

Drug Repurposing as a Source of Innovative Therapies in Chondrosarcoma

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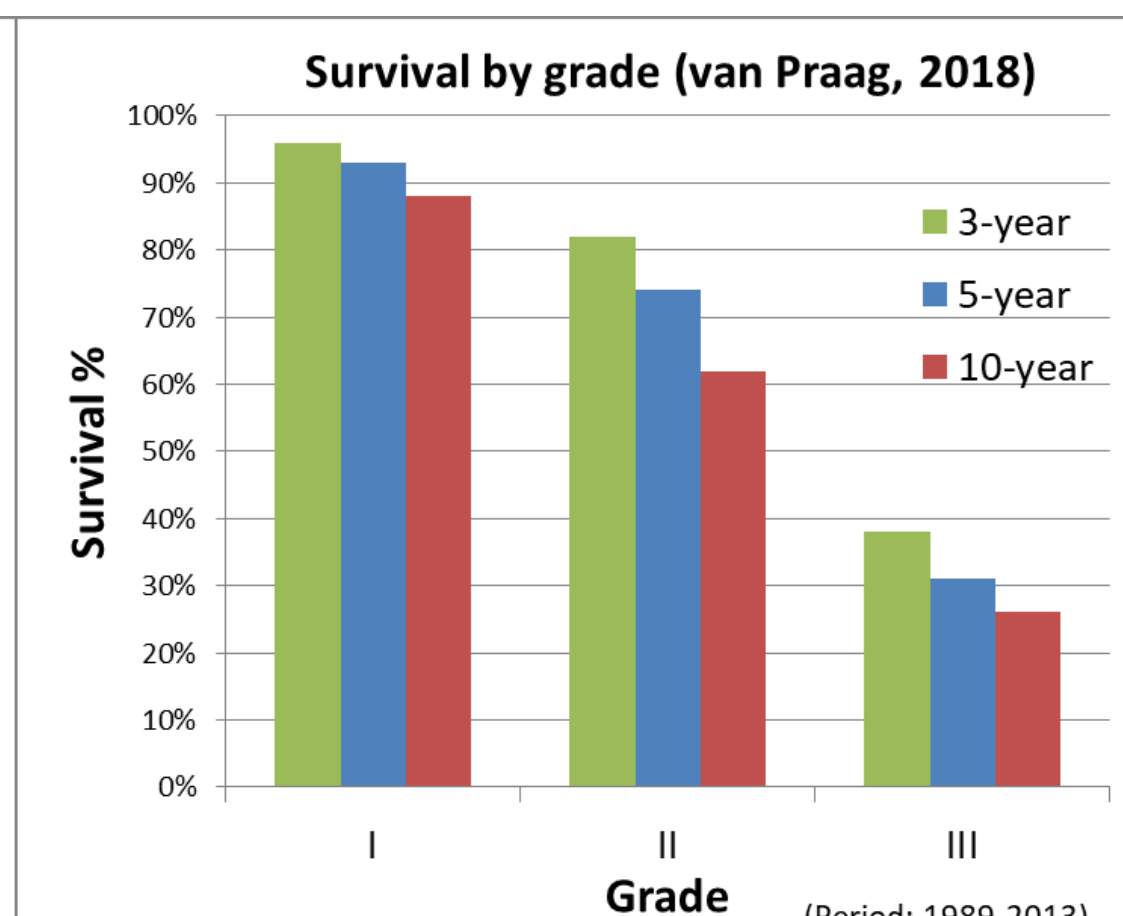
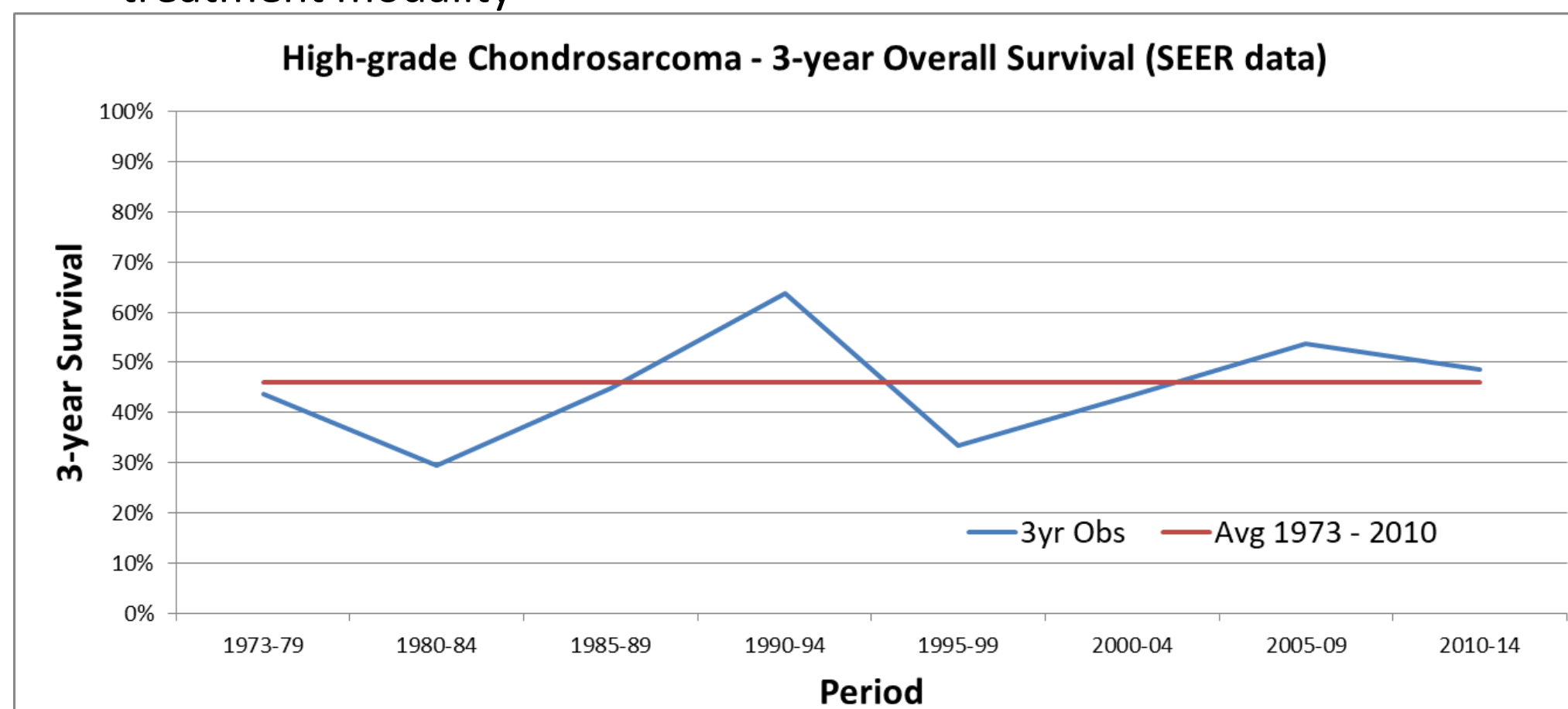
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Background

