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Review

Emerging Biological Treatments for Uterine Cervical Carcinoma

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Abstract

Cervical cancer is the third most common cancer worldwide, and the development of new diagnosis, prognostic, and treatment strategies is a major interest for public health. Cisplatin, in combination with external beam irradiation for locally advanced disease, or as monotherapy for recurrent/metastatic disease, has been the cornerstone of treatment for more than two decades. Other investigated cytotoxic therapies include paclitaxel, ifosfamide and topotecan, as single agents or in combination, revealing unsatisfactory results. In recent years, much effort has been made towards evaluating new drugs and developing innovative therapies to treat cervical cancer. Among the most investigated molecular targets are epidermal growth factor receptor and vascular endothelial growth factor (VEGF) signaling pathways, both playing a critical role in cervical cancer development. Studies with bevacizumab or VEGF receptor tyrosine kinase have given encouraging results in terms of clinical efficacy, without adding significant toxicity. A great number of other molecular agents targeting critical pathways in cervical malignant transformation are being evaluated in preclinical and clinical trials, reporting preliminary promising data.

In the current review, we discuss novel therapeutic strategies which are being investigated for the treatment of advanced cervical cancer.

Key words: advanced cervical cancer, therapy, clinical trials, molecular targeted agents, tyrosine kinase inhibitors.

1. INTRODUCTION

Cervical cancer incidence and mortality in the developed world have declined over the past 3 decades, but it is still the fourth leading cause of death in females worldwide and the second leading cause of mortality among women aged 19-39 years [1]. Up to 35% of patients with locally advanced cervical cancer previously treated with surgery or radiation will develop persistent/recurrent/metastatic disease, where platinum-based chemotherapy still represents the gold standard treatment [2]. Although other agents, including paclitaxel, ifosfamide and topotecan, have been investigated as single agents or in combination,

responses are often unsatisfactory and of short duration, thus optimal medical treatment in such unfavourable patient subset has to be defined. The development of innovative and effective therapies in advanced and refractory cervical cancer remains a high priority, and research is needed to elucidate new targets for therapy, also based on scientific rationale of viral carcinogenesis.

Human papillomavirus (HPV) infection is considered the necessary cause of cervical cancer, as more than 96% of cervical cancers are positive for high-risk HPV viruses, especially type 16, the most predominant type identified in precancerous lesions and in cervical cancer. Other high risk HPV types, such as 18, 31, 33, 35 are, even less frequently, involved in HPV related carcinogenesis from high-grade cervical intraepithelial neoplasia (CIN) to invasive carcinoma [3]. Malignant transformation by HPV is primarily related to 3 oncoproteins: E5, E6, E7. In cervical cancer E6 and E7 genes are consistently expressed, and mediate malignant transformation through degradation of p53 and inactivation of retinoblastoma (Rb) tumor suppressor proteins, respectively [4]. After genomic virus integration, dysregulation of p53 tumor suppressor gene is mediated by E6 through 2 different mechanisms. The first one involves blocking induction of p53 following DNA damage, which normally drive to DNA repair or to cell apoptosis. The second mechanism involves E6-induced p53 ubiquitination and degradation through its association with another protein, E6-AP, a component of the ubiquitin proteolytic pathway, and induces cell proliferation by dysruptin p53 and by targeting the expression of other apoptotic proteins. E7 exerts its oncogenic effects primarily by binding with retinoblastoma protein (pRb), and with other proteins, (p107, p130), which regulate cell proliferation. The binding with pRb results in proteasomal degradation of pRb and unrestricted transcriptional activity, so maintaining epithelial cells ready to enter phase S of cycle, leading to cell cycle deregulation [5,6], and resulting genomic instability. The role of E5 is less well defined. It is considered as an oncogene cooperating with E6/E7 in the early stages of cervical carcinogenesis, while in invasive cancers E5 is expressed in tumors which contain the episomal viral genome. E5, E6 and E7 have complex interactions with many growth factor signalling pathways, angiogenesis, inflammation and apoptotic response, abrogate cell cycle checkpoints and induce genomic instability leading to malignant transformation [3,7]. After viral integration, E6/E7 becomes constitutively expressed [8], and exert their functions. The integration of HPV virus with the host genome blocks the productive life cell cycle, determines immortalization and favours acquisition of additional mutations required for malignant transformation along with escaping immune control.

In the last decades, scientific efforts on cervical cancerogenesis have mainly focused on analysing the HPV oncoproteins, and in establishing their role in the transformation process. The most relevant results, in terms of primary and secondary prevention, include developing a prophylactic vaccine and HPV-based screening tests, respectively. However, the huge cascade of biological events and biomolecular pathways following the HPV-host interaction remains largely to be analysed. The understanding of these events is highly relevant from the clinical perspective, in order to identify innovative and more targeted pharmacological treatments.

The current review outlines the existing and emerging preclinical and clinical data concerning new agents targeting the most relevant pathways involved in cervical cancer development/progression. Table 1 reports the results of the main clinical trials with biological agents in advanced cervical cancer and Table 2 shows the most relevant ongoing clinical trials.

