Drug Repurposing as a Source of Innovative Therapies in Osteosarcoma

Gauthier Bouche[1*], Pan Pantziarka[1,2]

[1] Anticancer Fund, Brussels, Belgium [2] The George Pantziarka TP53 Trust, London, UK * presenting author

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Background

- Chemotherapy and surgery achieve a **5-year event-free survival of 60-70% in localized osteosarcoma** (OS).
- **Little additional progress has been made since the 1980s** (Figure).

Osteosarcoma 5-year Overall Survival per Decade
From Allison 2012 Sarcoma (US data)

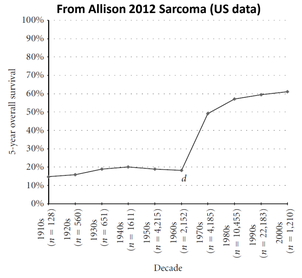
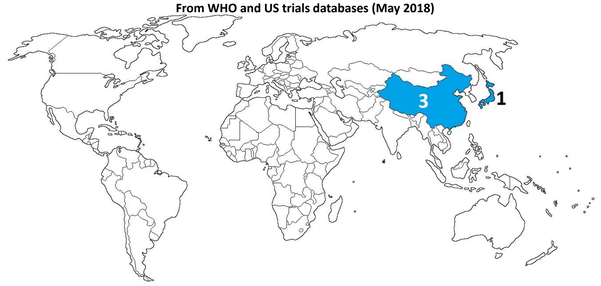


FIGURE 1: Osteosarcoma 5-year overall survival.

Location & Number of Randomized Trials in Localized Osteosarcoma powered for a Survival Endpoint
From WHO and US trials databases (May 2018)

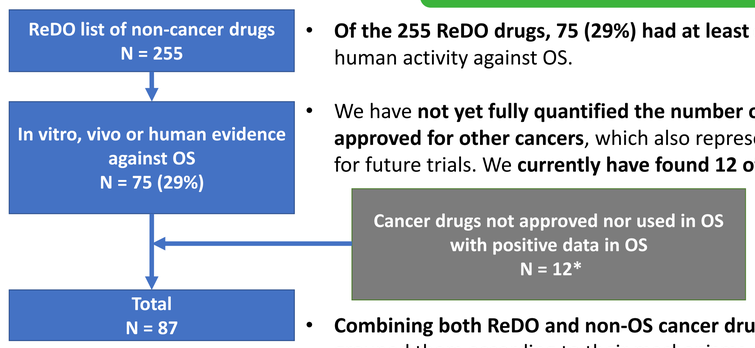


- **Few RCTs** with a survival endpoint in localized OS are ongoing (Map). No trial in Europe or North-America.
- Clinical research in OS is hampered by a **limited pipeline of new agents**.
  - **Drug repurposing**, an alternative development pathway that seeks to reuse existing drugs as the source of new treatment options, represents an interesting opportunity to solve this issue.
  - Repurposing benefits from existing data on safety, dosing and clinical use.
  - As of 22 May 2018, the **Repurposing Drugs in Oncology – ReDO – project** (Pantziarka 2014) has found 255 non-cancer drugs supported by evidence for use in cancer.

Objectives & Methods

- **<u>Objective:</u> Estimate the number of OS repurposing opportunities** of non-cancer drugs.
- **<u>Methods:</u>**
  - We started from our ReDO list of 255 non-cancer drugs with at least one peer-reviewed article showing an anticancer effect *in vitro*, *in vivo* or in humans.
  - We queried PubMed for each drug and the terms “osteosarcoma” and screened titles in search of articles reporting activity of the drug against OS. If at least one paper reported *in vitro*, *in vivo* or human data, it was considered positive. For a given drug, if all articles were about the management of disease-related or treatment-induced symptoms, it was not considered positive (e.g. antidepressant, anti-emetics).

