Drug repurposing as a potential source of innovative therapies in cervical cancer

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ABSTRACT

Objective Drug repurposing is an alternative development pathway that utilizes the properties of drugs approved for other diseases and builds on available safety and pharmacological data to develop the drug as a potential treatment for other diseases. A literature-based approach was performed to identify drug repurposing opportunities in cervical cancer to inform future research and trials.

Methods We queried PubMed for each drug included in two databases (ReDO_DB and CDcervix_DB, which include 300+ non-cancer drugs and 200+ cancer drugs not used in cervical cancer, respectively) and manually assessed all abstracts for relevance and activity in cervix cancer, and type of evidence. Subsequently, we also performed a search of clinical trial databases where we generated a list of registered trials in cervical cancer with all drugs from our databases.

Results Of the 534 drugs from both databases, 174 (33%) had at least one relevant abstract or registered trial in cervical cancer. 94 (18%) drugs had at least human data available, and 52 (10%) drugs were evaluated in registered trials. To prioritize drugs to consider for future trials, all 174 drugs were further assessed for strength of scientific rationale, feasibility for integration in cervical cancer standard of care, evidence of radiosensitization, and potential mechanism of action. Out of the 174 drugs, 38 (22%) potential drug candidates were selected.

Conclusion This study resulted in a list of candidate drugs for potential evaluation in cervical cancer. Many drugs might warrant additional (pre)clinical investigation, which could be done in a coordinated manner using platform trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There has been previous publication regarding repurposing drugs in cervical cancer but focusing on only radiosensitizing agents.

WHAT THIS STUDY ADDS

⇒ This comprehensive literature search resulted in a list of 38 potential drug candidates that warrant further investigation. This study highlights the basic characteristics of these drug candidates, summarizes relevant data on cervical cancer, and lists the registered cervical cancer trials and main results of human data.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a list of potential drug candidates that may be consulted to assist drug development, and potentially expand treatment options for cervical cancer patients.

INTRODUCTION

Cervical cancer is the fourth most common cancer in terms of incidence and mortality in women worldwide.[1] In countries with inadequate screening programs, it remains a significant cause of morbidity and mortality. In the treatment of patients with locally advanced cervical cancer, there has been little improvement in systemic therapy since the implementation of cisplatin as a radiosensitizer.[2] Neoadjuvant chemotherapy followed by radical surgery does not improve disease-free survival or overall survival compared with platinum-based chemoradiation.[3 4] Adjuvant chemotherapy combinations have not yielded any survival benefit either and have led to more severe side-effects than chemoradiation alone.[5] This lack of benefit of adjuvant chemotherapy was recently confirmed by the results of the international OUTBACK trial.[6]

For patients with metastatic cervical cancer, the addition of bevacizumab to standard palliative chemotherapy resulted in a modest overall survival benefit in selected patients.[7] More recently, adding pembrolizumab to chemotherapy and bevacizumab led to improvements in progression-free survival and overall survival in patients with recurrent, persistent, or metastatic cervical cancer.[8] In second-line treatment of metastatic cervical cancer, cemiplimab improved overall survival by a median of 3.5 months.[9] Earlier phase studies have shown promising clinical activity with anti-PD-1 combined with anti-CTLA4 antibody or with the antibody-drug conjugate tisotumab vedotin.[10 11] However, expensive targeted agents remain inaccessible to a vast majority of patients worldwide.[7 8] Therefore broadening research in cervical cancer and exploring new and other opportunities are essential.

Drug repurposing is an alternative development pathway that utilizes the properties of drugs approved for other diseases and builds on available safety and pharmacological data to develop new potential treatment options for a specific indication.[12] Classical

examples in oncology are thalidomide for multiple myeloma, imatinib for gastrointestinal stromal tumors, and zoledronic acid for bone metastases.[13] The Repurposing Drugs in Oncology (ReDO) project has used a literature-based approach to identify licensed non-cancer drugs with published evidence of anticancer activity. In this project a database of candidate drugs with at least one peer-reviewed publication showing relevant anticancer activity has been curated. This database, termed **ReDO_DB**, has been made available online.[14] Another comprehensive list of approved anticancer drugs, termed **CancerDrugs_DB**, has been generated as well.[15] Here, we sought to identify drug repurposing opportunities in cervical cancer by screening the literature and clinical trial databases in a systematic manner using the two aforementioned databases and used this to inform future research and trials.

