Identifying New Drugs in Ultra-Rare Indications + Off Label Use

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Identifying drugs in ultra-rare indications

- **1. Better understanding of biology**

- **2. Clinical trials**
  - Equitable access to clinical trials
    - Phase 1 trials
    - Recruitment of specific tumour types
    - Mismatch between clinical trial population + composition of general cancer population
  - Financial implications: > 150 sarcoma subtypes

- **3. Off label use**
  - Subtypes with NO standard systemic therapy
  - Ultra-rare subtypes: challenges performing prospective trials
  - Safety profile well documented
  - Can inform design of prospective trials
  - Using real world data to streamline drug approval?

Acuña-Villaorduña A et al. Am Soc Clin Oncol Educ Book 43; e389838: 2023

Identifying drugs in ultra-rare indications

- Should we try to incorporate all 3:
- **1. Better understanding of biology**
- **2. Clinical trials**
- **3. Off label use**

An example in a rare cancer


Brief Report

EFFECT OF THE TYROSINE KINASE INHIBITOR STI571 IN A PATIENT WITH A METASTATIC GASTROINTESTINAL STROMAL TUMOR

HEIKKI JOENSUU, M.D., PETER J. ROBERTS, M.D., MAARIT SARLOMO-RIKALA, M.D., LEIF C. ANDERSSON, M.D., PEKKA TERVAHARTIALA, M.D., DAVID TUVESON, M.D., PH.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., SASA DIMITRIJEVIC, PH.D., BRIAN DRUKER, M.D., AND GEORGE D. DEMETRI, M.D.

GASTROINTESTINAL stromal tumors are a group of mesenchymal neoplasms that arise from precursors of the connective-tissue cells

- Gastrointestinal stromal tumours “very rare” diagnosis prior to introduction of imatinib
- Good rationale for using imatinib off label
- Subsequent prospective trials confirming the efficacy + safety of imatinib
- GIST not as rare as previously thought

Rare Cancers: We need a change of approach

BJC

EDITORIAL

British Journal of Cancer (2017) 117, 1255–1257 | doi: 10.1038/bjc.2017.321

Rare cancers: the greatest inequality in cancer research and oncology treatment

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Rare Cancers

- 170,628 rare adult solid cancers
- 806,023 common adult solid cancers
- Rare cancers
  - 18% all cancer diagnoses (mean incidence)
  - 15% of total ten-year cancer prevalence during 2010–2019

- Overall 5-year survival
  - Rare cancers: 52%
  - Common cancers: 68.7%

- 1995–1999 and 2015–2019 5-year survival rates increase
  - Rare cancers from 46.2% to 52.6%: 6.4%
  - Common cancers from 56.9% to 70.1%: 13.2%
- **<u>Majority rare cancer entities NO improvement in 5-year survival</u>**

de Heus E et al. Eur J Cancer 167; 103-111: 2022

Rare Cancers: We need a change of approach

Context for Sarcomas

- < 1% of all adult cancers
- 150 different subtypes

- Clinical Trials
  - Difficult to find a "basket study" for all 150 sarcoma subtypes
  - Clearly not financially feasible
  - Many subtypes are "ultra rare"

- If there a strong rationale for off label use
  - Why deny patients access to novel agents?
  - Particularly important as safety profile of drug or schedule being used for off label use is established

Angiosarcoma Project

- US + Canadian patients remotely share clinical data + biospecimens for research
- Over 18 months: 338 patients registered

- Whole-exome sequencing 47 tumors
  - Recurrently mutated genes including *KDR*, *TP53* + *PIK3CA*
  - *PIK3CA*-activating mutations primary breast angiosarcoma: Therapeutic rationale

- Angiosarcoma head, neck, face + scalp associated with
  - High tumor mutation burden + a dominant ultraviolet damage mutational signature
  - Subset: Ultraviolet damage may be causative factor + role for checkpoint inhibitors
  - 2 patients off-label PD1 inhibitors exceptional responses
- Trials + case series: responses to checkpoint inhibitors in angiosarcoma

Painter CA et al. Nat Med 26(2); 181-187: 2020
Wagner MJ et al. J Immunother Cancer 9(8); e002990: 2021
Ravi V et al. Cancer 128(18); 3383-3391: 2022
Rosenbaum E et al. J Immunother Cancer 10(4); e004149: 2022
Florou V et al. J Immunother Cancer 7(1); 213: 2019

Epithelioid Hemangio Endothelioma (EHE)

- All patients
  - WW Domain Containing Transcription Regulator 1 [*WWTR1*]-positive, n = 37
  - Transcription factor E3 [*TFE3*]-positive, n = 1
  - Disease progression before starting sirolimus
- 37 patients evaluable for response

- Best RECIST responses
  - Partial response: 4 patients (10.8%)
  - Stable disease: 28 patients (75.7%)
  - Disease progression: 5 patients (13.5%)

- Median follow-up: 41.5-month
  - Median PFS: 13 months
  - Median OS: 18.8 months

Stacchiotti S et al. Cancer 127(4); 569-576: 2021

Change of approach: Off Label Use

- There should be a clear rationale for off label use
  - Not just shooting in the dark

- Alveolar Soft Part Sarcoma (ASPS): anti-angiogenic agents
  - Spontaneous regression on surveillance
  - Investigated in a clinical trial simply because access to phase 1 trials
- Not every sarcoma center will have access to phase 1 trials!

- Clinical trial entry encouraged but NOT possible for every patient with every rare sarcoma subtype

- Phase 1 trials increasingly enrol specific tumour types
  - Harder to explore novel therapies in rare sarcomas

Discussion

- Inequality of care between patients with rare + common cancers
  - Early diagnosis, research funding, drug development

- Regulatory agencies
  - More flexibility for rare cancers

- Off label drug use is a critical approach in rare cancers
  - Clear rationale + justification