possible by current vaccine treatment strategies alone.[61] In addition, adoptive T cells appear more effective in inducing tumour regression than lymphocytes generated by vaccines, suggesting greater ability to overcome tumour-mediated immune evasion mechanisms.[62]

Nine women with metastatic cervical cancer were enrolled in a trial that included HPV-related tumours.[63] T-cell cultures derived from fragments of metastatic tumour and expanded using IL-2 were tested for reactivity against the HPV-16 or HPV18 E6 and E7 antigens. Patients were given a single infusion of HPV-reactive tumour-infiltrating T cells. This was preceded by lymphocyte-depleting chemotherapy and followed by aldesleukin administration. Three patients showed objective tumour response and two of these had a durable complete clinical response that lasted more than a year (15 and 22 months). Most common toxicities were haematological and related to the lymphocyte-depleting conditioning regimen. It is suggested that adoptive T-cell therapy is potentially a viable salvage therapy for metastatic cervical cancer patients who currently have limited treatment options.

Genetic modification of T cells. Chimeric antigen receptor (CAR) T-cell therapy involves the *ex vivo* amplification of autologous T cells carrying genetically engineered T cell receptors (TCRs) which are designed to recognize specific tumour antigens. While T cell receptors are restricted in binding by MHC haplotype, CAR T cells are designed to allow MHC-independent antigen recognition; these modified T cells are subsequently re-administered to cancer patients.[64] A phase I study evaluated adoptive CD4+ T-cell therapy with retroviral transduction of a T cell receptor that recognized the melanoma-associated antigen-A3 in patients with metastatic solid tumour cancers.[65] The trial included 2 cervical cancer patients, one of these patients experienced an objective complete response that in August 2017 had been ongoing for 29 months. A Phase I trial of HPV-16 E7-oncoprotein-targeting T cell receptor therapy alone or in combination with PD-1 inhibitor Pembrolizumab is currently recruiting patients with HPV-associated cancers (NCT02858310).[66]

3. Conclusion and future directions

Diverse immunotherapy strategies are currently under evaluation for the treatment of high risk/locally advanced and recurrent/metastatic cervical cancer. Evidence from phase I and II clinical trials is encouraging; nonetheless, the optimal timing for delivering immunotherapy strategies is unclear and specific predictive biomarkers are lacking.

Screening programmes, sex education and treatment of pre-malignant lesions should be prioritized, in order to avoid the development of cervical cancer. The majority of women affected by this tumour live in countries with poor health care coverage and limited access to targeted therapy. This requires careful consideration and dialogue between pharmaceutical companies, health authorities, the wider scientific community, patients and their advocates, in order to improve access to newer therapies in low- and middle-income countries. The use of vaccines for the prevention of HPV infection has not been reviewed in this article. This approach has the potential to eradicate cervical cancer.

When cervical cancer develops, our efforts should focus on strategies to avoid relapse. Checkpoint inhibitors and/or therapeutic vaccines combined with radiotherapy and chemotherapy are currently been studied in this setting. For metastatic/relapsed disease, data is encouraging, however, results from phase III randomized trials are awaited.

Strategies such as adoptive cell therapy warrant further exploration but the complexity of such treatments limit their use to specialized centres at present.

In conclusion, immunotherapy for cancer treatment is a rapidly developing field, proven to be successful in several tumours. Further randomized clinical trial results are needed.

Results so far from phase II trials are encouraging, in particular given the limited efficacy of treatments beyond the first line. The next steps include the identification of optimal immunotherapeutic strategies, timing of treatment, management of toxicities and patient selection.

Conflict of interest

None declared.

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