METHODS

A literature-based approach was undertaken to identify which drugs from ReDO_DB or CancerDrugs_DB have been reported to be active in cervical cancer. ReDO_DB is a database of non-cancer drugs available for commercial purposes for which at least one article reported a possible effect on cancer, irrespective of the cancer type. ReDO_DB included 317 drugs at the time this work was performed. CancerDrugs_DB is a list of drugs approved in the treatment of one or more malignancies by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or national regulatory agencies. Since CancerDrugs_DB already contained drugs used and approved in cervical cancer, CDcervix_DB was created, which is a subset of the CancerDrugs_DB of 217 drugs after all drugs mentioned in the cervix cancer National Comprehensive Cancer Network guidelines and assimilated drugs were subtracted from CancerDrugs_DB. A list of all queried drugs included in both databases are available in the Online supplemental table S1.

The specific methodology to interrogate PubMed and the clinical trials databases (clinicaltrials.gov and World Health Organization-International Clinical Trials Registry Platform (WHO-ICTRP)) has been published.[16] In brief, a dataset of abstracts and other publication metadata from PubMed was generated by conjugating any drug name and synonym(s) from REDO_DB or from CDcervix_DB with 'uterine cervical neoplasms' (Mesh) as search terms to generate the PubMed query. This query was completed on January 5, 2022. The PubMed queries were electronically submitted to the Entrez system, and the results downloaded and merged into a single dataset for off-line processing.

Each abstract was manually assessed by one of the co-authors (RC or GB) as to whether it was relevant to cervical cancer. In case of doubt by one of the assessors, the relevance of the abstract was discussed between the two assessors and a consensus was reached. Abstracts were deemed relevant if any activity against cervical cancer was shown (cytotoxic activity in cervical cancer cell line or tumor growth inhibition in cervical cancer animal models or human data reporting clinical results in cervical cancer patients). In case the abstracts were deemed relevant, the type of evidence (*in vitro*, *in vivo*, case reports, observational studies, clinical trials, or review) was indicated.

Subsequently, a search of clinical trials databases (clinicaltrials.gov and WHO-ICTRP) was performed and a list of registered cervical cancer trials was generated by combining the search term 'cervical cancer' and any drugs from the ReDO_DB and CDcervix_DB. This search was completed on January 5, 2022. All trials were also assessed for their relevance, and any publications linked to relevant trials were searched and assessed using the same method as for abstract assessment.

To prioritize drugs to consider for future trials, relevant trials and abstracts and the corresponding published research were further assessed for each drug, independently by at least two of the authors (RC, SP, IB, PP and GB), with the instruction to tag drugs that should be excluded because of weak or limited evidence of efficacy (drugs with only *in vitro* results on a single cell line, drugs with negative or contradictory results), or non-supportive results in reported trials (results not justifying further investigation according to the assessors). Discrepant results were discussed until a consensus was reached. For each drug from the final selection, the type of evidence (*in vitro* results and/or *in vivo* results and/or human publications and/or registered trials) and the amount of data per relevant drug were summarized.

In accordance with the journal's guidelines, the authors will provide our data for independent analysis by a selected team by the editorial team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

Of the 534 drugs queried, 174 had at least one relevant abstract or registered trial in cervical cancer, 90 and 84 drugs from ReDO_DB and CDcervix_DB, respectively. Ninety-four drugs had at least human data available, with 52 drugs being or have been evaluated in registered trials. Only 41 drugs from the queried list had at most *in vitro* data. The results are summarized in Table 1. Of the 174 drugs with at least one relevant abstract or trial, 136 drugs were excluded during the prioritization step because of weak or limited evidence of efficacy or non-supportive results in prior trials.