2. ANTI-ANGIOGENETIC AGENTS

Overexpression of the vascular endothelial growth factor (VEGF) family proteins is associated with poor prognosis in many cancers, including squamous and adenocarcinomas of the cervix, and usually correlates with advanced stages and lymph node metastases [9-11]. Reports show a correlation between elevated serum VEGF levels and poor response/progression free survival (PFS) [12,13]. The mechanism involved in tumor-related neoangiogenesis in cervical cancer is driven by persistent HPV infection. p53 downregulation by HPV E6 oncoproprotein increases angiogenic potential through the induction of a series of pro-angiogenetic pathways, including up-regulation of VEGF [14]. Moreover, E6 enhances induction of hypoxia-inducibile factor-1α (HIF-1α), usually associated with poor prognosis, with increased VEGF [15]. It has been reported that E5 induces VEGF expression in cell lines, which involves EGFR phosphorylation, thus resulting in activation of MEK-extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphatidylinositol 3-kinase (PI3K)-Akt pathways [16]; these two pathways regulate VEGF expression through changes in its transcriptional activity. Cox-2-prostaglandin (PG) E2 pathway is also involved in VEGF expression by E5 [17]. Complex interactions occur among VEGF pathway and several growth factors, including epidermal growth factor receptor (EGFR) [18,19], and other pathways involving receptor tyrosine kinases (RTKs) have also been implicated in the development and progression of cervical cancer.

Table 1. Preliminary results of clinical trials of targeted agents in cervical cancer.

First author, year of publication	Pts enrolled	Phase	Target	Regimen	Clinical endopoint / ORR	Toxicity
Tewari., 2013 [23]	450	III	VEGF	Bevacizumab (15 mg/kg iv every 21 days) with or without four chemotherapy regimens	OS 17 months in bevacizumab arms versus 13 months in the chemotherapy arms	Treatment with B was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%).
Schefter, 2012 [24]	60	II	VEGF	Bevacizumab (10 mg/kg iv every 2 weeks for three cycles) in combination with definitive radiotherapy and cisplatin chemotherapy	No data	15 (31%) protocol-specified treatment-related AEs within 90 days of treatment start; the most common were hematologic (12/15; 80%). No treatment-related SAEs.
Zighelboim, 2013 [25]	27	II	VEGF	Bevacizumab (15mg/kg iv every 21days) with topotecan and cisplatin	ORR: 33.3%	Grade 3-4 hematologic toxicity was common (thrombocytopenia 82% leukopenia 74%, anemia 63%, neutropenia 56%). Most patients (78%) required unanticipated hospital admissions for supportive care and/or management of toxicities
Mackay, 2010 [26]	19	II	VEGF	Sunitinib 50 mg daily *per os*	No objective responses. Median TTP: 3.5 months.	High rate of fistula development (26%)
Goncalves, 2008[44]	30	II	EGFR	Gefitinib 500 mg daily *per os*	No objective responses, six (20%) patients experienced stable disease with a median duration of 111.5 days. Median TTP was 37 days and median OS was 107 days.	Gefitinib was well tolerated, the most common drug-related AEs were diarrhea, acne, vomiting, and nausea. No grade 4 events.
Schilder, 2009 [47]	28	II	EGFR	Erlotinib 150 mg daily *per os*	No objective responses with four (16%) achieving stable disease; only one patient had a PFS ≥ 6 months (4%).	Grade 3 related toxicities included diarrhea, nausea, emesis, dehydration and anorexia. One patient experienced grade 4 renal toxicity.
Santin, 2011 [53]	38	II	EGFR	Cetuximab 400 mg/m2 i.v. initial dose followed by 250 mg/m2 weekly	No objective responses with five patients (14.3%) survived without progression for at least 6 months. Median PFS and OS times were 1.97 and 6.7 months, respectively.	Grade 3 adverse events at least possibly related to cetuximab included dermatologic events, GI, anemia, constitutional symptoms, infection, vascular events, pain, and pulmonary, neurological, vomiting and metabolic events. No grade 4 events
Tinker, 2013 [86]	38	II	mTor	Temsirolimus (25mg i.v. weekly in 4week cycles),	One patient experienced a partial response (3.0%). 57.6% stable disease. Median PFS: 3.52months.	No toxicity grade 3/4 observed. Adverse effects were mild-moderate in most cases and similar to other temsirolimus studies.
Coronel, 2011 [100]	36	III, R	HDAC	Hydralazine and valproate (HV) added to cisplatin topotecan (hydralazine at 182 mg for rapid, or 83 mg for slow acetylators, and valproate at 30 mg/kg, beginning a week before chemotherapy and continued until disease progression)	4 PRs to CT + HV and 1 in CT + PLA. 29% and 32% stable disease, respectively. Median PFS: 6 months for CT + PLA, 10 months for CT + HV.	Low incidence of grades 3 and 4 toxicity in both arms. G2/3 thrombocytopenia, edema, drowsiness and tremor were statistically higher in CT+HV arm.
Zhou, 2013 [111]	40	II, R	Proteasome	rAd-p53 combined with chemotherapy (PCG arm) vs chemotherapy alone (CG arm)	ORR 95% in PCG arm versus 75% for the CG arm. 1-year OS: 90% and 65%, respectively.	Fever was found in 90% of PCG patients (mild to medium grade). No serious adverse events relative to rAd-p53 were observed.

ORR: Overall response rate; OS: Overall survival; TTP: Time to progression; PFS: Progression free survival; iv: intravenously; R: randomized; GI: gastrointestinal.

