Care for Cancer - Drug Repositioning/Repurposing

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Anticancer Fund

Conflict of Interest: Nothing to declare.
Drug costs prompt fears of ‘financial toxicity’ in cancer care

High prices subject some patients to long-term collateral damage to incomes and health.

FDA chief: Cancer treatment comes with ‘financial toxicity’

Cascade of costs could push CAR-T to $1.5M per patient

Financial toxicity of cancer treatment

Up, up and away

Keytruda in new milestone with UK funding decision
Issue: Financial Toxicity


Predicted global increase in the incidence of all-cancer cases from 12.7 million new cases in 2008 to 22.2 million by 2030

Many established drugs are not affordable in LMICs. Many new drugs are not affordable anywhere! Health disparities will worsen – both intra- and inter-country

Issue: Neglected malignancies

Despite impressive improvements in some cancers – and incremental change in others – improvements in overall survival are stalled in sarcomas, ovarian, pancreatic and other solid tumours. Metastatic disease remains problematic in most cancer types.

Desouza et al. Has the survival of patients with glioblastoma changed over the years? *Br J Cancer* 2016

Osteosarcoma 5-year Overall Survival per Decade, (Allison 2012 Sarcoma - US data)
Issue: ‘Abandoned’ patients

Where do patients go when they have reached the end of the line?

Palliative care
- Go home and arrange your affairs...
- But doctor I’m still fit enough to carry on!

Clinical trials
- You’re eligible for this clinical trial
- Will it benefit me?

Off-label?
- There may be an option – but it’s not licensed....
- I’ve seen this cancer cure on the internet...

Lost to health system
- Go home and arrange your affairs...
- There’s a treatment in another country...

End of guideline treatments

Is it ethical to send a patient to an early phase trial or palliative care when there may be a potential therapy that is safe but unapproved in that indication?
Can repurposing make a difference?

The use of an existing licensed medication for a new medical indication

Existing drugs have:
- Extensive data on common and rare side effects
- Understanding of pharmacokinetics, pharmacodynamics, posology, etc.
- Widespread availability and (often) low costs
- Decades of clinical experience
- Knowledge of mechanisms of action

Faster

Speed up development lifecycle

Cheaper

Safer

Convenient

User-friendly

Example - Propranolol

On-label uses:
- Hypertension
- Angina
- Arrhythmias
- Thyrotoxicosis
- Anxiety
- Migraine prophylaxis
- Infantile hemangioma
- Angiosarcoma
- Perioperative therapy

Future Uses?

Commercial repurposing:
- Infantile hemangioma
The hemangioma story...

Incidental observation in a child treated with propranolol shows rapid and sustained effects on infantile hemangioma – results repeated in 10 other children.

Results confirmed in numerous patients and trials


Drug reformulated for infants

Hemangeol – FDA Approved March 2014

Hemangiol – EMA Approved Feb 2014

Successfully repurposed

But oncology?

Our focus is on the use of non-cancer drugs in oncology.

Evidence sources come from:
- Preclinical studies – in vitro, in vivo
- In silico modelling
- High-throughput screening
- Case reports (lucky accidents), case series
- Retrospective analyses
- Small clinical trials

The ReDO project uses a literature-based approach to explore all forms of data for hypothesis generation.

<table>
<thead>
<tr>
<th>All cancers (ReDO list – snapshot 22/03/18)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cancer drugs with anticancer evidence</td>
<td>252</td>
<td>100%</td>
</tr>
<tr>
<td>Have human data (cases, observational, trial)</td>
<td>180</td>
<td>71%</td>
</tr>
<tr>
<td>At least 1 trial</td>
<td>166</td>
<td>66%</td>
</tr>
<tr>
<td>Off-patent</td>
<td>214</td>
<td>85%</td>
</tr>
<tr>
<td>Included in WHO Essential Medicines List</td>
<td>83</td>
<td>33%</td>
</tr>
<tr>
<td>Validated molecular targets</td>
<td>1090</td>
<td>-</td>
</tr>
</tbody>
</table>

Most of these drugs are potential off-label treatments – used as-is at standard dosing – no commercial interest from pharma.