Table 1 Summary results of queries

Number of drugs	REDO	CDcervix	Total
Queried	317	217	534
With at least one relevant abstract or trial in cervical cancer	90 (28%)	84 (39%)	174 (33%)
With human data	36 (11%)	58 (27%)	94 (18%)
With registered trials	14 (4%)	38 (18%)	52 (10%)
With no human data	54 (17%)	26 (12%)	80 (15%)
In vitro only	32 (10%)	9 (4%)	41 (8%)

Table 2 Type of evidence and number of occurrence per selected drug repurposing candidate

Drug	*In vitro* results	*In vivo* results	Human results	Registered trials in databases
Arsenic trioxide	23	7	0	2
Artesunate	5	4	0	0
Atovaquone	1	1	0	0
Bortezomib	11	4	0	2
Cetuximab	7	2	8	8
Chlorpromazine	3	0	1	0
Cidofovir	6	6	3	2
Decitabine	21	0	2	0
Deferoxamine	2	2	0	0
Doxycycline	4	3	0	1
Erlotinib	4	1	4	2
Everolimus	3	0	1	2
Fulvestrant	3	1	0	1
Gefitinib	4	0	4	2
Hydralazine	7	1	3	3
Interferon α-2b	9	2	18	1
Ipilimumab	0	0	2	6
Lovastatin	3	0	1	0
Lurbinectedin	2	2	0	0
Melatonin	5	2	0	0
Metformin	20	6	4	3
Mifepristone	9	2	0	0
Nelfinavir	6	3	0	3
Niclosamide	1	0	0	0
Nicotinamide	1	1	1	0
Niraparib	0	0	0	4
Olaparib	4	2	0	6
Pazopanib	0	0	1	3
Plerixafor	4	3	0	0
Porfimer	2	0	1	0
Ribavirin	2	2	0	0
Ribociclib	2	1	0	0
Rucaparib	2	1	0	3
Ruxolitinib	1	1	0	0
Sacituzumab govitecan	1	1	0	0
Sonidegib	1	1	0	0
Valproic acid	11	7	3	4
Zoledronic acid	4	2	0	1

The type and amount of data are summarized in Table 2 for the 38 drugs (22%) deemed to be potential repurposing candidates. For the drugs not selected, the data are available as Online supplemental table S2.

For the 38 potential repurposing candidates, the scientific rationale and feasibility for integration in cervical cancer standard of care were reviewed. Table 3 presents basic characteristics of each drug (patent status and main approved indications) and summarizes relevant data on cervical cancer (the potential mechanism of action, available biomarker, possible role (radiosensitizer and/or immunomodulator)) based on the data found in the relevant publications for each drug. It also lists the registered cervical cancer trials and main results of human data currently available. In addition, it outlines the potential setting in which these drug candidates can be repurposed based on the data found in the publications and the combined general knowledge of the authors.

Table 3 List of potential drug candidates in cervical cancer

Drug characteristics			Relevant data on cervical cancer					Potential setting in cervical cancer
Drug	**Main approved indications**	**Off-patent**	**Mechanism of action(s) in cervical cancer**	**Candidate biomarker(s)**	**Registered cervical cancer trials and main results of human data**	**Role(s)***		▶ **First line, with chemoradiotherapy** ▶ **First line, adjuvant** ▶ **First line, maintenance** ▶ **Recurrent/metastatic**
						Radio-sensitizer	**Immune-modulator**	
Arsenic trioxide	Acute promyelocytic leukemia	Yes	Prevention of migration through CXCR4 inhibition, direct cytotoxicity, radiosensitization	No prominent biomarker identified	NCT00005999: completed trial with single agent in recurrent setting. No results available. ChiCTR1900023822: ongoing trial as neoadjuvant treatment with carboplatin. No results available	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Artesunate	Malaria	Yes	Direct cytotoxicity, radiosensitization, enhancement of TRAIL-induced cell death, inhibition of HOTAIR expression	No prominent biomarker identified	None	Yes	No	▶ First line, with chemoradiotherapy
Atovaquone	Toxoplasmosis, *Pneumocystis carinii* pneumonia	Yes	Inhibition of mitochondrial respiratory chain complex III	Hypoxia biomarker(s)	None	No	No	▶ Recurrent/metastatic
Bortezomib	Multiple myeloma, mantle cell lymphoma	Yes	Inhibition of NF-κB, proteasomal activity and hypoxia-related HIF-1α expression, enhancement of the apoptosis-inducing TRAIL receptor antibody efficacy and induction of apoptosis	No prominent biomarker identified	NCT00106262: terminated trial because of lack of accrual. NCT00329589: completed trial in combination with chemoradiotherapy. No results available	Yes	Yes	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Cetuximab	Squamous cell head and neck cancer, colorectal cancer	Yes	Inhibition of EGFR, radiosensitization	EGFR protein expression	NCT00957411, NCT00101192, NCT00499031, NCT00104910, NCT00518193, NCT00997009: 6 completed or terminated trials with results available, although always showing limited or no benefit. 2006-003759-19 and NCT00292955: trials with unknown status or prematurely terminated without any results available	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Chlorpromazine	Psychotic disorders, nausea and vomiting, anxiety, hiccups	Yes	Radiosensitization	No prominent biomarker identified	No registered trial, but publication of human data showing a 53% complete response in combination with radiotherapy compared with 39% complete response with radiotherapy alone[29]	Yes	No	▶ First line, with chemoradiotherapy
Cidofovir	CMV-retinitis in AIDS	Yes	Decrease E6 and E7 expression, DNA damage by incorporation into DNA, radiosensitization	No prominent biomarker identified	NCT02515877 and NCT00811408: Prematurely discontinued trials showing a complete response in 8 out of 9 patients with 2 year and 4 year overall survival rates estimated at 93% and 84%, respectively, and 2 year progression-free survival is 76%	Yes	No	▶ First line, with chemoradiotherapy

