Latest news about drug repurposing in oncology #17

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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 stories

Effect of Metformin vs Placebo on Invasive Disease-Free Survival in Patients With Breast Cancer: The MA.32 Randomized Clinical Trial
Published in Jama
In this multi-national Phase 3 randomised, placebo-controlled, double-blind trial in non-diabetic women with operable breast cancer, (n=3649), the effect of metformin on invasive disease-free survival was assessed. Analysis showed no significant differences on a range of survival outcomes with the addition of metformin to standard of care, with these results consistent when stratified by hormone receptor status. However, a subgroup analysis of ERBB2+ patients did show statistically significant overall survival and invasive disease-free survival benefits for metformin - a result which requires further trial replication.

Clinical data

Clinical trials

METNET: a phase II trial of metformin in patients with well-differentiated neuroendocrine tumours
Published in Ecancer Medical Science
This small (n=28) single arm, Phase II trial (NCT02279758), assessed the use of metformin monotherapy in patients with advanced/metastatic well-differentiated pancreatic neuroendocrine tumours. The disease control rate was 46% at 6 months, there were no objective responses, but one patient with refractory carcinoid syndrome had complete symptom relief, lasting for more than 5 years. Overall the trial finds that metformin monotherapy shows only modest anti-tumour activity in this patient population.

Shifting the Soil: Metformin Treatment Decreases the Protumorigenic Tumor Microenvironment in Epithelial Ovarian Cancer
Published in Cancers
In this translational study of patient samples from a trial in epithelial ovarian cancer patients treated with metformin (NCT01579812), changes in the tumour microenvironment are analysed and reported. Changes in cancer-associated mesenchymal stem cells and in regulatory T-cell populations are reported, leading to a more immune-permissive environment. The authors suggest that metformin may be more appropriate in early stage disease or in association with immune therapies.

A Phase I Trial to Determine the Safety and Tolerability of Autophagy Inhibition Using Chloroquine or Hydroxychloroquine in Combination With Carboplatin and Gemcitabine in Patients With Advanced Solid Tumors
Published in Frontiers in Oncology
We have two Phase I studies looking at chloroquine (CQ) or hydroxychloroquine (HCQ). In the 1st trial heavily pre-treated solid tumour (multiple types) patients, n=22, were treated with CQ or HCQ in combination with gemcitabine and carboplatin. Analysis of the results is complicated by a switch from CQ to HCQ due to drug supply issues. The reported disease control rate was 68% at 6-months, and the response rate was 71%.

Phase I Trial of Regorafenib, Hydroxychloroquine, and Entinostat in Metastatic Colorectal Cancer
Published in the Oncologist
In the second trial, metastatic colorectal cancer patients were treated with HCQ in combination with entinostat and regorafenib. In contrast to the previous

study, this one reports that the treatment had poor tolerability and no meaningful activity.

Oral metronomic chemotherapy after definitive chemoradiation in esophageal squamous cell carcinoma: a randomized clinical trial
Published in Esophagus
Celecoxib, in combination with weekly metronomic oral methotrexate, was investigated as a treatment following definitive chemoradiotherapy in locally advanced resectable esophageal or gastroesophageal junction carcinoma - a disease with very high unmet needs. In this open-label Phase II/III study patients, (n=151), were randomised to treatment for 12 months or observation, with a primary outcome of PFS for the Phase II study. Results showed that outcomes in the treatment arm were inferior compared to the observation only arm - for both PFS and OS. Oral methotrexate and celecoxib does not improve outcomes in this patient population and may even reduce survival.

Comparison of Efficacy of Aspirin Plus EOX vs. EOX Alone in Patients with Locally Advanced and Metastatic Gastric Cancer: a Randomized Clinical Trial
Published in Journal of Gastrointestinal Cancer
Locally advanced or metastatic gastric cancer patients were randomised to chemotherapy (epirubicin, oxaliplatin and capecitabine) with or without daily aspirin (150 mg) in this open label phase 2 trial (n=95). The primary outcome was overall response rate. The trial showed no differences between the two arms in terms of response rates, PFS or OS in this unselected patient population.

A Phase II Study of Preoperative Chemoradiotherapy with Capecitabine Plus Simvastatin in Patients with Locally Advanced Rectal Cancer
Published in Cancer Research and Treatment
The addition of simvastatin to preoperative chemoradiotherapy in locally advanced rectal cancer did not improve the pathological complete response rate in this open-label single arm Phase 2 trial. While treatment was safe and tolerable, the trial did not achieve a statistically significant primary outcome.

