DRUG REPURPOSING AS A SOURCE OF INNOVATIVE THERAPIES IN CERVICAL CANCER

Rica Capistrano I.[1], Sonz Paul[2], Ingrid A. Boere[3], Pan Pantziarka[1,4], Supriya Chopra[5], Remi A. Nout[3], Gauthier Bouche[1]

[1]Anticancer Fund, Brussels, Belgium; [2] Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Navi Mumbai, India; [3]Erasmus MC Cancer Institute, Erasmus University Medical Center Rotterdam, the Netherlands; [4]The George Pantziarka TP53 Trust, London, UK, [5]Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute, Navi Mumbai, India

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INTRODUCTION

Cervical cancer is the fourth cancer in terms of incidence and mortality in women worldwide. Relative to other cancers, there has been limited progress in the discovery of effective new therapies. Drug repurposing is an alternative development pathway that utilise the properties of drugs approved for other diseases and builds on available safety and pharmacological data to develop the drug as a potential cervical cancer drug.

We screened the literature to identify drug repurposing opportunities in cervical cancer to inform future research and trials.

METHODOLOGY

- A literature-based approach was undertaken to identify whether the drugs included in ReDO_DB or CDcervix_DB might be active in cervix cancer.
- **ReDO_DB** is a database of 317 non-cancer drugs on the market with at least one article reporting a possible effect on any cancer type (https://www.anticancerfund.org/en/redo-db).
- **CDcervix_DB,** which is a subset of the CancerDrugs_DB (https://www.anticancerfund.org/en/cancerdrugs-db) contains 217 drugs approved for one or more malignancies by a regulatory agency, but excluding drugs currently used in cervical cancer.
- PubMed was queried for each drug and all abstracts were assessed for relevance and type of evidence (*in vitro*, *in vivo*, clinical trial, *etc*.). Subsequently, a clinical trial database (clinicaltrials.gov and WHO-ICTRP) search was performed to generate a list of registered trials in cervical cancer with drugs from our databases.

RESULTS

- We queried 534 drugs from our drug databases. Of these, 169 drugs had at least one relevant abstract or registered trial in cervical cancer. Ninety-three drugs had at least human data available with 52 drugs evaluated in registered trials. Forty-two drugs had at most *in vitro* data.
- All 169 drugs were assessed for strength of scientific rationale, feasibility for integration in cervical cancer standard of care, evidence of radiosensitisation, availability of the drug for clinical trials and experience with the use of the compound. Out of these 169 drugs, 39 drugs have been selected as potential candidate for further investigation.
- Here, we present 5 examples (table), *i.e*. nelfinavir, hydralazine with valproate, sonidegib, plerixafor and cetuximab, out of the 39 potential candidates.

CONCLUSION

This study has identified potential candidates that are worth evaluating in cervical cancer. Although many drugs warrant additional preclinical and clinical investigation, we are exploring the possibility of conducting international collaborative exploratory multi-arm trials with one or several of these drugs.

LIST OF THE 39 POTENTIAL DRUG CANDIDATES

Arsenic trioxide	Deferoxamine	Ipilimumab	Nicotinamide	Rucaparib
Artesunate	Doxycycline	Lovastatin	Niraparib	Ruxolitinib
Atovaquone	Erlotinib	Lurbinectedin	Olaparib	Sacituzumab govitecan
Bortezomib	Everolimus	Melatonin	Pazopanib	Sonidegib
Cetuximab	Fulvestrant	Metformin	Plerixafor	Zoledronic Acid
Chlorpromazine	Gefitinib	Mifepristone	Porfimer	
Cidofovir	Hydralazine & valproate	Nelfinavir	Ribavirin	
Decitabine	Interferon Alfa-2b	Niclosamide	Ribociclib	

Table: Selection of 5 drugs out of 39 for further consideration in cervical cancer research

Drug *Main approved indication*	Proposed mechanism of action in cervical cancer	Potential role(s) *single agent/ radiosensitizer/ immunomodulation*	Proposed setting(s)	Cervical cancer trials
Nelfinavir *HIV*	PI3K-Akt inhibition and induction of endoplasmic reticulum stress	radiosensitizer	with CRT	NCT03256916 NCT01485731 NCT02363829
Hydralazine & valproate *Hypertension & epilepsy, respectively*	HDAC and DNA methyltransferase inhibition	radiosensitizer immunomodulation	with CRT, adjuvant, recurrent/ metastatic	NCT00532818 NCT00404326 NCT02446652 NCT03357757
Sonidegib *Basal cell carcinoma*	smoothened inhibition and radiosensitizer	radiosensitizer	with CRT, adjuvant	No
Plerixafor *Mobilisation of haematopoietic stem cells*	prevention of CRT-induced CXCL12/CXCR4 signaling	radiosensitizer immunomodulation	with CRT	No
Cetuximab *Squamous cell head and neck cancer*	EGFR inhibition and radiosensitizer	radiosensitizer	with CRT, recurrent/ metastatic	NCT00957411 NCT00997009 NCT00101192 NCT00499031 NCT00292955 NCT00104910 NCT00518193