Continued

Table 3 Continued

Drug characteristics			Relevant data on cervical cancer					Potential setting in cervical cancer
Decitabine	Acute myeloid leukemia	Yes	Inhibition of the nucleic acid synthesis	No prominent biomarker identified	No registered trial, but publication of phase II study in recurrent and/or metastatic patients showing an 8/21 partial response and 5/21 stable disease in combination with cisplatin. Median progression-free interval is 16 weeks and median survival is 19 weeks[30]	No	No	► Recurrent/metastatic
Deferoxamine	Acute iron intoxication, chronic iron overload	Yes	Increase hCtr1 and TfR1 expression through upregulation of Sp1 and induce TfR1 expression through the Sp1–NF-κB p65-dependent pathway, platinum sensitization	No prominent biomarker identified	None	No	No	► First line, with chemoradiotherapy ► Recurrent/metastatic
Doxycycline	Respiratory, urinary tract and ophthalmic infection	Yes	Direct cytotoxic, inhibition of MMP2 and MMP9 expression, induction of apoptosis and inhibition of EMT and migration	No prominent biomarker identified	NCT02874430: ongoing phase II trial. No results available	No	No	► First line, with chemoradiotherapy ► Recurrent/metastatic
Erlotinib	Non-small cell lung cancer, pancreatic cancer	Yes	Inhibition of EGFR	EGFR protein expression	NCT00031993: completed trial showing a 94% complete response in combination with chemoradiotherapy. The 2 year and 3 year cumulative overall- and progression-free survival rates were 92% and 81%, and 80% and 74%, respectively. As single agent erlotinib seems to be inactive. NCT00428194: withdrawn trial because of lack of accrual	No	No	► First line, with chemoradiotherapy ► Recurrent/metastatic
Everolimus	Neuroendocrine tumors, renal cell carcinoma, HR+ breast cancer	Yes	Radiosensitization, induction of apoptosis by targeting PI3K/AKT/mTOR pathways, inhibition of proliferation by inactivation of the HPV E7 oncoprotein	Alterations in the PI3k/AKT/mTOR pathway	NCT00428194: completed trial determining 5 mg/day as maximum tolerated dose of everolimus in combination with cisplatin and radiotherapy in locally advanced patients. NCT00967928: withdrawn trial because of lack of enrollment	Yes	No	► First line, with chemoradiotherapy
Fulvestrant	HR+ breast cancer	Yes	Inhibition of aromatase	ER-α expression in stromal cells	NCT04579380: ongoing phase II trial. No results available	No	No	► First line, with chemoradiotherapy ► Recurrent/metastatic
Gefitinib	Non-small cell lung cancer	Yes	Inhibition of EGFR	EGFR protein expression	No results available for the registered trials (CTRI/2017/12/010726 and NCT00049556), but publication of human data resulting in a median disease-free interval of 15 months in advanced or metastatic patients after recurrence. The median progression-free survival and median overall survival were 4 months and 5 months, respectively.[31] Neoadjuvant chemotherapy, chemoradiation, followed by gefitinib maintenance in patients with locally advanced cervical cancer showed a 3 year overall survival of 70%, and 3 year progression-free survival of 51%[32]	No	No	► First line, maintenance ► Recurrent/metastatic

