Latest news about drug repurposing in oncology #18

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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

Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in limb-salvage surgery for osteosarcoma: A retrospective analysis
Published in Medicine
Osteosarcoma remains desperately in need of new treatment options, as has been noted here before. This observational study compared osteosarcoma patients treated with limb-salvage surgery either with propofol-based total intravenous anesthesia (TIVA) or desflurane (DES) anesthesia. In addition, patients in the TIVA group had lower risks of postoperative recurrence and metastasis than those administered DES anesthesia. These retrospective data are highly supportive of prospective study, particularly as the choice of anesthesia is independent of chemotherapy backbone and therefore open to international study.

Propranolol blocks osteosarcoma cell cycle progression, inhibits angiogenesis and slows xenograft growth in combination with cisplatin-based chemotherapy
Published in Scientific Reports
Propranolol has already become one of the most interesting repurposing candidates in soft tissue sarcoma, particularly in angiosarcoma, and it is interesting to see that a number of groups are now looking at it in connection with bone sarcomas. In this study, the effects of propranolol were assessed *in vitro*, in 3-d spheroids and *in vivo*, alone and in combination with cisplatin. The results show that propranolol has multiple effects including reduced mitosis, G0/G1 cell cycle arrest, downregulation of Cyclin D1 and reduced migratory activity. The work is interesting, although the use of PDX models would be of benefit, as would the check of potential synergy with doxorubicin to complement these results with cisplatin.

Doxycycline inhibits the progression of metastases in early-stage osteosarcoma by downregulating the expression of MMPs, VEGF and ezrin at primary sites
Published in Cancer Treatment and Research Communications
Another *in vivo* osteosarcoma study, in this case using doxycycline to assess impacts on primary sites in xenograft models and on metastatic spread, including post-surgical pulmonary metastasis. The results are encouraging, showing effects on both primary disease and on metastasis. However, while encouraging, this is very preliminary work which requires further investigation in PDX models.

Nitazoxanide inhibits osteosarcoma cells growth and metastasis by suppressing AKT/mTOR and Wnt/β-catenin signaling pathways
Published in Biological Chemistry
Similarly, this paper is a pre-clinical study looking at nitazoxanide, an anti-parasitic drug, as a possible osteosarcoma candidate. Again, we have a mixture of *in vitro* and *in vivo* data showing that the drug reduces proliferation, migration and induces apoptosis in osteosarcoma cells. For a long time there has been little in the way of repurposing work in osteosarcoma, so it is a positive development to see four different candidates being published in this newsletter.

Clinical data

Clinical trials

A Phase II Randomized Trial of Chemoradiation with or without Metformin in Locally Advanced Cervical Cancer
Published in Clinical Cancer Research
In this small (n=13) randomised (2:1) window-of-opportunity trial, patients with hypoxic tumours were randomised to metformin + chemo-radiotherapy or

chemo-radiotherapy alone. All patients were assessed for changes in tumour fractional hypoxic volume after one week of treatment. Ten patients in the metformin arm showed reduction in hypoxic volume, compared to the three patients in control arm who showed an increase in hypoxic volume (p = 0.027). After 2.8 years of follow-up, the disease-free survival was 67% for the metformin arm vs 33% for controls (p=0.09). However, these results are severely limited by the small sample size and need replication in larger trials.

Metformin with Temozolomide for Newly Diagnosed Glioblastoma: Results of Phase I Study and a Brief Review of Relevant Studies
Published in Cancers
Another small (n=7) metformin dose-finding trial, in newly diagnosed glioblastoma patients who have completed standard treatment of chemo-radiotherapy. The key finding is that the phase II dose in this population should be 2250 mg/day, which is the highest dose used for type II diabetes. With such small patient numbers no conclusions can be drawn on efficacy, although the authors report that 5 of the 7 patients showed stable disease, and the 6-month PFS rate is 86%.