Previous snapshot has been published as a pre-print: https://www.biorxiv.org/content/early/2017/10/06/197434
Oncology – hard vs soft repurposing

Definitions:

**Soft repurposing** – taking a drug from one form of cancer and using it in another or in a different stage of treatment

**Hard repurposing** – taking a drug from outside oncology and using it as a cancer treatment

Soft repurposing is essentially the standard model in oncology – the majority of oncology treatments are developed and licensed for a specific oncology indication: one specific stage of treatment for one specific cancer type. Later this is extended to other cancers and other stages.

Hard repurposing is actually very rare. Examples include thalidomide for multiple myeloma, ATRA for APL, diclofenac for desmoid tumours.
ReDO’s initial round of selected drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Original Indication</th>
<th>MoA</th>
<th>Area of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole</td>
<td>Anti-parasitic</td>
<td>Microtubule disruption, Hedgehog pathway inhibition, anti-angiogenic</td>
<td>Adrenocortical, colorectal, NSCLC, melanoma</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Antacid</td>
<td>Cellular proliferation, immunomodulatory, cell adhesion</td>
<td>Colorectal, pancreatic, glioblastoma</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Antibiotic</td>
<td>Anti-angiogenic, direct anti-tumour effects, immunomodulation</td>
<td>Multiple myeloma, NSCLC, lymphoma</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Antifungal</td>
<td>Hh pathway inhibition, anti-angiogenic, autophagy induction, reverse MDR</td>
<td>BCC, NSCLC, prostate, breast (TNBC), pancreatic</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Angina</td>
<td>Chemo/radio-sensitisation, anti-hypoxic (HIF1-alpha)</td>
<td>NSCLC, prostate, colorectal</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>NSAID</td>
<td>Anti-angiogenic, immunomodulation, inhibition of platelet function ...</td>
<td>Desmoid tumors, neuroblastoma, periop</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Anti-hypertensive</td>
<td>Cellular proliferation &amp; migration, immunomodulation, anti-angiogenic</td>
<td>Angiosarcoma, breast cancer, periop</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Anti-malarial</td>
<td>Autophagy pathway, immune modulation, stromal effects</td>
<td>Glioblastoma, lung cancer</td>
</tr>
<tr>
<td>PDE5 inhibitors</td>
<td>Erectile dysfunction</td>
<td>Immune modulation, treatment sensitisation, anti-hypoxic</td>
<td>Head &amp; neck cancers, glioblastoma, melanoma</td>
</tr>
</tbody>
</table>

The full ReDO database will be published online later this year
Why is hard repurposing hard?

- Funding
- Licensing
- Buzz
- Experience
Efficacy is the single most important criterion by which to judge a repurposed drug – the same standards of evidence are required as for all other drugs in medicine.

Funding is required for...

- Clinical trials – pivotal clinical trials are expensive to design and run
- Pharma trials with expensive drugs are often cheaper for an institution to run than trials of generic drugs
- There is competition for patients – pharma pays a patient premium for recruitment to trials
- Public and philanthropic funding is often linked to having IP-protection (e.g. Horizon 2020)
- Statistical, logistical and administrative costs not covered by pharma
Licensing

Off-label prescribing can be effective in some indications –

- It is already a recognised standard treatment for that condition
- An ultra-rare disease where there is a consensus amongst all treating clinicians

Off-label use has downsides –

- Too dependent on individual physician preference
- No central repository for outcomes research or analysis
- Increased level of liability for prescribing physicians
- Drug may stop being used for primary indication

A new licence or label extension to an existing licence can trigger...

- Inclusion of the new indication in national formularies
- Updates to clinical guidelines
- HTA assessment and reimbursement
- Increased patient and clinician confidence
- Post-marketing surveillance and recording of outcomes

On-label use is preferred – but this depends on drug licensing
Licensing...

