Latest news about drug repurposing in oncology #6

12 April 2021

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 research context.

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

Top story

Indomethacin is an effective treatment in adults and children with bone Langerhans cell histiocytosis (LCH) Br J Haematol
This paper reports the results of indomethacin treatment in 63 Italian paediatric and adult patients with bone Langerhans cell histiocytosis. Indomethacin was given, at a dose ranging from 1 to 2 mg/kg/day. All but one patient (62/63) had a response, which was complete for 32 of them. The high response rate and favourable safety profile of indomethacin makes it an interesting treatment option compared to chemotherapy. Based on these findings, it is now included in the Italian guidelines for adults with unifocal or multifocal bone Langerhans cell histiocytosis.

Clinical data

Clinical trials

Adjuvant sirolimus does not improve outcome in pet dogs receiving standard of care therapy for appendicular osteosarcoma: A prospective, randomized trial of 324 dogs
Clin Cancer Res
In this randomized trial in 324 pet dogs diagnosed with treatment-naïve appendicular osteosarcoma, the addition of sirolimus to the standard treatment (amputation of the affected limb and adjuvant carboplatin) had no effect on survival with superimposable disease-free interval and overall survival curves (no HR reported). The main limitation reported by the authors was the late introduction of sirolimus (with the 4th cycle of carboplatin).

A proof of concept phase I/II pilot trial of LSD1 inhibition by tranylcypromine combined with ATRA in refractory/relapsed AML patients not eligible for intensive therapy
Leukemia
The trial reported in this article tested the combination of all-trans retinoic acid (ATRA) with tranylcypromine, an antidepressant from the monoamine oxidase inhibitor family, that irreversibly inhibit lysine-specific demethylase 1 (LSD1) and induces myeloid differentiation in AML blasts in combination with ATRA. 18 patients with relapsed/refractory AML ineligible for intensive treatment received the combination. Three out of the 15 evaluable patients had an objective response. This trial confirms that the combination can induce differentiation of AML blasts and lead to clinical response in heavily pre-treated patients with acceptable toxicity.

Valproic acid combined with cisplatin-based chemoradiation in locally advanced head and neck squamous cell carcinoma patients and associated biomarkers
Ecancermedicalscience
In this Brazilian trial in patients with locally advanced head and neck squamous cell carcinoma, valproic acid was initiated 2 weeks before concomitant chemo-radiation and continued until the last fraction of radiotherapy. The trial had to be stopped after the inclusion of 10 patients because of a too high rate of hematologic toxicity and infections, making this combination unsuitable for future research in this disease.

Adjuvant melatonin for the prevention of recurrence and mortality following lung cancer resection (AMPLCaRe): A randomized placebo controlled clinical trial
EClinicalMedicine
In this phase 3 placebo-controlled randomized trial, 709 participants with

NSCLC received either melatonin (20 mg) or placebo for one year following surgical resection of primary NSCLC. There was no difference in disease-free survival (HR 1.01 (95% CI 0.83-1.22) and in quality of life between groups.

Observational studies

Improved survival without increased toxicity with influenza vaccination in cancer patients treated with checkpoint inhibitors
Oncoimmunology
In this retrospective cohort study at three Swedish centres, 303 patients with metastatic cancer who received checkpoint inhibitors were included. 67 patients had received an influenza vaccination around the time of checkpoint inhibitor initiation. Having received an influenza vaccination was associated with a higher overall survival in the multivariate analysis (HR = 0.53, 95% CI = 0.30–0.93). The association remained in the sensitivity analyses conducted to account for a potential immortal-time bias.

Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients
Eur J Cancer
In this study the effects of carvedilol on breast cancer growth are assessed in vitro and in vivo. Data shows that carvedilol treatment reduces in vitro tumour cell invasion and in vivo slows tumour growth and metastasis. Supporting data from Norwegian breast cancer patients is analysed and suggests that, while not statistically significant, there may be an association between carvedilol treatment and improved survival (HR =0.41; 95% CI = 0.15 - 1.09; p = 0.076).

Preclinical data

Functional reconstruction of human AML reveals stem cell origin and vulnerability of treatment-resistant MLL-rearranged leukemia
Science Translational Medicine
Zeisig et al identified two distinct origins of leukemic stem cells (LSC) in Mixed Lineage Leukaemia AML (MLL-AML). One lineage is chemo-sensitive while the other is chemo-resistant (that originating from hematopoietic stem cells). The chemo-resistant cells LSC had higher ABCC3 expression, which can be targeted with fidaxomicin, an antibiotic drug. Fidaxomicin successfully sensitized the chemo-resistant LSCs to chemotherapy.

Targeting cancer stem cells by disulfiram and copper sensitizes radioresistant chondrosarcoma to radiation
Cancer Lett.

This paper first shows that chondrosarcoma stem cells are radioresistant and then confirms the efficacy of disulfiram (with copper gluconate) as an effective radiosensitizer. In an orthotopic xenograft model, the survival of mice treated with radiation, disulfiram and copper gluconate, both at doses compatible with human use, was increased compared to the use of radiation alone.

Mycophenolic acid is a drug with the potential to be repurposed for suppressing tumor growth and metastasis in osteosarcoma treatment
Int J Cancer
This paper builds on prior bioinformatics work done by the authors suggesting that mycophenolate mofetil, ribavirin, leflunomide, azathioprine and digoxin were repurposing candidates against osteosarcoma. In this study, they report that mycophenolate mofetil, an immunosuppressant, is the best of the 5 candidates. In mouse models of osteosarcoma implanted with 143B cells, mycophenolate mofetil reduced tumour growth and metastatic spread through inosine monophosphate dehydrogenase inhibition, at dose compatible with human use.

Cholesterol Pathway Inhibition Induces TGF-β Signaling to Promote Basal Differentiation in Pancreatic Cancer
Cancer Cell
In this paper, authors show that, in mouse models driven by KrasG12D expression and homozygous Trp53 loss, statins promote transformation of pancreatic cancer from the less aggressive glandular phenotype to the more aggressive basal (mesenchymal) phenotype. Using patients' surgical specimen, they found a correlation between statin exposures and mesenchymal features.

Sulfasalazine modifies metabolic profiles and enhances cisplatin chemosensitivity on cholangiocarcinoma cells in in vitro and in vivo models
Cancer Metab
Sulfasalazine, an anti-inflammatory drug, synergizes with cisplatin in a mouse model of cholangiocarcinoma to reduce tumour growth. They show that sulfasalazine target CD44 variant 9 positive cells, cancer stem cells which presence is associated with a poor prognosis.

Low dose amiodarone reduces tumor growth and angiogenesis
Sci Rep
Amiodarone, an antiarrhythmic drug, shows strong antiangiogenic properties in a mouse corneal neovascularization model and a matrigel plug assay. Thanks to its antiangiogenic effect, amiodarone was able to reduce tumour growth in a glioblastoma xenograft model. The human equivalent dose used in this model was more than 100 times lower than the approved dose. This very low dose

makes clinical translation quite attractive as it may circumvent toxicity issues that comes with amiodarone administration for a long duration.

Ivermectin converts cold tumors hot and synergizes with immune checkpoint blockade for treatment of breast cancer
NPJ Breast Cancer
In vivo work showing that ivermectin, in combination with check-point inhibition, improves survival in mouse models of breast cancer. The mechanism is shown to be associated with an increase in immunogenic cell death due to ivermectin treatment. Effects shown in different stages of disease/treatment, including neoadjuvant, adjuvant and in metastatic disease.