Intraoperative lidocaine infusion in patients undergoing pancreatectomy for pancreatic cancer: a mechanistic, multicentre randomised clinical trial
Published in British Journal of Anaesthesia
Lidocaine has been identified as a possible anticancer agent in a number of pre-clinical studies. In this large randomised (n=563) trial intraoperative lidocaine infusion was assessed for impact on overall and disease-free 3-year survival in pancreatic cancer patients. Overall outcomes were similar in lidocaine and placebo groups, and although there were group differences in use of opioid consumption this did not translate into a reduced rate of complications. And a

reduction in circulating neutrophil extracellular traps due to lidocaine did not lead to a reduction in tumour infiltration.

Observational studies

Does the Combined Use of Aspirin and Immunotherapy Result in Better Outcomes in Non-Small Cell Lung Cancer Than Immunotherapy Alone?
Published in Cureus
In this retrospective analysis, non-small cell lung cancer patients treated with immune checkpoint inhibition (ICI) and aspirin were compared to similar patients treated with ICI alone. While finding no significant differences in outcomes across the population, when stratified by ICI-type (anti-PD1 vs anti-PDL1), patients treated with anti-PDL1 and aspirin showed a highly statistically significant reduced risk of having progressive disease. These findings suggest that NSCLC patients receiving PD-L1 inhibitors could benefit more from daily aspirin than patients treated with PD-1 inhibitors - although prospective data is now required.

Statin use improves the efficacy of nivolumab in patients with advanced renal cell carcinoma
Published in European Journal of Cancer
This multinational retrospective analysis reviewed data for 219 metastatic renal cell carcinoma patients treated with 2nd or 3rd line nivolumab. Outcomes assessed were overall survival, PFS and overall benefit rate. Statin use was associated with improvements in all outcomes, both in terms of statistical and clinical significance. In this patient population statin use was highly prognostic.

Case reports

Cyclic Metronomic Chemotherapy for Pediatric Tumors: Six Case Reports and a Review of the Literature
Journal of Clinical Medicine
In this case series report, paediatric refractory cancer patients (n=6), were treated with metronomic cyclophosphamide or etoposide, on an alternating 21-day cycle, combined with celecoxib and/or valproic acid. Of the six patients, three had complete responses, two of them very long lasting, and three patients had partial responses. These cases join other reports which indicate that the combination of metronomic chemotherapy and repurposed drugs have clinically meaningful activity in some paediatric cancer patients. However, more work is required to turn these hypotheses into active clinical trials.

[Perioperative Arginine Prevents Metastases by Accelerating Natural Killer Cell Recovery After Surgery]
Published in Molecular Therapy
This paper reports on the perioperative use of l-arginine on surgery-induced myeloid-derived suppressor cells (SxMDSCs) which are associated with natural killer (NK) cell suppression after cancer surgery, and are associated with post-surgical metastasis and recurrence. In animal models surgery was shown to induce SxMDSCs leading to a reduction in arginine bioavailability and that dietary intake of arginine reduced the rate of metastasis by increasing the rate of NK cell recovery. The study also reports data from colorectal cancer patients showing that post-operative arginine levels correlated with their Sx-MDSC levels.

Preclinical data

[Beta-blockers disrupt mitochondrial bioenergetics and increase radiotherapy efficacy independently of beta-adrenergic receptors in medulloblastoma]
Published in eBioMedicine
Propranolol continues to be an intriguing repurposing candidate in oncology. In this wide-ranging paper the authors investigate the use of beta blockers, including propranolol, on a range of medulloblastoma cell lines, patient-derived xenograph cells, 3D spheroids and a cerebellar organotypic model. Results show that low-dose beta blockade potentiated the effects of radiotherapy, and that this effect was via an increase in mitochondrial ROS production rather than via the canonical beta adrenergic receptors. These results are supportive of clinical exploration in paediatric medulloblastoma patients.

[cGAS-STING drives the IL-6-dependent survival of chromosomally instable cancers]
Published in Nature
Chromosomal instability (CIN) is implicated in cancer cell evolution, metastasis and therapy resistance. In patients it is associated with poor prognosis in multiple cancer types. In this paper the authors show inactivation of cGAS–STING signalling selectively impairs the survival of triple-negative breast cancer cells that display CIN. They show that cGAS–STING signalling upregulates IL-6–STAT3 and NF-κB. Furthermore, experiments show that inhibition of IL6 signalling by tocilizumab, which targets the IL-6 receptor, selectively targets triple-negative breast cancer cells that exhibit CIN. The growth of high-CIN tumours, in multiple cancer types (lung, ovarian and breast), is impaired by tocilizumab. Finally, the authors speculate that repurposing tocilizumab in combination with drugs like vincristine pr paclitaxel, which induce CIN in cancer cells, is a strategy that warrants further exploration.