Latest news about drug repurposing in oncology #20

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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

Canagliflozin primes antitumor immunity by triggering PD-L1 degradation in endocytic recycling

The Journal of Clinical Investigation

Finding drugs which can improve the response to checkpoint inhibitors is a major growth area in drug repurposing in oncology. In this paper the authors show that the anti-diabetic drug canagliflozin (an SGLT2 inhibitor) reduces expression of PD-L1 expression in NSCLC cell lines, including from patient derived cells. Mechanistically they show that this is an on-target effect, and that inhibition of SGLT2 triggers degradation of PD-L1 on the cell surface. In vivo this leads to increased activity of antitumor cytotoxic T cells. Treatment of immunocompetent mice with canagliflozin was associated with reduced tumour growth, to the same extent as treatment with immune checkpoint inhibitors. Finally, NSCLC patients with high expression of SGLT2 also showed

high PD-L1 expression and had statistically significantly lower PFS and overall survival. Given the low toxicity associated with this drug, this study is strong support for clinical exploration of the combination of checkpoint inhibition and canagliflozin.

Clinical data

Clinical trials

A phase I trial of metformin in combination with vincristine, irinotecan, and temozolomide in children with relapsed or refractory solid and central nervous system tumors: A report from the national pediatric cancer foundation
Published in Cancer Medicine
In this paediatric trial in relapsed and refractory solid and CNS tumours, the aim was to find a recommended Phase II dose (RP2D) of metformin in combination with a standard paediatric chemotherapy backbone of vincristine, irinotecan and temozolomide. At study close the RP2D of metformin was 1666 mg/m2/day - quite a high dose for a paediatric population. As expected most of the toxicities were gastrointestinal, although there were some haematological but with a chemo backbone it's not possible to say to what degree these were metformin-related. Among 16 patients evaluable for best response, there were one complete response (Ewing sarcoma), three partial responses (Ewing sarcoma, glioblastoma multiforme, and alveolar rhabdomyosarcoma), and five patients with stable disease. However, this was not an efficacy trial and similar responses have been seen from chemo alone. More informative Phase 2 trials are necessary to assess whether metformin improves outcomes.

Effect of Disulfiram and Copper Plus Chemotherapy vs Chemotherapy Alone on Survival in Patients With Recurrent Glioblastoma
Published in Jama Network Open
The combination of anti-alcoholism drug disulfiram and copper has shown very promising activity in preclinical studies, particularly in glioblastoma (GBM), and dose and toxicity were established in a previous Phase 1 trial. This trial reports on a Phase II/III trial in recurrent GBM, with patients randomised to standard of care (SOC) (n=45) or disulfiram + copper + SOC (D+C) (n=43). Results show that there was no significant difference in median overall survival (8.2 vs 5.5 months, SOC vs D+C), or median progression free survival (2.6 vs 2.3 months, SOC vs D+C). Additionally, the D+C had a higher rate of toxicity and 10 patients (24%) discontinued disulfiram treatment because of adverse effects. Overall this trial does not support further evaluation of this combination in this patient population.

[Phase I Study of a Combination of Fluvastatin and Celecoxib in Children with Relapsing/Refractory Low-Grade or High-Grade Glioma (FLUVABREX)]
Published in Cancers
This complex open-label Phase 1 trial, funded by the Anticancer Fund, tested the use of two repurposing candidates in paediatric gliomas - both high-grade (HGG) and low-grade (LGG). Based on preclinical data the trial used two oral drugs - fluvastatin and celecoxib in paediatric patients with recurrent and/or refractory disease. The combination showed little activity in HGG, but more promising results in children with LGG among whom there were a number with long-term stable disease (four patients free of disease progression at 17, 35, 41 and 84 months after study entry). While other regimens have shown similar promising results, the authors note that in low and middle income countries this simple and low-cost treatment may be suitable as a maintenance therapy in high-risk LGG patients.

[Neoadjuvant intratumoral influenza vaccine treatment in patients with proficient mismatch repair colorectal cancer leads to increased tumor infiltration of CD8+ T cells and upregulation of PD-L1: a phase 1/2 clinical trial]
Published in Journal of Immunotherapy for Cancer
Perioperative therapies aim at improving cancer outcomes by intervening at the time of surgery - the aim is to improve immune response and/or reduce the risk of post-surgical recurrence. In this small (n=10) proof of concept trial colorectal cancer patients undergoing surgical resection were injected intratumourally with flu vaccine. The primary outcome was safety, which was confirmed. Colorectal cancer is one of those cancers in which responses to immune checkpoint inhibition have been relatively poor, assumed to be because most are proficient in mismatch repair whereas mismatch repair definicient cancers have better responses. In addition to the safety and feasibility, results here showed that the intervention increased CD8+T-cell infiltration and upregulation of PD-L1 - potentially associated with an improving response to checkpoint inhibition - which needs assessing in further trials.