Table 2. Ongoing clinical trials of targeted agents in cervical cancer

Study	Estimated Enrollment	Phase	Regimen	Target	Primary endopoint
DDPDRO-002	30	I/II	Sorafenib with radiation and cisplatin	Multikinase	Determine the biologic activity of sorafenib in cervix cancer
NCT01229930	130	II	Carboplatin and paclitaxel with or without cediranib maleate	VEGF	Overall progression-free survival
NCT01065662	50	I/IB	Temsirolimus with cediranib	VEGF	Maximum tolerated dose of cediranib with temsirolimus
NCT01267253	51	II	Brivanib alaninate monotherapy	VEGF and FGFR	Progression-free survival for at least 6 months, objective tumor response, adverse events as assessed by NCI CTCAE v4.0
NCT00957411	76	II	Cisplatin and pelvic radiotherapy with or without cetuximab	EGFR	Recurrence-free survival at 2 years
NCT01158248	50	II	Panitunumab with cisplatin and radiotherapy	EGFR	Progression-free survival at 4 months and rate of skin and/or gastrointestinal toxicity CTCAE grade 4 at 4

					months
NTC0188347	42	I/II	Mapatumumab with chemoradiation	TRAIL-R1	Safety, tolerability and efficacy
NCT01281852	66	I/II	Veliparib given with paclitaxel and cisplatin	PARP	Toxicities and objective tumor response
NCT01266447	60	II	Veliparib with topotecan and filgrastim or pegfilgrastim	PARP	Objective response, overall survival time, progression-free interval
NCT01237067	72	I	Olaparib with carboplatin	PARP	Pharmacokinetics and pharmacodynamic effects of the sequence of administration of olaparib and carboplatin and the schedule-associated safety of the combination
NCT01076400	7	I/II	MK-1775 with cisplatin and topotecan	WEE1	Objective response rate and maximum tolerated dose
NCT01711515	18	I	Ipilimumab after adjuvant chemoradiation	CTLA-4	Maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of adjuvant ipilimumab

2.1 Antibodies

Bevacizumab, a humanized monoclonal antibody directed against VEGF-A, was the first clinically available antiangiogenetic agent successfully tested in many solid tumors [20], including cervical cancer. In 2006, a small retrospective trial suggested activity of bevacizumab in combination with 5-fluorouracil in pretreated cervical cancer patients [21] and, since then, several clinical trials have been carried out. The multicenter GOG 227C phase II trial, evaluating bevacizumab as single agent in recurrent squamous cervical cancer patients, showed encouraging results in response rates (11%), percentage of patients without progression at 6 months (24%), median PFS (3.4 months) and median overall survival (OS) (7.2 months), even if toxicities related to bevacizumab were reported [22]. Since results observed were not inferior to other reports with single chemotherapy agents in this setting, this justifies a phase III trial in combination with chemotherapy in advanced and recurrent cervical cancer, evaluating four chemotherapy regimens with or without bevacizumab, recruiting a total of 450 patients. Preliminary results of this trial showed an advantage in OS, with 17 months in bevacizumab arms versus 13 months in the chemotherapy arms [23]. Another trial investigated the combination of bevacizumab with radiotherapy and cisplatin in untreated locally advanced cervical carcinoma; 60 patients with stage IB-IIIB were enrolled, and preliminary results showed the feasibility of the regimen [24]. The combination of bevacizumab with topotecan and cisplatin as first-line treatment for recurrent or persistent cervical cancer was evaluated in 27 patients, with objective responses in 33.3% of the patients, a median PFS of 7.1 months and a median OS of 13.2 months, but relevant toxicity was observed, most patients requiring unanticipated hospital admission for supportive care or managing side effects [25].

2.2 Receptor tyrosine kinase (RTK) inhibitors

Novel VEGF RTK inhibitors, such as *sunitinib, sorafenib, imatinib, pazopanib*, *cediranib*, are being tested in phase I-II clinical trials in cervical cancer. A phase II trial of *sunitinib* in locally advanced or metastatic pretreated cervical cancer has recently reported no objective responses and 84% of stable disease in 19 enrolled patients, with high rate of fistula development [26]. *Sorafenib* is being tested in DDPDRO-002 trial in T1b-3b N0/1 cervical carcinoma, in combination with cisplatin and radiation. *Imatinib,* an inhibitor of ABL tyrosine that inhibits PDGFR and c-kit, has been tested as a single agent in recurrent cervical cancer expressing PDGFR-α, but no responses were observed, even though >10% of tumor cells express PDGFR- α in all patients enrolled [27]. A phase II study of *pazopanib* or *lapatinib* monotherapy compared with their combination was carried out in 228 stage IV pretreated cervical cancer patients. The combination arm was discontinued because the futility boundary was crossed for combination therapy versus lapatinib monotherapy as well as toxicity, while pazopanib as a single agent improved response rate and PFS over lapatinib, with a favourable toxicity profile [28,29]. Another VEGF receptor inhibitor, *cediranib,* is being tested in combination with carboplatin, paclitaxel or temsirolimus in phase II (NCT01229930) and phase I trials (NCT01065662) in advanced cervical cancer. Other compounds targeting angiogenesis, such as *brivanib*, an oral dual inhibitor of VEGF and the fibroblast growth factor (FGF) receptors, are currently under clinical evaluation (NCT01267253).

2.3 Angiopoietins

Angiopoietins (ANGPTs) are ligands of endothelial cell receptor TIE2, where both ANGPT1 and ANGPT2 play a role in angiogenesis in maintaining the integrity of existing vessels [30]. Based on preclinical evidence, two ANGPT traps are in early clinical development in cervical cancer, *AMG386* and *PF-4856884*.