- Label extension can only be applied for by an existing license (market authorisation) holder.
- A label extension incurs additional costs.
- For generic drugs a manufacturer who invests in a new license risks competitors benefiting (no ROI).
- No mechanisms exist for a ‘public interest’ label extension.

*Verbaanderd et al. Repurposing Drugs in Oncology: Next Steps. Trends in cancer, 2017*
Oncology is like all fields of endeavour – we respond to incentives!

Scientific excitement (or hype) is a key driver

Academic KPIs are based on publications for communicating with peers

No direct incentives for clinicians to drive licensing

We need clinicians to run trials – but there are more pay-offs when working with the latest generation of sexy drugs than with old drugs like aspirin, metformin, propranolol etc:

- Publication in top journals
- Excitement of cutting edge science
- Good conference slots
- Pharma company benefits
- Institutional approval
- Intellectual excitement

Do we want oncology to be buzz-driven or patient-centric?
The literature is full of examples of successful repurposing trials – but they lead nowhere. Why?

- Small trials – often lacking suitable end points or large enough sample size
- Clinician-led – lacking the development mindset from pharma
- Publication is the final outcome – no momentum for follow up
- Low impact – missing the excitement of big pharma results

We can learn a lot from how commercial development proceeds

Pantziarka P. Scientific advice - is drug repurposing missing a trick? Nat Rev Clin Oncol 2017
Moving forward...

Increasing levels of scientific interest

More clinical trial activity:
- Metformin = 98
- Propranolol = 50
- Aspirin = 48
- Celecoxib = 22
- Itraconazole = 13
- etc

Drug repurposing is on the agenda at oncology conferences – big and small

Increasingly a subject discussed with policymakers: EMA, MHRA, national governments etc

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Proposed framework publicly-driven repurposing

Public/philanthropic investments

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Investigator-driven interventional trials

Clinical data on use of a non-oncology drug for a cancer indication

Free protocol assistance and/or scientific advice

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Other available data sources (e.g. bibliographic data, clinical observations)

Assessment by regulators: conditional label extension?

Clinical trial design?
- Low-interventional trials
- Pragmatic trials (e.g. Registry-based RCTs)
- Platform trials (e.g. adaptive MAMS trials)

Additional trials or RWE captured in cancer registries

Additional evidence required by regulators and HTA bodies to come to a final decision

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Increasing the range of drugs you can use increases the actionable targets.

The 250+ drugs on the ReDO list have 1100 validated targets between them.

It’s important to record the data – both for precision trials and clinical practice.

Many of the ‘old’ drugs are considered ‘dirty’ – but they are multi-targeted agents.

Response to angiotensin blockade with irbesartan in a patient with metastatic colorectal cancer.


Pantziarka et al. Front. Pharmacol, 2018
How do we make more progress?

1. More trials: we need better designed trials (more innovation needed in trial design!), more patients, more centres
2. Increased public and private funding for repurposing trials
3. Create new pathways to ensure positive early phase trial results are followed up
4. Create a ‘public interest’ label extension mechanism
5. Include data for all drugs in all precision medicine trials
6. Central repository for off-label usage data
7. Patients, doctors and other stakeholders need to lobby for change
Angiosarcoma is a rare vascular soft-tissue sarcoma with an incidence of 1 – 2 per million per year (SEER or NCIN data). They make up 2%-3% of all soft tissue sarcomas. Standard first line treatments are taxane or anthracycline-based chemotherapy, with surgery and radiotherapy options.

First-line anthracyclines:

Response rate around 25%. Median PFS 4.9 months. Median OS 9.9 months.

Wide range of evidence sources for anticancer effects of propranolol – lab work, animal models, retrospective human data, case reports, some trials...


Angiosarcoma/propranolol – multiple published case reports, on-going clinical trial. Anticancer Fund granted ODD


More prospective data needed! Other trials planned
Thank you for your attention

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