Continued

Table 3 Continued

Drug characteristics			Relevant data on cervical cancer					Potential setting in cervical cancer
Hydralazine and valproate	Hypertension (hydralazine), epilepsy and bipolar disorder (valproate)	Yes	Inhibition of HDAC and DNA methyltransferase, unmasking of chronic viral infection (valproate)	No prominent biomarker identified	NCT00532818 and NCT00404326: 2 completed trials on the combination showing improved progression-free survival in combination with topotecan/ cisplatin over topotecan/cisplatin alone, also safety data with chemoradiotherapy	Yes	Yes	▶ First line, with chemoradiotherapy ▶ First line, adjuvant ▶ Recurrent/metastatic
Interferon α-2b	Hairy cell leukemia, chronic hepatitis B and C	No	Immunomodulation	No prominent biomarker identified	NCT00138151: terminated trial showing that IFN α-2b in combination with paclitaxel and 13-cis retinoic acid is safe. Mixed results in other trials and limited role with radiotherapy, though results of one trial support testing IFN α-2b given before radiotherapy	Yes	Yes	▶ First line, with chemoradiotherapy
Ipilimumab	Melanoma, renal cell carcinoma, non-small cell lung cancer	No	Inhibition of CTLA4 on T-cells	No prominent biomarker identified	NCT01711515: completed trial showing safety and preliminary efficacy as adjuvant therapy after chemoradiotherapy. NCT01693783 (phase II), NCT04256213, NCT03508570 (phase I), NCT03755739 (phase II-III), NCT03452332 (phase I): 5 trials ongoing. No results available	No	Yes	▶ First line, adjuvant ▶ Recurrent/metastatic
Lovastatin	Hypercholesterolemia, coronary heart disease	Yes	Inhibition of the mevalonate pathway	HMG-CoA reductase expression	No registered trial, but publication of human data defining recommended phase II dose and showing disease stabilization in 3/12 recurrent or metastatic cervical cancer patients[33]	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Lurbinectedin	Squamous cell lung cancer	No	DNA alkylation, elimination of cancer stem cells, inhibition of myeloid-derived suppressor cells	No prominent biomarker identified	None	No	Yes	▶ First line, adjuvant ▶ Recurrent/metastatic
Melatonin	Primary insomnia	Yes	Production of reactive oxygen species in cancer cells (pro-oxidant)	No prominent biomarker identified	None	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Metformin	Diabetes type 2	Yes	Inhibition of mitochondrial respiratory complex I leading to decreased tumor hypoxia and to radiosensitization	Hypoxia biomarker(s)	NCT02874430, NCT04275713 and NCT02394652: 3 phase II trials ongoing. No results available.	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Mifepristone	Abortion, Cushing syndrome	Yes	Enhancement of chemoradiotherapy, prevention of cell migration	No prominent biomarker identified	None	Yes	No	▶ First line, with chemoradiotherapy ▶ First line, adjuvant
Nelfinavir	HIV	Yes	Inhibition of PI3K-Akt and induction of endoplasmic reticulum stress	No prominent biomarker identified	NCT03256916: ongoing phase III trial. No results available. NCT01485731 and NCT02363829: completed trials showing safety and tolerability of 1250 mg twice daily added to cisplatin-based chemoradiotherapy in patients with locally advanced cervical cancer	Yes	No	▶ First line, with chemoradiotherapy
Niclosamide	Tapeworm infections	Yes	Inhibition of mitochondrial respiratory complex I and mTOR	No prominent biomarker identified	None	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic

