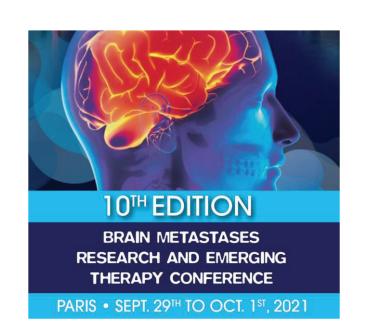


Drug repurposing candidates in the treatment of brain metastases

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Background

- Treatment of brain metastases (BM) remains a clinical challenge despite existing and emerging therapeutic tools.
- New drugs impose a financial burden in high income countries and are unaffordable in many low and middle-income countries.
- Drug repurposing is an alternative development pathway that seeks to reuse existing medications, including non-cancer medications, as a source of new treatment options with limited costs.
- We aimed to identify non-cancer drugs with supportive evidence to be developed in the treatment of BM.

Materials & Methods

- A literature-based approach to identify non-cancer drugs supported by pre-clinical or clinical evidence for repurposing in BM.
- Using 336 drugs listed in the Repurposing Drugs in Oncology (ReDO) database (https://www.anticancerfund.org/en/redo-db), a PubMed query and a clinicaltrials.gov query were performed in June 2021.
- Drugs with ≥ 1 peer-reviewed article reporting an effect against BM or included in ≥ 1 trial to treat BM were considered.

Results

- We reviewed 435 abstracts. Out of the 336 initial drugs, 61 (18%) drugs had at least one relevant abstract, and 15 (4%) drugs are being or have been tested in BM trials.
- We selected 10 drugs for further consideration in BM research (Table) based on the quality of the research and of the level of evidence.

Table: selection of 10 non-anticancer drugs for further consideration in BM research

Drug	Rationale	Primary tumour(s) &	Main reference(s)	Clinical Trials in BM
Main indication	Restricted to articles stemming from our methodology	proposed setting(s)		
Aspirin <i>Analgesia</i>	 Prevents migration through p38 suppression & E-cadherin activation. Confirmed with erlotinib in NSCLC xenograft (A549) model. Positive association between concomitant use of aspirin with osimertinib and PFS in BM patients (HR 0.43; 95%CI 0.27-0.69) 	NSCLC with EGFR inhibitors	Hu 2018 Oncol Lett Liu 2020 Lung Cancer	None, though 1 RCT of aspirin+osimertinib in advanced EGFR+ NSCLC patients
Chloroquine Malaria	 CNS control rate superior in patients treated with chloroquine and WBRT than with WBRT alone in a phase 2 RCT. High control rate in another independent single arm trial with WBRT. 	All solid tumours with RT, with IDO2 a candidate biomarker	Rojas-Fuentes 2013 Radiat Oncol Eldredge 2013 J Radiat Oncol	2 trials completed
Deferoxamine Iron overload	 Cancer cells use lipocalin-2 to outcompete other cells in the leptomeninges for iron. Deferoxamine, an iron chelator, is effective against LM metastases in BC (MDA231) and NSCLC (PC9) mouse models. 	NSCLC and BC patients presenting with LM metastases	Chi 2020 Science	None
Fluphenazine Psychosis	 In a TNBC (4T1) BM model, fluphenazine highly concentrated in the brain and was specifically effective against BM. Possibly a class effect as trifluoperazine was also effective in a BM melanoma model (B16) 	TNBC as BM treatment or prevention of BM recurrence	Xu 2019 Am J Cancer Res Xia 2021 Pharmacol Res	None
Macitentan Pulmonary hypertension	 In the presence of BM, brain stromal cells express high levels of endothelins, promoting BM cells survival. Macitentan, an endothelin receptor antagonist is effective with paclitaxel in BM NSCLC (PC-14) and BC (MDA-MB-231) models. Also effective with TDM-1 in HER2+ BC BM model. 	BC & NSCLC. With paclitaxel in both or with TDM-1 in HER2+ BC.	Lee 2016 Neuro-Oncol Askoxylakis 2019 MBJ Breast Cancer	None
Meclofenamate Analgesia (NSAID)	 By inhibiting connexin 43, meclofenamate modulates carcinoma-astrocyte gap junction. Effective in BC and NSCLC BM mouse models as a single agent & with carboplatin 	BC & NSCLC possibly with carboplatin	Chen & Boire 2016 Nature	1 trial (NCT02429570) Active, not recruiting
Pioglitazone Type 2 diabetes	 E-cadherin loss in primary tumours is associated with BM in NSCLC patients Pioglitazone increases E-cadherin expression in NSCLC (NCI-H358) BM mouse models. 	NSCLC, prevention of BM recurrence	Yoo 2012 J Neuro-Oncol	None
Propranolol Hypertension	 TNBC BM cells proliferate and migrate in response to β2-adrenergic receptor activation, which is abrogated by the β2-adrenergic receptor blocker propranolol. In a TNBC mouse model (MDA-MB-231BR), cells pre-treated with propranolol established BM at a decreased rate. 	TNBC as BM treatment or prevention of BM recurrence	Choy 2016 Oncol Rep	None
Riluzole Amyotrophic lateral sclerosis	• Riluzole acts as a radiosensitizer in a melanoma (C8161) mouse model in both a flank model and a BM model.	Melanoma with RT	Khan 2011 Clin Cancer Res Wall 2015 Pigment Cell Melanoma Res	1 trial (NCT01018836) Terminated for slow accrual
Vardenafil Erectile dysfunction	 The phosphodiesterase 5 inhibitor vardenafil augments tumour permeability to high molecular weight molecules, including trastuzumab. The combination of vardenafil and trastuzumab was more effective than trastuzumab alone in 2 HER2-positive intracranial tumour models. 	All solid tumours to increase intracranial delivery of effective drugs (BC with HER2-directed agents in particular)	Hu 2010 Plos One	1 trial (NCT02279992) Terminated with no accrual

Conclusion

- The number of drugs that could be repurposed in BM is not negligible, with several candidates ready for a clinical translation
 in BM from different tumour types, either as single agent or with current standard treatments.
- Some other drug candidates deserve additional preclinical research to better characterise their possible role in BM.
- Efficient clinical trial designs, such as platform trials may both accelerate testing of these and other agents in BM patients who have limited therapeutic and trial options, while also limiting the risk of trial execution failure.