Overall, preliminary results on antiangiogenetic agents in cervical cancer are encouraging, and many other clinical studies are ongoing, but larger phase III trials are needed to better define the role of agents targeting angiogenesis in this disease.

3. EPIDERMAL GROWTH FACTOR (EGF) RECEPTOR FAMILY INHIBITORS

The EGF family comprises four different RTKs: EGFR (HER1), ErbB-2 (HER2), ErbB3 (HER3), ErbB4 (HER4). They all possess an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic tyrosine kinase-containing domain. After endogenous ligand-binding to the extracellular domain, EGFR forms homo or heterodimers and activates the intrinsic tyrosine kinase-containing domain, and consequently a complex network of signal transduction pathways promoting proliferation, invasion and angiogenesis is activated [31]. In squamous cervical cancer EGFR is overexpressed in up to 85% of cases, usually correlating with higher stages and poor prognosis [32,33]. The HPV-16 E6 and E7 proteins stimulate EGFR expression on epithelial cells, and E5 protein increases recycling of the EGFR to cell surface and alters EGF endocytic trafficking [34]. Disruption of EGFR gene inhibits development of papilloma and carcinoma from immortalized epithelial cells in mice, thus confirming that the EGFR activation pathway is crucial for progression to cervical cancer. The expression of all four members of EGFR/HER family is being evaluated in bioptical samples of various stages of progression from normal to invasive cervical cancer in an ongoing study from our group. The preliminary results showed low or no expression of HER receptors in most normal tissues/CIN1, whereas a high expression of EGFR, combined with moderate/weak expression of the other three members of HER family have been observed in CIN2-CIN3. An increased expression of EGFR, HER2 and HER4 was reported in invasive cervical cancer, while no HER3 expression was observed, suggesting HER3 overexpression being linked to an early gene of high risk HPV [35].

EGFR modulates tumor chemosensitivity and radiosensitivity [36], while radiotherapy seems to increase its expression in tumor cells [37]. Moreover, the co-expression of EGFR and HER2 receptor in locally advanced cervical cancer patients treated with concurrent chemoradiation had a negative prognostic significance in terms of PFS and disease free survival (DFS) [38]. The EGFR expression is related to shorter DFS and a higher rate of pelvic recurrence in patients with cervical cancer treated with chemoradiation, thus confirming an increase in radio-resistance [39,40]. The relation between EGFR and cisplatin or radiotherapy response might be explained by the fact that EGFR is involved in DNA double-strand break repair, and radiation-induced EGFR activation through the PI3k/Akt pathway results in DNA break repair [41,42]. Moreover, radiation may activate EGFR even in the absence of ligand binding, causing inhibition of apoptosis and promotion of cell proliferation [43]. There is less evidence for the prognostic significance of the other receptors of the EGFR family, because HER2 is rarely expressed, and HER3 did not show any correlation with survival, while HER4 seems to be associated with good DFS in cervical cancer patients after radiation [11].

EGFR/HER family inhibitors, such as *gefitinib, erlotinib, cetuximab, lapatinib*, *trastuzumab, panitumumab*, are being evaluated in cervical cancer.

G*efitinib*, an oral EGFR tyrosine kinase (TK) inhibitor, was investigated as a single agent in a phase II trial in patients with recurrent cervical cancer, with no response rate and disease stabilization of almost 3 months in 21% of patients treated as second-third line [44]. *Erlotinib*, a small molecule that reversibly competes with ATP for binding the tyrosine kinase domain of EGFR, was investigated against HPV-infected cells. It was observed that it prevented immortalization of human cervical epithelial cells by the complete HPV-16 genome or the E6/E7 genes; this translates into apoptosis in cells expressing E6/E7, and senescence stimulation in surviving cells [34]. Since viral oncoproteins play a crucial role in early events in carcinogenesis process, thus, preventing cells immortalization through blocking EGFR function by erlotinib or other EGFR inhibitors may represent a novel strategy for chemoprevention or treatment in early stages of cervical carcinogenesis. Erlotinib showed synergistic effects with cisplatin or doxorubicin in preclinical studies [45,46], and EGFR-blocking sensitizes cells to radiation [37]. The activity of single agent erlotinib on invasive squamous cervical cancer patients was tested by GOG 227D trial, with no objective responses [47]. *Cetuximab* is a chimeric immunoglobulin G2 monoclonal antibody (MoAb) derived from the murine MoAb 225. Preclinical studies in cervical cancer showed sensitivity to cetuximab-mediated cellular cytotoxicity and tumor growth inhibition [48]. A previous small retrospective analysis of cetuximab as a single agent in cervical cancer patients reported disappointing results [49]. The preliminary results of a GOG completed trial are negative: the addition of cetuximab to cisplatin in persistent or recurrent cervical cancer patients showed to increase toxicities only [50]. A phase II trial evaluating cetuximab plus cisplatin and topotecan showed 32% of objective responses, but considerable toxicity was observed [51]. Moreover, a 14% of *KRAS* mutation was described in adenocarcinomas, while it was observed only in 1.4% of squamous cervical cancers; this suggests a possible role of KRAS mutation in EGFR-targeting agents activity in cervical carcinoma [52]. At present, no advantage in PFS and OS have been reported in other clinical experiences with ce-

tuximab, alone or in combination with standard chemotherapy [49,51,53]. A phase II trial incorporating cetuximab, cisplatin and radiation in women with locally advanced cervical cancer is currently ongoing (NCT00957411). *Lapatinib*, an oral EGFR-TK inhibitor with anti-HER2 activity, as previously reported in the antiangiogenetic paragraph, was investigated in cervical cancer patients versus *pazopanib*, another oral TK inhibitor targeting VEGFR, PDGFR, and c-kit, versus the combination of the two agents, and the results indicated superiority of pazopanib over lapatinib [28,29].