Continued

Table 3 Continued

Drug characteristics			Relevant data on cervical cancer					Potential setting in cervical cancer
Nicotinamide	Pellagra	Yes	Multiple, including radiosensitization (with carbogen in particular) through ROS generation and decreased hypoxia	Hypoxia biomarker(s)	No registered trial, but publication of human data showing safety with chemoradiotherapy and carbogen[34]	Yes	Yes	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Niraparib	Ovarian cancer	No	Inhibition of PARP, radiosensitization and platinum sensitization	No prominent biomarker identified	NCT04395612, NCT04068753, NCT03644342 and EudraCT2019-001226-10: 4 ongoing phase II trials. No results available	Yes	No	▶ First line, with chemoradiotherapy ▶ First line, adjuvant ▶ Maintenance
Olaparib	Ovarian cancer	No	Inhibition of PARP, radiosensitization and platinum sensitization	Poly-ADP-ribosylation level	NCT04641728, NCT04487587, NCT04483544, NCT03162627, jRCT2031210096 and NCT01237067: 4 ongoing phase II, 1 ongoing phase I, and 1 completed trials. No results available	Yes	No	▶ First line, with chemoradiotherapy ▶ First line, adjuvant ▶ First line, maintenance
Pazopanib	Renal cell carcinoma, soft tissue sarcoma	No	Inhibition of VEGF and PDGF receptors (anti-angiogenesis)	No prominent biomarker identified	NCT00430781 and NCT00561795: 2 completed trials showing an overall response rate of 9% as single agent and increased progression-free survival and overall survival compared with lapatinib. NCT02348398: withdrawn trial. No results available	No	No	▶ First line, adjuvant ▶ Recurrent/metastatic
Plerixafor	Mobilization of hematopoietic stem cells	No	Prevention of chemoradiotherapy-induced CXCL12/CXCR4 signaling resulting in intratumoral accumulation of myeloid cells	No prominent biomarker identified	None	Yes	Yes	▶ First line, with chemoradiotherapy
Porfimer	Esophageal cancer	Yes	Radiosensitization by enhanced production of reactive oxygen species	No prominent biomarker identified	No registered trial, but case report showing a complete response[35]	Yes	No	▶ Recurrent/metastatic
Ribavirin	Hepatitis C	Yes	Inhibition of eIF4E to overcome chemotherapy resistance	Eukaryotic translation initiation factor 4E expression	None	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Ribociclib	Breast cancer	No	Inhibition of cyclin-dependent kinase 4 and 6	No prominent biomarker identified	None	No	No	▶ Recurrent/metastatic
Rucaparib	Ovarian cancer	No	Inhibition of PARP, radiosensitization and platinum sensitization	No prominent biomarker identified	NCT03476798, NCT04171700 and NCT03795272: 2 ongoing phase II trials and one withdrawn trial. No results available	Yes	No	▶ First line, with chemoradiotherapy ▶ First line, adjuvant ▶ First line, maintenance
Ruxolitinib	Myeloproliferative neoplasms	No	Restoration of CADM1, radiosensitization	Loss of CADM1 expression	None	Yes	No	▶ First line, with chemoradiotherapy ▶ Recurrent/metastatic
Sacituzumab govitecan	Recurrent triple negative breast cancer	No	Inhibition of DNA topoisomerase I following cell internalization after binding to Trop-2, antibody-dependent cellular cytotoxicity	Trop-2 expression	None	No	No	▶ Recurrent/metastatic

Continued

Table 3 Continued

Drug characteristics			Relevant data on cervical cancer				Potential setting in cervical cancer
Sonidegib	Basal cell carcinoma	No	Inhibition of hedgehog pathway activation, radiosensitization	Hedgehog pathway activation	None	Yes	No	▲ First line, with chemoradiotherapy ▲ First line, adjuvant
Zoledronic acid	Osteoporosis, skeletal related events	Yes	Direct cytotoxicity, inhibition of MMP-9 (indirect anti-angiogenesis)	No prominent biomarker identified	NCT00966992: terminated trial. No results available	Yes	No	▲ First line, with chemoradiotherapy ▲ Recurrent/metastatic

