Latest news about drug repurposing in oncology #22

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Drug repurposing is a strategy for identifying new uses for approved drugs, outside the scope of the original indication. It is one of the focus areas of the Anticancer Fund.

Below, we have listed recent findings about the repurposing of generic drugs in oncology. Our intention is to help bring these findings to the attention of the broader cancer research community.

Being listed is no endorsement of the results and conclusions of the article. All articles need to be critically assessed and viewed in their broader context.

Please get in touch if you're interested in discussing research based on the findings presented below (info@anticancerfund.org).

Top story

An Il-4 Signalling Axis In Bone Marrow Drives Pro-Tumorigenic Myelopoiesis
Published in Nature
The suppression of anti-tumour immunity is investigated in this series of investigations in non-small cell lung cancer models and human patients. A key finding is that IL4Ralpha inhibition in early myeloid progenitors in bone marrow

Clinical data

Clinical trials

Phase II trial of nivolumab and metformin in patients with treatment-refractory microsatellite stable metastatic colorectal cancer
Published in Journal for Immunotherapy of Cancer
The idea of turning immunologically 'cold' cancers 'hot' so that checkpoint inhibition can be more effective is being increasingly explored in clinical trial settings. This small (n=24, 18 evaluable) Phase II trial tested the addition of metformin to nivolumab in metastatic microsatellite stable (MSS) colorectal cancer (CRC). Primary outcome was overall response rate, with OS and PFS as secondaries. While corellative biological studies showed that the drug combination had some effects, such as increasing the percentage of tumour-infiltrating leukocytes, there were no clinically meaningful effects and the trial was stopped for futility. The small patient numbers, relatively low metformin dose (1000mg/day) and short metformin treatment duration (starting two weeks before commencement of nivolumab) make drawing hard conclusions difficult, but there are no clear dramatic effects from the addition of metformin in this patient population.

Postoperative adjuvant aspirin for patients with hepatitis B virus-related hepatocellular carcinoma and portal vein tumor thrombus: An open-label, randomized controlled trial
Published in Heliyon
This adjuvant randomised open-label trial (n=80) compared OS and time to recurrence for patients with HBV-associated hepatocellular carcinoma and portal vein tumour thrombus treated with low-dose (75mg/day) aspirin vs no aspirin following surgical resection. While there was a clear trend to better OS in the aspirin group (16.2 vs 13.4 months, aspirin vs no aspirin respectively), HR=0.664 (95% CI, 0.419–1.052), this was not statistically significant (P=0.078). Subgroup analysis of the type of portal vein thrombus showed that patients with type I and II PVTT in the adjuvant aspirin group had a better OS (20.5 months vs. 15.4 months, P = 0.033). Time to tumour recurrence was also not statistically significantly different. However, median time to recurrence of portal vein thrombus was 12.0 months vs 5.4 months, HR=0.425 (95% CI, 0.258–0.700, P = 0.001). As a single institution study with relatively small patient numbers these findings are indicative only, but there looks to be a signal of efficacy here, particularly given the low cost and low toxicity of the intervention. A larger multi-centre study would therefore be the logical next step.

[Safety And Antitumor Activity Of Metformin Plus Lanreotide In Patients With Advanced Gastro-Intestinal Or Lung Neuroendocrine Tumors: The Phase Ib Trial Metnet2]
Published in Journal of Hematology and Oncology
This Phase I/II trial in head and neck cancer patients receiving palliative therapy investigated the use of the proton pump inhibitor (PPI) pantoprazole, delivered IV, to improve the response to chemotherapy. Despite the strong biological rationale, the trial failed to show any positive changes in response. Response rates, PFS and OS were broadly similar in patients treated with and without IV pantoprazole. It is notable that a similar intervention has previously been tried in metastatic castrate-resistant prostate cancer, (PMID: 30952818), with no signs of efficacy in that population either.

[Sustained Survival Benefit In Recurrent Medulloblastoma By A Metronomic Antiangiogenic Regimen: A Nonrandomized Controlled Trial]
Published in Jama Oncology
Medulloblastoma recurrence in children who have previously been treated with radiotherapy has no standard therapy and very poor outcomes. In this single arm study, 40 patients, with different medulloblastoma molecular subtypes, were treated with metronomic chemotherapy (including daily thalidomide) combined with a two non-cancer drugs (fenofibrate and celecoxib) and bevacizumab. The primary end-point was PFS. Of the 40 patients in the study, 23 (58%) achieved disease control after 6 months of treatment. Median OS was 25.5 months (range, 10.9-40.0 months), and median PFS was 8.5 months (range, 1.7-15.4 months) - with no clear differences between the molecular subtypes of the disease. In patients demonstrating (n=18) a response, mean 5-year PFS was 49.7% , and for patients who remained progression free for the first 12 months of treatment, mean 5-year PFS was 66.7%. Given the patient population these positive results urgently warrant further investigation.