HER2 overexpression has been rarely (<20%) reported in invasive cervical cancer, and more frequently in adenocarcinoma than in squamous cell carcinoma [54]. Moreover, in contrast with breast carcinoma, the overexpression of HER2 has controversial prognostic significance [19], being associated with both poor survival and favourable results [55,56]. Due to the low expression of HER2 in invasive cervical cancer, there is little rationale for testing anti-HER2 treatments such as *trastuzumab* in patients with cervical carcinoma. *Panitumumab*, another MoAb targeting EGFR and blocking tumor growth and cells spread [57], is being tested in combination with cisplatin and radiotherapy in stages IB-III KRAS wild-type cervical cancer (NCT01158248).

4. CYCLOOXYGENASE-2 INHIBITORS

Cyclooxygenase-2 (COX-2), an enzyme converting arachidonic acid to prostaglandins (PG), is involved in inflammatory processes, and it is frequently expressed in CIN, in cervical cancer and not in normal cervical tissue. Moreover, it is usually associated with apoptosis inhibition and angiogenesis promotion [58]. E6 and E7 oncoproteins contribute to carcinogenesis through enhancing COX-2 transcription by activating EGFR-Ras MAP kinase pathway, while E5 upregulates COX-2 expression through EGFR pathway [59,60]. COX-2 pathway plays a role in radiotherapy response, with its inhibition being related to higher responses, through an inhibition of DNA damage repair after radiation, with immunostaining of COX-2 related to poor survival, and the co-expression with EGFR confirming the negative impact on prognosis [61-64].

It has been reported that in *celecoxib* (a selective Cox-2 inhibitor)-treated cervical cancer patients tumor biopsies showed a decrease in COX-2, ki-67 and CD31, as well as a decrease in microvessel density, with increased prostaglandin E2 (PGE2) expression [65]. In a phase II trial in locally advanced cervical cancer, patients treated with definitive chemoradiation in combination with celecoxib, no advantages in response rates have been observed, and unexpected cardiotoxicity and fistula formation have been reported [66]. Recently, COX-2 expression and survival of patients with locally advanced cervical cancer treated with chemoradiation and celecoxib was analysed, showing a low COX-2 expression in pre-treatment biopsies associated with worse OS [67]. Despite promising evidence of celecoxib radiosensitizer in various tumors, no significant benefits have been reported in cervical cancer, with increase in toxic effects; however, celecoxib has shown some potential as medical treatment for cervical pre-invasive disease [68].

5. SRC INHIBITORS

Src kinases are signal transducers activated by different classes of cell-surface receptors, mainly EGFR, insulin growth receptor (IGF-R), hepatocyte growth factor receptor (HGF-R), focal adhesion kinase (FAK), cytokine receptors and others, and most of invasive cervical cancers overexpress EGFR, HGF-R, IGF-R, Src and VEGF [18,69,70]. Preclinical studies report that HPV 16 oncoproteins upregulates Src family kinases via post-transcriptional mechanisms. Moreover, E7 enhances the activating phosphorylation of Src kinases expresses in keratinocytes [71], thus, the Src kinase family may be a potential target for the treatment of this cancer.

Src inhibitors have recently been approved in some malignancies [72], and preclinical studies suggest that downregulation of Src TK with Src inhibitors contributes to growth inhibition of cervical cancer cells [73-75]. On the basis of preclinical reports, Src inhibitors, such as *dasatinib*, may represent promising therapeutic agents for human cervical cancer, even if clinical trials are necessary to verify this hypothesis.

6. mTOR INHIBITORS

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that regulates cell growth and cell cycle progression integrating signals from growth factors. Aberrant activation of the mTOR pathway may occur through increased signalling from IGFR, EGFR, activating mutations or amplification of kinase genes, or by loss of function of phosphate and tensin homolog (PTEN) [76]. Evidence suggest an interaction between HPV oncoproteins and mTOR pathway [77,78].

The pathway of mTOR is activated in a wide range of malignancies, including cervical cancer. Preclinical studies evidenced PI3K overexpression in cervical cancer cell lines, and growth inhibition with a PI3K inhibitor [79]. Squamous cervical tumors have shown overexpression of phosphorylated mTOR and its downstream mediators compared to normal cervical epithelium [78]. Chromosomal gain has been

observed in cervical cancer progression, in the locus of putative PI3KCA, and an increased copy number is reported in up to 70% of cases [80,81]. E6 interacts and degrades tuberous sclerosis complex 2 (TSC2), leading to enhanced mTOR activity [82]. Moreover, overexpression of mTOR in pre-invasive and invasive squamous cell carcinoma results in the phosphorylation and activation of mTOR target 4E-BP1, which in turns leads to translational synthesis of E7 [83]. mTOR inhibition by *rapamicin* decreases cell lines proliferation and down-regulates mTOR/4EBP1 expression [84]. Recently, it has been reported that in cervical cancer patients treated with chemoradiation, PIK3CA mutations, frequently observed in squamous subtype, are associated with poor PFS and OS in FIGO stages IB/II, while this correlation was not found in more advanced stages [85]. Preliminary results of a phase II trial with *temsirolimus,* a mTOR inhibitor, in patients with locally advanced or metastatic cervical cancer showed modest activity [86]. The feasibility of combination of weekly temsirolimus and topotecan has been evaluated in advanced gynaecologic malignancies, including cervical cancer [87]. Further clinical trials with temsirolimus, alone or in combination with chemoradiation, are currently ongoing [88].