*'No' means there is either no evidence it can play a role or there is evidence it does not play a role.
AKT, protein kinase B; CADM1, cell adhesion molecule 1; CMV, cytomegalovirus; CTL4, cytotoxic T-lymphocyte antigen-4; CXCL12, C-X-C chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; EGFR, epidermal growth factor receptor; eIF4E, eukaryotic translation initiation factor 4E; EMT, epithelial-mesenchymal transition; ERα, estrogen receptor subtype alpha; hCtr1, human copper transporter 1; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor-1 alpha; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HOTAIR, HOX transcript antisense RNA; HPV, human papillomavirus; HR, hormone receptor; IFN, interferon; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PARP, poly adenosine diphosphate-ribose polymerase; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; TfR1, transferrin receptor protein 1; TRAIL, TNF-related apoptosis-inducing ligand; Trop-2, tumour-associated calcium signal transducer 2; VEGF, vascular endothelial growth factor.

DISCUSSION

Summary of Main Results

Of the more than 500 drugs that have been screened, we found data supporting a possible therapeutic role in cervical cancer for 38 of them. The list contains drugs already approved for other cancer indications as well as for non-cancer indications, for example, the antibiotic doxycycline or antipsychotic chlorpromazine. We have highlighted not only some basic characteristics of the listed drugs but also a summary of relevant data on cervical cancer, an overview of the registered trials in cervical cancer, and any relevant published human results. For all 38 drugs, a potential setting in which these drugs can be used are suggested.

Results in the Context of Published Literature

Our study identified drug repurposing opportunities in cervical cancer. Other work has been published in the past but with a focus on only radiosensitizing agents.[17]

Sonidegib (Odomzo) is a hedgehog pathway inhibitor approved by the EMA and FDA since 2015 to treat adults with locally advanced basal cell carcinoma that is not treatable with surgery or radiotherapy. The hedgehog pathway could represent a valid cervical cancer therapeutic target. Sonidegib enhances the efficacy of cisplatin-based chemoradiotherapy in a cervical cancer xenograft model without increasing gastrointestinal toxicity. We consider that targeting the hedgehog pathway in patients undergoing chemoradiotherapy with sonidegib is therefore a promising hypothesis.[18] With no cervical cancer trials using sonidegib, a logical next step would be to further explore its mechanism of action and confirm activity in a preclinical assessment, and then run an early phase clinical trial evaluating its addition to chemoradiation in cervical cancer.

Another example is the drug nelfinavir (Viracept), a protease inhibitor used against HIV. There is a wealth of preclinical data on the potential use of nelfinavir in cervical cancer.[17] Several clinical trials are being conducted (or have been completed) to determine whether nelfinavir is effective as a cancer therapeutic agent in humans. Most of those trials are in cancer types where chemoradiotherapy is a major component of the treatment, such as rectal cancer, non-small cell lung cancer, and glioblastoma. To date, there are two registered trials (NCT03256916 and NCT01485731/NCT02363829, two registrations of the same phase I trial) with nelfinavir in cervical cancer. The phase I study demonstrated the safety and tolerability of 1250 mg nelfinavir twice a day in combination with cisplatin-based chemoradiotherapy in patients with locally advanced squamous cell cervical cancer. Clinical outcomes were deemed promising compared with historic controls.[19] The other trial is a randomized trial of 300 patients with locally advanced cervical cancer conducted by one of the authors (SC). The study has recruited 60 patients to date and early futility analysis is planned at 32 of the 192 events.

The poly ADP-ribose polymerase (PARP) inhibitors—niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca)—are another example. This class of drugs has shown activity in ovarian, breast, prostate and pancreatic cancers, with the largest benefits seen in BRCA1/2 mutated ovarian cancer. Mainly it is used as a maintenance treatment after response to platinum-based chemotherapy. PARP is an intracellular protein involved in the repair of single stranded DNA breaks and is found at higher levels in cervical

