Latest news about drug repurposing in oncology #16

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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 research context.

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

Top stories

Anti-invasive efficacy and survival benefit of the YAP-TEAD inhibitor Verteporfin in preclinical glioblastoma models
Published in Neuro Oncology
The photosensitiser verteporfin is shown to be active *in vitro* in glioblastoma (GBM) cell lines via multiple mechanisms of action, including inhibition of YAP/TAZ-TEAD activity which is implicated in GBM tumour invasiveness. Using mouse models the study confirmed the brain penetrance of verteporfin before assessing activity in a variety of orthotopic PDX models. In both newly diagnosed and recurrent PDX models the drug was shown to be non-toxic and to have meaningful anti-GBM activity - including a survival benefit. This is another study that is strongly supportive of replication and further development, including clinical trial development.

Polyamines drive myeloid cell survival by buffering intracellular pH to promote immunosuppression in glioblastoma
Published in Science Advances
In this second GBM study, the immunosuppressive effect of tumour-associated myeloid cells (TAMCs) is investigated *in vivo*. In particular this study focuses on the role of the arginine-ornithine-polyamine axis, which is highly upregulated in GBM. Specifically they show that active de novo synthesis of highly basic polyamines facilitates the survival of these highly immunosuppressive TAMCs. Treatment with DFMO aka eflornithine, already a high-profile repurposing candidate in neuroblastoma, decreased intracellular pH in TAMCs and was associated with improved survival, more so when combined with immunotherapy or radiotherapy.

Clinical data

Clinical trials

A lead-in safety study followed by a phase 2 clinical trial of dabrafenib, trametinib and hydroxychloroquine in advanced BRAFV600 mutant melanoma patients previously treated with BRAF-/MEK-inhibitors and immune checkpoint inhibitors
Published in Melanoma Research
This clinical trial investigated the use of combined BRAF-/MEK-inhibition with dabrafenib and trametinib plus hydroxychloroquine in patients with advanced BRAFV600 mutant melanoma who had progressed on previous treatment with BRAF-/MEK-inhibitors and immune checkpoint inhibitors. The rationale was based on preclinical data showing that hydroxychloroquine can inhibit resistance due to treatment-induced autophagy. The decision was made to terminate the trial for futility after the first 10 patients, of whom 2 experienced a partial response (20% response rate), though it is unclear why the trial parted from its initial plan to look at futility only after 15 patients had been included.

Mebendazole; from an anti-parasitic drug to a promising candidate for drug repurposing in colorectal cancer
Published in Life Sciences
In this small (n=40) randomised trial patients with metastatic colorectal cancer were treated with bevacizumab and FOLFOX4 with mebendazole (500 mg BID) or placebo for 12 weeks. Biomarker analysis showed mebendazole treatment was associated with statistically significant reduction in VEGF. Median PFS (9.25 months mebendazole vs. 3 months placebo) and overall response rate (65% mebendazole vs. 10% placebo) were also statistically significantly improved. OS was not significantly improved. This is a small study using only per protocol analysis so results are tentative but encouraging for further investigation.

[Ritonavir-Boosted Exposure of Kinase Inhibitors: an Open Label, Cross-over Pharmacokinetic Proof-of-Concept Trial with Erlotinib]
Published in Pharmaceutical Research
This paper reports on an innovative way for using existing non-cancer drugs to reduce the dose and to potentially improve efficacy of approved expensive anticancer drugs. This pharmacokinetic study (n=9) compared half-dose erlotinib (75 mg/day) with the HIV drug ritonavir (200 mg/day) with full-dose erlotinib (150 mg/day). Results showed that the addition of ritonavir, a CYP3A4 inhibitor, resulted in similar AUC, Cmax, Cmin and plasma concentration as full-dose. The same strategy may be applicable to other expensive TKI drugs, leading to cost savings - and may also make such treatments affordable in LMICs. It is also discussed that inhibiting CYP3A4 in tumour cells may lead to higher treatment efficacy and prevention of drug resistance.