Pembrolizumab, radiotherapy, and an immunomodulatory five-drug cocktail in pretreated patients with persistent, recurrent, or metastatic cervical or endometrial carcinoma: Results of the phase II PRIMMO study
Published in Cancer Immunology, Immunotherapy
This trial, supported by the Anticancer Fund, explored the use of a 5-drug immunomodulatory cocktail (low-dose cyclophosphamide, aspirin, lansoprazole, vitamin D, and curcumin) in two cohorts of pretreated persistent/recurrent/metastatic cervical or endometrial cancer in combination with anti-PD1 + radiotherapy. The trial failed to acheive its primary objective in either cohort. Some patients did experience benefit, but we cannot exclude the fact that similar responses have been seen in patients treated with anti-PD1 therapy alone.

A randomized, open-label, multicenter, phase 3 study of high-dose vitamin C plus FOLFOX +/- bevacizumab versus FOLFOX +/- bevacizumab in unresectable untreated metastatic colorectal cancer
Published in Clinical Cancer Research
In this phase 3 randomised trial metastatic colorectal cancer patients (n=442) were treated with chemotherapy + bevacizumab + high-dose intravenous vitamin C or chemotherapy + bevacizumab alone. While overall survival, PFS and overall response rate were similar in both arms, a pre-specified subgroup analysis showed that patients harbouring RAS mutations had longer PFS in the vitamin C group (median PFS, 9.2 vs 7.8 months; HR, 0.67; 95% CI, 0.50-0.91; P =

0.01). This latter finding should therefore be directly tested in an appropriate clinical trial.

Phase II Proof of Concept Study of Atorvastatin in Castration Resistant Prostate Cancer
Published in BJUI International
In this small phase II single arm trial (n=12) patients with castration resistant prostate cancer (CRPC) were treated with androgen deprivation therapy and the addition of atorvastatin for six weeks. The primary end point was the proportion of patients achieving ≥50% PSA reduction from baseline PSA level. The study would have continued recruitment if two or more patients achieved this, but only one patient reached this level so further recruitment was stopped. Further analysis showed that of the 12 patients, half had a flattening of PSA velocity which is suggestive of disease stabilisation. The authors suggest that the study was supportive of statin activity but that the end point was too ambitious and the treatment period too short to give a stronger signal.

Observational studies

Concomitant medication of cetirizine in advanced melanoma could enhance anti-PD-1 efficacy by promoting M1 macrophages polarization
Published in Journal of Transnational Medicine
Given the wide heterogeneity in the responsiveness to treatment with checkpoint inhibitors in many cancers, the race is on to identify other agents which can either increase the number of patients who respond and/or the duration of those responses when they do occur. In this retrospective analysis advanced melanoma patients treated with anti-PD1 with concomitant cetirizine were compared to patients not taking cetirizine. Cetirizine-treated patients had longer PFS (28 vs 15 months, HR 0.46, 95% CI: 0.28–0.76; p=0.0023) and OS (36 vs 23 months, HR 0.48, 95% CI: 0.29–0.78; p=0.0032). Transcriptomic analysis revealed that M1 macrophage polarization may be induced by cetirizine through the interferon-gamma pathway, and that this may synergise with checkpoint inhibition.

Perioperative Beta-Blocker Supply and Survival in Women With Epithelial Ovarian Cancer and a History of Cardiovascular Conditions
Published in Journal of Clinical Oncology
Another propranolol study, this time a retrospective analysis of women over the age of 50 with epithelial ovarian cancer and cardiovascular conditions treated with perioperative beta blockers. The analysis compares women treated with non-selective beta blockers (mainly propranolol) versus women treated with selective beta blockers. Using a causal inference approach, the model suggests that perioperative use of NSBBs, mostly propranolol, is associated with overall

and cancer-specific survival for women diagnosed with ovarian cancer over age 50 years with a history of cadiovascular conditions. The survival advantage of perioperative NSBB supply was time dependent and became most apparent around 1-2 years after surgery, and was maintained at least 8 years post surgery - suggestive of a role in reducing post-surgical metastasis.