cancer cells compared with normal cells. *In vitro* and *in vivo* data suggest that PARP inhibitors are highly active in cervical cancer preclinical models. PARP inhibitors compromise DNA repair and prevent repair of single strand breaks. They also work synergistically with other DNA damaging agents inducing DNA breaks, such as cisplatin and radiotherapy.[20] Rucaparib also exerts antiproliferative effects and showed potential as a radiosensitizer in cervical cancer *in vitro*.[21] Aside from preclinical studies, there are several ongoing trials investigating PARP inhibitor therapies in cervical cancer patients. Unfortunately, no clinical results are available yet for these three PARP inhibitors. For niraparib, four ongoing trials have been registered (NCT04395612, NCT04068753, NCT03644342, and EudraCT2019-001226-10). Three trials have been registered for rucaparib, with one withdrawn (NCT03795272) and two ongoing (NCT03476798 and NCT04171700). For olaparib, five trials are ongoing (NCT04641728, NCT04487587, NCT04483544, NCT03162627, and jRCT2031210096) and one has been completed (NCT01237067). The data on the efficacy of PARP inhibitors in cervical cancer are still limited and the results of the aforementioned studies will hopefully determine if PARP inhibitors have a role in the treatment of cervical cancer either as a low dose radiosensitizer or as maintenance treatment. These are just examples of potential repurposing candidates. Two are in a more advanced stage of drug development, while one is still in an early phase and warrants further investigations.

Strengths and Weaknesses

With this systematic approach, we have captured potential repurposing candidates in cervical cancer. Although our ReDO_DB and CancerDrugs_DB contain an extensive list of drugs, we might have missed approved drug products with published activity against cervical cancer. For instance, a trial testing the combination of an approved human papillomavirus preventive vaccine with an anti-PD-1 antibody is ongoing in China in cervical cancer patients (NCT04096911). Also, the biology of cervical cancer together with data from other cancer types may form a strong rationale for the repurposing of other drugs in cervical cancer. Maraviroc, a CCR5 inhibitor used in HIV, is such an example with a strong rationale for targeting CCR5 in cervical cancer, and clinical data coming from other cancer types.[22] Recent data also point to the rationale of combining warfarin, acting as a MERTK inhibitor, with radiotherapy.[23] Another limitation is that the assessment of the available data and the selection of the candidates, although performed by our multidisciplinary team, remains subjective. For some drugs, it was clear that the published activity is probably not worthy of further investigation due to negative activity or lack of activity. As an example, sorafenib showed in a phase I clinical trial a potential detrimental effect, or the drug celecoxib, for which it was shown in two trials that the potential toxicity of COX-2 inhibitors probably offsets any small benefit that might exist.[24 25] But what most drugs have in common is that additional (pre)-clinical studies are still needed. This list therefore identifies drugs that, based on their scientific properties, may enhance chemoradiotherapy or may have a synergistic effect with radiotherapy or immune therapy. But ultimately, in most cases, the existing scientific evidence for their effects on cancer is limited and further scientific and clinical research is warranted.

Implications for Practice and Future Research

Since limited success in the discovery of new cancer therapies that are widely applicable has occurred in cervical cancer, drug repurposing represents an interesting strategy and development pathway. However, it comes with a set of challenges.[26] Here, we have attempted to address the first challenge that academic clinical researchers face when it comes to repurposing drugs in their disease of interest: navigating the scientific literature to filter putative drugs.[27] The other main challenges are pharmacological, clinical, strategic, regulatory, and financial. From a clinical trial perspective an efficient way to test multiple candidates is by setting up efficient trials, such as multi-arm multi-stage (MAMS) trials.[28] This would allow the pace of clinical research to be accelerated and expose as few patients as possible to ineffective or toxic regimens. Large platform or MAMS trials that address global clinical cancer research questions, such as treatment of cervical cancer, are yet to be developed. Collaboration between institutions in low- or middle-income countries and high-income countries and substantial funding will be essential for these efforts to deliver and ultimately succeed in improving cancer patient outcomes globally.

CONCLUSION

This study resulted in a list of potential candidates that are worth evaluating in cervical cancer. Although some of the drugs warrant additional preclinical and clinical investigation, repurposing of approved drugs may bring additional therapeutic options to patients. An efficient and coordinated manner to evaluate several of these drug candidates would be in platform trials, which are a type of randomized clinical trial that simultaneously compare multiple intervention groups against a single control group. This type of trial design can evaluate treatment options with fewer patients, less time, and with potentially higher success rates than traditionally designed trials.

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