[A phase 1 study of simvastatin in combination with topotecan and cyclophosphamide in pediatric patients with relapsed and/or refractory solid and CNS tumors]
Published in Pediatric Blood and Cancer
This Phase 1 trial tested high-dose simvastatin with topotecan and cyclophosphamide in a mixed group of relapsed/refractory paediatric cancers. The primary outcome was maximum tolerated dose of simvastatin with chemotherapy in a paediatric population - which was found to determined to be 100 mg/m2/dose. While there was one Ewing's sarcoma who showed a partial

response, and four cases of stable disease, overall the combination did not show high levels of activity in such a heavily-pretreated population.

A Phase II Open-Label Trial of Binimetinib and Hydroxychloroquine in Patients With Advanced KRAS-Mutant Non-Small Cell Lung Cancer
Published in The Oncologist
Preclinical data has shown that in RAS-mutant tumours, combined MEK and autophagy inhibition leads to synthetic lethality in cancer cells. In this small Phase 2 study the combination of MEK inhibitor binimetinib and hydroxychloroquine (HCQ) was tested in patients (n=9) with advanced KRAS-mutant non-small cell lung cancer. Pre-specified futility rules led to the early closure of the trial at the end of stage 1, with no responses seen in patients.

Efficacy and safety of metformin plus low-dose temozolomide in patients with recurrent or refractory glioblastoma: a randomized, prospective, multicenter, double-blind, controlled, phase 2 trial (KNOG-1501 study)
Published in Discover Oncology
In this randomised controlled trial patients with recurrent/refractory GBM were allocated to metformin + low-dose temozolomide (TMZ) (n=38) or placebo + TMZ (n=43). Primary outcome was PFS, with OS and disease control and response rate as secondary outcomes. The results were negative, with no significant differences between the metformin and control arms in any outcome.

Preclinical data

Beta-blockade enhances anthracycline control of metastasis in triple-negative breast cancer
Published in Science Translational Medicine
This study, assessing the impact of beta blockade in triple-negative breast cancer (TNBC) in animal models, is interesting for a number of reasons. Firstly, it shows how doxorubicin treatment leads to an increase in nerve growth factor release by tumour cells. This increases sympathetic nervous system signalling within the tumours, which is in turn associated with metastatic spread. Secondly, beta blockade with propranolol abrogated these effects. These findings, in two mouse models of TNBC (4T1.2 and MDA-MB-231) showed that the combination of propranolol and doxorubicin was associated with reduced metastatic progression. In retrospective analysis of two cohorts of TNBC patients, the authors show that concurrent beta blocker use and anthracycline chemotherapy was associated with reduced risk of metastasis, relapse and risk of death. This study adds to the weight of evidence supporting clinical evaluation of propranolol in TNBC.

[The Antiepileptic Drug Oxcarbazepine Inhibits the Growth of Patient-Derived Isocitrate Dehydrogenase Mutant Glioma Stem-like Cells]
Published in Cells
Patients with IDH-mutant gliomas are prone to developing seizures, often being the symptom that leads to initial diagnosis and subsequently may also be associated with poor prognosis. It would make sense, therefore to see whether any anti-epileptic drugs (AEDs) also have anticancer properties - which is exactly what the authors of this study have done. They screened 20 FDA approved AEDs against a panel of six patient-derived IDHmut glioma stem-like cells. Of the screened drugs two, oxcarbazepine and perampanel, demonstrated an antiproliferative effect. Further *in vitro* testing showed that only oxcarbazepine was active at concentrations achievable in humans. Such screens are hypothesis generating only - next steps are necessary, for example *in vivo* testing or retrospective analysis to see if glioma patients have been treated with oxcarbazepine and what the responses are compared to similar cohorts treated with other AEDs.

[Dual antiplatelet therapy inhibits neutrophil extracellular traps to reduce liver micrometastases of intrahepatic cholangiocarcinoma]
Published in Cancer Letters
The role of neutrophil extracellular traps (NETs) in cancer metastasis is being increasingly elucidated in a range of cancers. In this paper the authors show that NETs play a role in itrahepatic cholangiocarcinoma (iCC), and that together with platelets play a key role in metastatic spread. In particular they show that iCC cells promote NET induction by binding to platelets (via P-selectin), and in turn these NETs promote motility of iCC cells. Dual anti-platelet therapy using the common combination of aspirin and ticagrelor, as used in coronary artery disease, was shown in vitro to reduce NET induction. In vivo, combination treatment reduced the induction of hepatic micrometasis in an animal model. Given the very high unmet needs in this disease, further validation of these results and subsequent clinical investigation are warranted.

Other

[Drug evidence watch: a process to the benefit of public health.]
Published in Lancet (London, England)
Getting new repurposed treatments to patients is not simply a question of scientific research - as we've highlighted before, there are also regulatory obstacles that have to be overcome along the way. In this perspectives article in the Lancet we propose that regulators should adopt an 'efficacy vigilance' approach that tracks data on licensed drugs not just for toxicity, as they do now, but also for evidence of efficacy in new indications. Increasingly, we will be

finding that implementation of positive data for repurposing is dependent on incentives, medical regulation and health economics.