[Efficacy And Safety Of Chlorpromazine As An Adjuvant Therapy For Glioblastoma In Patients With Unmethylated Mgmt Gene Promoter: Ractac, A Phase Ii Multicenter Trial]
Published in Frontiers in Oncology
This single arm Phase II trial investigated the addition of chlorpramazine, a classical anti-psychotic agent, to standard of care chemotherapy in newly diagnosed glioblastoma patients. The trial evaluated 41 patients, with unmethylated MGMT, treated with temozolomide and oral chlorpramazine. The primary outcome was six-month PFS rate, with a target of 55% (20 patients), which was exceeded - 66% (27 patients) - showed no progression at six months. At study close median PFS was 8.0 months (95% CI: 7.0-9.0) and median OS 15.0 months (95% CI: 13.1-16.9) - deemed promising in this patient population. These

positive results clearly warrant further investigation in a randomised controlled trial powered to show efficacy.

[A Phase 1 Study Of Mebendazole With Bevacizumab And Irinotecan In High-Grade Gliomas]
Published in Pediatric Blood and Cancer
High-grade gliomas have a dismal prognosis and the search for new treatments has to contend with the blood-brain-barrier as a major obstacle (literally). Mebendazole, an anti-parasitic drug, has been on the radar as a potential candidate for a number of years. In this small (n=10) Phase 1 trial in children, mebendazole was combined with bevacizumab and irinotecan to assess safety and tolerability. The results confirmed that mebendazole at a relatively high dose of 200 mg/kg/day was tolerable in combination with the other drugs. While not designed to test efficacy, some patients experienced clear benefit. The overall response rate was 33%, with two subjects achieving a partial response and one subject achieving a complete response sustained for 10 months.

Observational trials

[Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score-Matched Survival Outcome Comparisons]
Published in Journal of Clinical Oncology
This study used a propensity score matching approach to compare patients with high-risk neuroblastoma, after immunotherpay treatment, treated with or without eflornithine (DFMO). Drawing on patient-level data from a non-randomised clinical trial (NCT02395666) of patients treated with DFMO, and compared them to an external control arm derived from the dinutuximab arm of NCT00026312. Patients were matched 1:3, and balanced on all key covariates. Primary outcomes of the comparison were event-free and overall survival. DFMO after completion of immunotherapy was associated with improved EFS (hazard ratio, 0.50 [95% CI, 0.29 to 0.84]; P=0.008) and OS (HR, 0.38 [95% CI, 0.19 to 0.76]; P=0.007). This analysis was sufficient for the FDA to approve DFMO to reduce the risk of relapse in adult and paediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy. DFMO becomes, therefore, one of the small number of 'hard' drug repurposing examples of a non-oncology drug reaching approval for a cancer indication.

Preclinical data

Alpha-1 Adrenergic Antagonists Sensitize Neuroblastoma to Therapeutic Differentiation
Published in Cancer Research
The authors of this study carried out a drug screen looking for small molecules that could synergise with isotretinoin, one of the standard treatments for neuroblastoma (NB) and used to decrease the risk of disease relapse. The screen identified isorhamnetin, a food-derived flavonoid, as inhibiting NB cell viability in combination with isotretinoin. The authors then investigated the mechanism for this activity, finding that it was related to adrenergic receptor a1B (ADRA1B) signalling, and that blockade of ADRA1B increased NB cell sensitivity of isotretinoin. Thus the next logical step was to assess the activity of currently licensed drugs that inhibit ADRA1B, with doxazosin, which is used in paediatrics, selected for testing *in vivo* - confirming the synergistic effects seen *in vitro*. These results warrant clinical investigation in children as high-risk neuroblastoma relapse.

Repurposing Clemastine to Target Glioblastoma Cell Stemness
Published in Cancers
Targeting brain tumour-initiating cells (BTICs) is a common research strategy to address resistance to existing cancer treatments or reduce the risk of relapse. This preclinical study explores the approach in glioblastoma, a cancer characterised by the emergence of resistance to temozolomide. The authors use a pro-differentiation approach, using the over-the-counter anti-histamine clemastine to target a subset of GBM cells with stem-like properties. *In vitro* the drug reduces stemness features of BTICs and suppressed the propagation of primary BTIC cultures bearing PDGFRA amplification. Exploration suggests that the effects may be related to inhibition of emopamil binding protein (EBP). *In vivo*, clemastine improved survival in a GBM mouse model, with no apparent toxicity, although it was not an orthotopic model. Further work is required - does the drug combine with temozolomide and radiotherapy, can the work be replicated in other models etc?

Lithium Carbonate Revitalizes Tumor-Reactive Cd8+ T Cells By Shunting Lactic Acid Into Mitochondria
Published in Nature Immunology
The acidic tumour microenvironment is known to be a driver for the loss of anti-tumour immunity, leading to many investigations on how to ameliorate the phenomenon. In this study the authors investigate the role of lactic acid, a cancer cell metabolite implicated in multiple pro-cancer mechanisms. The authors use lithium carbonate, which has been shown to reduce lactate levels in depressed patients, to investigate activity in the tumour microenvironment.

Using mouse models they show that lithium acts to channel lactate from the cytosol to mitochondria where it can be metabolised. This acts both to reduce the acidification of the microenvironment but also provides an energy source for CD8+ T cells. Using patient derived pleural effusions, breast cancer and colon cancer cells and a variety of *in vivo* models the report indicates that lithium is associated with improved immunity and longer mouse survival. The conclusion is that lithium should be clinically investigated as a means of improving immunotherapy responses in patients.