- Chondrosarcoma is the second most common bone malignancy after osteosarcoma, making up about 25% of all bone cancers. They are characterised as being relatively radio- and chemo-resistant – surgical resection is the prime treatment modality



- High-grade tumours are highly metastatic, particularly to the lungs
- Only 9 Phase II+ trials globally** – single Phase III trial on-going is proton beam therapy (NCT01182753)
- Clinical research in chondrosarcoma 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.
 - 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.
 - Previous work has shown that 75 of the non-cancer drugs on the ReDO database have evidence of activity against osteosarcoma (Bouche 2018), and 130 drugs against pancreatic cancer (Pantziarka 2018)

Objectives & Methods

- Objective:** Estimate the number of chondrosarcoma repurposing opportunities of non-cancer drugs.
- Methods:**
 - 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 term “chondrosarcoma” and screened abstracts in search of articles reporting activity of the drug against chondrosarcoma. If at least one paper reported *in vitro*, *in vivo* or human data (case report, observational or clinical trial 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).
 - A non-systematic search was made of drugs licensed for use in other cancers for PubMed articles showing activity in chondrosarcoma – *in vitro*, *in vivo* or human data

Results

ReDO list of non-cancer drugs
N = 255

In vitro, vivo or human evidence against chondrosarcoma
N = 20 (8%)

Total
N = 39

- Of the 255 ReDO drugs, 20 (8%) had at least one article reporting *in vitro*, *in vivo* or in human activity against chondrosarcoma.
- 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 have currently identified 19 with some human data.**

Cancer drugs not approved for use in chondrosarcoma but with human data (case reports, retrospective or clinical trial)
N = 19*

Repurposed non-cancer drugs

* Human data exists, (case report, observational or clinical trial). Underlined, on-going clinical trial

Acetylsalicylic acid	<u>Chloroquine</u> *	Melatonin	Plerixafor
Alendronic Acid	Ciprofloxacin	<u>Metformin</u>	Simvastatin
Amiloride	Disulfiram	Midazolam	<u>Sirolimus</u> *
<u>Caffeine</u> *	Doxycycline	Omeprazole	Valproic Acid
Celecoxib	Esomeprazole	Pioglitazone	<u>Zoledronic Acid</u> *

Repurposed cancer drugs

* Retrospective or early phase trial data exists

Carboplatin	<u>Gemcitabine</u> *	<u>Pembrolizumab</u> *	Vinblastine
Cisplatin	Imatinib	Ramucirumab	Vincristine
<u>Cyclophosphamide</u> *	Interferon Alfa-2b	Sunitinib	<u>Vismodegib</u> *
Epirubicin	Nivolumab	Temozolomide	Vorinostat
Etoposide	Pazopanib	<u>Trabectedin</u> *	

Conclusions

- The number of opportunities to repurpose non-cancer drugs in chondrosarcoma is relatively limited compared to some other cancers. Adding cancer drugs to this list increases the number of potential candidates.
- Making an objective selection is difficult because of the volume and heterogeneous quality of the data. Only 4 repurposed drugs (chloroquine and metformin (together), zoledronic acid and sirolimus) are currently being tested in early phase trials
- Additional pre-clinical work is required to identify new drug candidates. High-throughput screening, ‘omics analyses, data mining and other methods should be investigated
- We are currently looking for expression of interest from clinicians, researchers, patient advocates and funders to further explore opportunities for expanding clinical research in chondrosarcoma