7. DEMETHYLATING AGENTS, HISTONE DEACETYLASE INHIBITORS

DNA methylation is a well-known contributor to regulating gene transcription, mostly through transcriptional silencing, and differences in promoter hypermethylation and subsequent silencing contribute to prognosis and responses to anticancer agents observed in various tumors. In cervical cancer, carcinogenesis is related to aberrant methylation of CpG island of p16, fragile histidine triad (FHIT) tumor suppressor gene, retinoic acid receptor beta, E-cadherin, death-associated protein kinase, HIC-1 gene, anaphase-promoting complex (APC) and Ras family genes [89]. Preclinical data show how hypermethylation of the CpG island located at the long control region of the HPV genome may regulate the expression of E6 and E7, and reports show downregulation of E6 gene transcription by long control region methylation in cervical cancer cells [90]. Aberrant hypermethylation of the mitotic checkpoint gene CHFR correlates with lack of sensitivity to taxanes in cervical cancer cells [91]. Other reports suggest how aberrant DNA hypermethylation of WRN gene, a gene related to DNA repair mechanisms and replication, increased sensitivity of cervical cancer cells to CPT-11[89]. Demethylating agents, such as *decitabine* or *5-aza-2′ deoxycytidine,* may determine re-expression of some tumor suppressor genes and are considered amongst the most innovative therapeutic strategies in cancer treatment, including cervical cancer [92,93].

Histone acetylase (HAT) and histone deacetylase (HDAC) regulates the transcriptional activity of many genes, and inhibition of HDACs can modulate tumor suppressor gene expression and cooperate with other therapeutic modalities. In HPV positive cells, HDAC binds to E7 preventing HDAC binding to E2F promoter, leading to upregulation of E2F and increase proliferation [94]. *Tricostatin A*, a HDAC inhibitor, can compete with E6 for p53 binding, resulting in p53 hyperacetylation and increased apoptosis, and clinical trials in combination with chemoradiation are ongoing [95,96]. *Vorinostat*, another histone deacetylase inhibitor, is under evaluation in respiratory papillomatosis, a disease related to HPV virus other than 16 and 18 [97]. *Valproic acid (VPA)* is a HDAC inhibitor tested, alone and in combination with retinoids or somatostatin receptor 2 cytotoxic conjugate agents, in preclinical studies of cervical HeLa cells [98,99]. Preliminary results of a phase III randomized trial of *hydralazine-valproate* versus placebo added to cisplatin/topotecan showed advantages in PFS for epigenetic treatment [100].

8. PROTEASOME INHIBITORS

Cervical cancer cells have shown an increased requirement for ubiquitin-dependent protein degradation and an elevated metabolic turnover rate, related to HPV E6-targeted degradation of p53 and PDZ domain-containing protein. E6 binds the E3 ubiquitin ligase E6-AP and redirects its activity towards p53 and other tumor suppressor proteins for their ubiquitin-mediated proteasomal degradation [101]. Proteasome inhibitors, by preventing ubiquitin-proteasome protein degradation, can modulate p53 degradation [102]. *MG132* increases p53 protein levels and transcriptional activity in cervical cancer cell lines, sensitizes cells to TRAIL-receptor or apoptosis, and radiosensitizes under hypoxia [103]. *Bortezomib*, a selective proteasome inhibitor, has synergy with cisplatin in cervical cancer cell lines [104] and, combined with radiation, showed feasibility in initial reports [105]. The HIV protease inhibitor and proteasome inhibitor *lopinavir* [106,107] has been shown to stabilize p53 protein and to induce apoptosis in HPV positive cell lines [108]. A recent preclinical study on cervical carcinoma cell lines confirmed sensitivity to *lopinavir,* suggesting its hypothetical role in treating pre-neoplastic HPV-related lesions [109]. Moreover, the combination of *bortezomib* and *nelfinavir*, a HIV protease inhibitor, showed efficacy in chemoresistant cervical cancer cells [110].

An alternative to proteasome inhibition in inducing p53 stabilization is increasing wild-type p53 production by recombinant adenovirus-p53(*rAd-p53*).

To evaluate efficacy and safety of *rAd-p53* combined with chemotherapy in locally advanced cervical cancer, a phase II randomized trial is currently evaluating the combination treatment versus chemotherapy only, with preliminary results showing feasibility and higher efficacy in terms of response rate and 1-yr survival in the combination arm [111]. Extrinsic apoptotic pathway can be activated by binding apoptosis-inducing death ligands, such as Fas ligand (FasL) or tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL) to cell surface receptors, with subsequent activation of apoptotic cascade [112]. Proteasome inhibition can enhance recombinant TRAIL-induced apoptosis in HPV positive cervical cells, and MoAbs against TRAIL have shown preclinical activity [113]. A clinical phase I-II trial is ongoing, evaluating mapatumumab with chemoradiation in locally advanced cervical cancer (NTC01088347).

