Drug repurposing candidates in the treatment of brain metastases

Sergio Crispino[1], Klara Rombauts[1], Pan Pantziarka[1,2], Gauthier Bouche[1*]

[1] The Anticancer Fund, Brussels, Belgium [2] The George Pantziarka TP53 Trust, London, UK - * presenting author

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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 *Main indication*	**Rationale** *Restricted to articles stemming from our methodology*	**Primary tumour(s) & proposed setting(s)**	**Main reference(s)**	**Clinical Trials in BM**
Aspirin *Analgesia*	• 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.