Results



- **Of the 255 ReDO drugs, 75 (29%) had at least one article** reporting *in vitro*, *in vivo* or in human activity against OS.
- We have **not yet fully quantified the number of repurposing opportunities of drugs approved for other cancers**, which also represents an interesting source of interventions for future trials. We **currently have found 12 of them**.
- **Combining both ReDO and non-OS cancer drugs**, we **selected drug candidates** and grouped them according to their mechanisms of action **(Table 1)**.

Table 1: Selection of drugs grouped by their main mechanism of action & type of evidence for repurposing in OS

MoA Category	Drug *(main indication)*	Type of evidence	Main reference(s)	Comments
Cell differentiation	Calcitriol *(vitamin D deficiency)* All-trans retinoic acid *(APL)*	Animal model Case report / Animal model	*Shimizu Cancer Sci 2017* *Zhou Cancer Immunol Res 2017*	 Also immune modulation
Cytotoxicity & potentiation of chemotherapy	Simvastatin *(hypercholesterolemia)* Glucocorticoids *(inflammation)* Caffeine *(infant apnea)* Esomeprazole *(peptic ulcer)* Verapamil *(hypertension)* Piroxicam *(osteoarthritis)*	Animal model Animal model Human trial / Animal model Human trial / Animal model Case reports / In vitro Canine trials / Animal model	*Kamel Mol Cancer Ther 2017* *Kudawara Eur J Cancer 2001* *Kimura J Orthop Sci 2009* *Ferrari J Trans Med 2013* *Oudard Bull Cancer 1996* *London Plos One 2015*	 Used in OS patients in Japan Most research from the 1990s Piroxicam widely used in canine OS
Stem cells cytotoxicty	Metformin *(type 2 diabetes)* Disulfiram *(alcohol dependency)*	Animal model In vitro	*Ko Korean J Pediatr 2016* *Yu BMC Cancer 2017*	
Immunomodulation	Sirolimus *(prevention organ rejection)* Thalidomide *(multiple myeloma)*	Human trial / Animal model Case report / Animal model	*Morrow Clin Cancer Res 2016* *Tsai Lancet Oncol 2005*	
Epigenetic modifications	Decitabine *(AML)* Valproic acid *(epilepsy)* Vorinostat *(T-cell lymphoma)*	Animal model Animal model Animal model	*Al-Romaih Cancer Cell Int 2007* *Wang Front Immunol 2018* *Parrales Plos One 2018*	Also immune modulation Also immune modulation Also immune modulation
Cell-cell interaction	Aspirin *(CVD prevention)* Heparin *(VTE)* Warfarin *(embolisation)* Plerixafor *(stem cell mobilization)*	Animal model Animal model Human trial / Animal model Animal model	*Liao Clin Cancer Res 2015* *Ichikawa Cancer 2012* *Hoover Cancer 1978* *Liao Oncol Rep 2015*	 Also stem cells cytotoxicity

AML: Acute Myeloid Leukemia; APL: Acute Promyelocytic Leukemia; CVD: Cardio-Vascular Diseases; MoA: Mechanism of Action; OS: OsteoSarcoma; VTE: Venous ThromboEmbolism.

Conclusion

- **The number of opportunities to repurpose non-cancer drugs in osteosarcoma is large**. Adding cancer drugs to this list improves the number of candidates even further.
- **Making an objective selection is difficult because of the volume and heterogeneous quality of the data**. Only 2 drugs (neoadjuvant lithium & neoadj zoledronic acid) are currently being tested in RCTs in localized OS.
- **We have presented several other drugs that have a good rationale to be trialed in OS**.
- Implementing **the infrastructure for a multi-arm multi-stage platform trial** would be a great service to patients. An independent drug selection committee could assess drug candidates supported by human and/or *in vivo* evidence and make recommendations if additional evidence is needed. **We are currently looking for expression of interest** to participate in (clinicians, researchers, patients advocates) and fund (governments, philanthropic organizations) this effort.