[Pharmacodynamic and therapeutic pilot studies of single-agent ribavirin in patients with human papillomavirus-related malignancies]
Published in Oral Oncology
This paper reports on two small studies on the effects of the antiviral drug ribavirin in patients with HPV-associated cancers. The first is a pharmacodynamic study showing that ribavirin inhibits eukaryotic translation initiation factor 4E (eIF4E) in 4 of 6 evaluable patients, confirming that it is hitting the therapeutic target. In the therapeutic study in patients with recurrent and/or metastatic disease (n=12), treatment was shown to be tolerable but there was no signal of efficacy, with median PFS less than two months in 9 evaluable patients.

[RMAC study: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post salvage surgical resection in those who are ineligible for re-irradiation]
Published in Oral Oncology
This phase 2/3 trial assessed the combination of metronomic chemotherapy and celecoxib in recurrent head and neck cancer patients ineligible for re-irradiation. Patients were randomised to treatment or observation groups and followed for six months. At a median follow up of 30 months the 1- and 2-year DFS and the 1- and 2-year OS figures were significantly inferior in the treatment arm compared to the control arm and the trial therefore didn't move to its phase 3 part. 6-months of weekly low-dose methotrexate and daily celecoxib (200mg BID) is ineffective in this population.

[Pembrolizumab and maraviroc in refractory mismatch repair proficient/microsatellite-stable metastatic colorectal cancer - The PICCASSO phase I trial]
Published in European Journal of Cancer

In this phase I trial, (n=20), heavily pre-treated patients with refractory metastatic colorectal cancer and mismatch repair proficient/microsatellite stable tumours were treated with anti-PD1 and the anti-HIV drug maraviroc. This is a population which shows little response to checkpoint inhibition and there were few positive responses to treatment, although the main end-point of feasibility was achieved. However, patients treated with subsequent therapies, including rechallenge with previous treatments some showed very encouraging responses - intriguingly suggesting the combination treatment may work to reverse drug resistance in this population with few other options.

Preclinical data

Cell death-induced immunogenicity enhances chemoimmunotherapeutic response by converting immune-excluded into T-cell inflamed bladder tumors
Published in Nature Communications
As we have mentioned in previous newsletters, the search for repurposing agents able to turn immunologically 'cold' tumours into 'hot' tumours is highly active at the moment. In this study focusing on muscle-invasive bladder cancer, the authors show that chemotherapy induces the release of prostaglandin E2 from dying cancer cells, which in turn inhibits CD8+ infiltration into tumours. Using animal models the authors use celecoxib to block PGE2 and the reduction in CD8+ infiltration and cytotoxicity after chemotherapy treatment. In particular using this approach they show that immune checkpoint inhibition become 'visible' to immune checkpoint inhibitors. Clinical investigation of this approach, particularly with respect to the sequencing of chemotherapy and immunotherapy, is warranted.

Ribavirin inhibits cell proliferation, metastasis and prolongs survival in soft tissue Sarcomas by down-regulating both type I PRMT1 and Type II PRMT5
Published in Basic & Clinical Pharmacology & Toxicology
This preclinical study investigated the effects of the antiviral drug ribavirin on a panel of bone and soft tissue cell lines, showing that the anticancer actions of the drug were associated with downregulation of PRMT1/PRMT5.
Furthermore, *in vivo* treatment with doxorubicin, ribavirin or the combination was compared to untreated controls in mice bearing S180 allografts. Treatment with each drug alone reduced tumour growth but the combination was significantly more effective than either drug alone. Notably, ribavirin alone was shown to reduce the number of pulmonary metastases. These encouraging results in a class of hard to treat tumours warrants further preclinical and clinical investigation.

Other news in drug repurposing

European patent protection for medical uses of known products and drug repurposing

Published in Nature Biotechnology

It is often claimed that difficulty obtaining patent protection for drugs repurposed for a new medical use is a limiting factor in the success of drug repurposing. In this analysis the authors,(from the Centre for Law, Medicine, and Life Sciences at Cambridge University), put this idea to the test by examining data from the European Patent Office and the EMA to assess the evidence for this claim. The intriguing results show not only a very healthy growth of new medical use patents in Europe, but also that these outstrip the number of EMA approvals for repurposed drugs. Also notable is that the majority of the new use patents are held by pharma companies, and that they maintain (pay to renew) their portfolio. These findings raise more questions of course, but for those of us in repurposing this data-driven approach is welcome.