9. PARP INHIBITORS

PARP (Poly ADP-ribose) polymerase -1 and 2 is a family of 17 enzymes, where only PARP1 and PARP2 are known to be involved in the double-strand break DNA repair by homologous recombination (HR) system [114]. PARP inhibitors might potentiate the cell-killing ability of cisplatin and heterogeneous results are described in cervical cell lines (HeLa) [115]. A relevant synergy effect is described with other DNA-damaging agents and with ionizing radiation. In cervical cancer cell lines treated with radiation or topotecan, this synergy was confirmed, supporting enhanced radio-chemotherapy toxicity in cancers proficient in DNA double-strand repair when PARP is inhibited by *veliparib,* an oral PARP inhibitor [116]. Synergy may in part be explained by the PARP inhibitor induction of apoptosis in cervical cancer cells [117]. Moreover, in cervical cancer, the 11p15 chromosomal region where BRCA and Fanconi anemia complementation group F (FANCF) is mapped, shows frequent loss of heterozygosity, and FANCF is commonly inactivated by epigenetic alteration, leading to other genes inactivation, i.e. BRCA1-2, with chromosomal hypersensitivity to DNA-damaging agents [118]. Two clinical phase I-II trials are now ongoing in the USA (NCT 01281852; NCT01266447), evaluating *veliparib*, in combination with paclitaxel and cisplatin or topotecan, in patients with advanced, persistent or recurrent cervical cancer. Moreover, a phase I ongoing trial is evaluating *olaparib* in combination with carboplatin/paclitaxel in advanced cervical cancer (NCT01237067).

10. WEE1 AND CELL CYCLE CONTROL

Entry into mitosis is regulated by the cyclin-dependent kinase-1 (CDK1)/cyclin B complex, whose activity is balanced by inactivating phosphorylation by the protein kinase WEE1 and myelin transcription factor 1 (MYT1), and by activating dephosphorylation by CDC25. WEE1 gene is overexpressed in cervical cancer cells, and may be silenced by siRNA, and this, in combination with adriamycin, results in apoptosis. Moreover, given that p53 is a key regulator in the G(1) checkpoint, p53-deficient tumors, such as cervical cancer, rely only on the check G(2) checkpoint after DNA damage, and WEE1 inhibition selectively sensitized these tumors to DNA damaging agents. The combination of *MK1775,* a WEE1 inhibitor, with carboplatin in cervical HeLa-luc xenografts, resulted in tumor growth inhibition [119]. Recently, a number of small molecules WEE1 inhibitors were evaluated in early clinical trials, as single agents, or in combination with chemotherapy, including *MK-1775*, which is being tested in combination with cisplatin and topotecan in advanced cervical cancer (NCT01076400).

11. ANTIOXIDANTS

Oxidative stress represents an interesting promoting factor in HPV related carcinogenesis, and it is known to perturb cellular redox status leading to gene expression response alteration through activation of redox sensitive transcription factors, thus affecting cell growth and death. During cervical carcinogenesis an increase in oxidative DNA damage has been reported, as shown by the progressive increase in levels of 8-OHdG from normal tissue to CIN and to invasive cervical cancer [120]. Among antioxidant agents, *polyphenols* demonstrated to inhibit the proliferation of HPV-immortalized and HPV-positive cancer cells, and have been found to be promising drugs for cervical cancer. They display many other biological functions, including induction of apoptosis, growth arrest, DNA synthesis inhibition, and modulation of other signal transduction pathways. *Polyphenol* activity as cisplatin chemosensitivity enhancement is also described in cervical cancer cells through apoptosis induction [121]. Ongoing clinical trials show encouraging preliminary data [122].

12. NOTCH SIGNALLING

The Notch gene family encodes heterodimeric type I transmembrane receptors, which is involved in cell-cell communication, playing a role in proliferation, differentiation, and apoptosis. Notch receptors and ligands are aberrantly expressed in cancers, including cervical cancer, acting as either a tumor suppressor or as an oncogene [123]. Notch signalling pathway is a key determinant in keratinocyte differentiation and growth cycle arrest, and has a tumor suppressor function in the skin, so there is a link with

the HPV life cycle. In particular, cutaneous beta-HPV E6 protein inhibits Notch signalling [124]. Notch signalling may have different role during cervical cancer cancerogenesis, Notch 1 being upregulated in the early stages and reduced in the late stages of cervical cancer. It has recently been reported that Notch 1-induced tumor suppression may be related to somatostatin (SST) signalling. It also reported an activation of somatostatin receptor (SSTR), enhancing SSTR-mediated target therapy. *VPA*, previously described as a hystone deacetylase inhibitor, suppresses cell growth and upregulates the expression of Notch 1 and SSTR2, acting also as an activator of Notch and SST signalling, consequently having an additive effect in suppression combining VPA and the SSTR2-targeting cytotoxic conjugate in cervical cancer HeLa cells [123], thus suggesting other relevant molecular targets in cervical cancerogenesis.

13. MICRO RNAs (miRNA) and RNA INTERFERING (siRNAs)

MicroRNAs (*miRNA*) are a new family of small endogenous RNAs with diverse sequences, implicated in post-transcriptional regulatory mechanisms for silencing sequence-specific genes. *miRNAs* act on mRNA by arresting the translation or by inducing the cleavage of target mRNA [125], and regulating individual components of multiple oncogenic pathways. Downregulation of miRNA may be associated with worse prognosis in cervical cancer, and may be considered a potential therapeutic target and prognostic marker. Short interfering RNA (*siRNAs)* are non-coding RNAs 21-25 nucleotides in length that mimic endogenous miRNA which can effectively inhibit the translation of target mRNA by binding to their 3'-UTR. *siRNA*, antisense oligodeoxynucleotides or ribozymes specific for E6 and E7, have shown preclinical activity in cervical cancer cells or animal models through transcriptional genes silencing, restoring normal p53 and Rb functions leading to cells apoptosis [8,126]. In preclinical studies therapeutic *siRNAs* targeting E6/E7, alone and in combination with chemoradiation or chemotherapy, significantly inhibit tumor growth [127,130]. A better selection of cloning vectors, molecular transport vehicles, dosing and schedule of *siRNAs* are still under evaluation, as well the optimal combination with chemotherapy, radiation or immunotherapy in cervical cancer.

14. ANTIVIRAL AGENTS

In the early phases of viral cancerogenesis several different antiviral approaches have been considered, mainly acting through the inhibition of the oncoprotein E6 and E7 directly or by interfering with their related functions [131-134]. *Lopinavir*, an antiviral agent employed in HIV disease, interacts with p53, and has shown activity in cervical cancer cell lines [109], suggesting possible clinical use. Another approach was based on a close and complex interaction between E1 viral protein and the cellular protein p80, which leads to HPV DNA replication [135], thus suggesting a hypothetical therapeutic role of peptides inhibiting E1-p80 binding. Indeed, an *E1-derived N40-inhibitory peptide* is known to be able to lock HPV DNA replication in vitro. Other small molecular compounds have been found by inhibiting E1/E2, and some of them act at low molecular concentration, suggesting a possible clinical utilization in the near future. Finally, *cydofovir,* an acyclic nucleoside phosphonate with broad spectrum anti-viral activity, has been topically employed in CIN2/CIN3 lesions in a randomized trial, with favourable results [136].

15. MISCELLANEOUS

A number of other molecular pathways are involved in cervical cancer cancerogenesis, where preclinical studies suggest they may be potential therapeutic targets. Among them, aberrant activation of *Wingless-type (Wnt)/beta-catenin* signalling, increased expression of *NFBD1/MDC1 protein*, increased expression of *Hedgehog signalling*, or *HIF-1A* signalling [118,137], and preclinical studies are currently ongoing. Preliminary results of *immunological treatments* and of *therapeutic vaccines* are promising, but they are still in the early phases of development focusing mainly on pre-neoplastic cervical lesions.

16. CONCLUSIONS

There is an urgent need for more effective treatments in recurrent/advanced cervical cancer and many molecularly targeted agents have recently been evaluated in clinical trials. At present, the main focus of interest is tumor angiogenesis, with many antiangiogenetic agents being tested in randomized trials, and bevacizumab achieving promising results [23]. Beside angiogenesis, other molecular pathways have been explored, and many other agents targeting various biological pathways are still under evaluation, most of them still in the early phases of development. Moereover, there is also a clinical need for preneoplastic lesions. The biological and clinical behaviour underlying CIN2-CIN3 is still uncertain, since only an unpredictable part of them will progress to invasive cancer when untreated. Thus, a therapeutic strategy capable of interrupting the progression to malignancy for this wide subset of patients remains a significant challenge. Innovative technologies, such as whole genome sequencing, will further provide the individual with a tumor genetic profile, facilitating the selection of a more personalized therapeutic program.

However, it is absolutely necessary to improve our understanding on the key points involved in the malignant transformation and progression of cervical cancer. Translational studies are currently focusing on these issues, trying to better elucidate the mechanisms involved in this complex cancerogenesis and aiming to identify valid prognostic and predictive biomarkers in selecting more personalized treatments.

Abbreviations

VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor; HPV: Human papillomavirus; CIN: cervical intraepithelial neoplasia; PFS: progression free survival; HIF-1α: hypoxia-inducibile factor-1α; PI3K: phosphatidylinositol 3-kinase; ERK1/2: MEK-extracellular signal-regulated kinase 1/2; PG: prostaglandin; RTK: receptor tyrosine kinase; FGF: fibroblast growth factor; DFS: disease free survival; TK: tyrosine kinase; MoAb: monoclonal antibody; COX-2: Cyclooxygenase-2; OS: overall survival; IGF-R: insulin growth receptor; HGF-R: hepatocyte growth factor receptor; FAK: focal adhesion kinase; mTOR: mammalian target of rapamycin; PTEN: phosphate and tensin homolog; TSC2: tuberous sclerosis complex 2; HAT: Histone acetylase; HDAC: histone deacetylase; *rAd-p53:* recombinant adenovirus-p53; FasL: Fas ligand; TNF: tumor necrosis factor; TRAIL: TNF-related apoptosis inducing ligand; PARP: Poly ADP-ribose polymerase; HeLa: cervical cell lines; HR: homologous recombination; FANCF: Fanconi anemia complementation group F; CDK1: cyclin-dependent kinase-1; MYT1: myelin transcription factor 1; SST: somatostatin; SSTR: somatostatin receptor; *miRNA*: microRNAs; *siRNAs*: short interfering RNA.

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Authors' contributions

The outline was conceived by PV. All authors contributed to initial drafts, edited version, and the final version. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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