Molecular markers and clinical trial design – parallels between oncology and rare diseases?

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Problems of clinical trial design for targeted therapies

- “Personalized medicine”, often also called “precision medicine” is a form of medicine that uses information about a person’s genes, proteins and environment to prevent, diagnose and treat disease. (Definition according to the National Cancer Institute)

- Traditionally, the site of tumor origin, together with histology, was used to make treatment decisions. This approach has been changed to include molecular tumor characteristics.

- Markers presently used to guide decisions for precision medicine treatment with targeted agents are either protein based or based on the detection of genetic aberrations.

- With multiple targets based on multiple markers we are often close to the situation that we are faced with in rare diseases.


Design for predictive biomarker validation

- Marker-Interaction or Enrichment-Design?
- Marker-based Strategy Design
- Reverse Marker-based Strategy Design

Aim: Validate a given predictive biomarker
Figure 1. Four designs for marker validation studies. Shaded boxes indicate the arms used in the planned analysis. Parameters below each box are the expected response rate in each arm using the notation in Section 3. Designs 1–3 are described in [4]. Design 4 is a novel proposal.

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Design 2: Marker-Based Strategy

Register
Randomize

Marker Based Strategy Arm

Marker + Treatment A
Marker - Treatment B

Non-Marker Based Strategy Arm

Treatment B

\[ \phi_1 = \pi \theta_{A^+} + (1-\pi) \theta_{B^-} \]

\[ \phi_2 = \theta_B \]

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Design 3: Modified Marker-Based Strategy

Register
Randomize

Marker Based Strategy Arm

Marker + Treatment A
Marker - Treatment B

Non-Marker Based Strategy Arm

Treatment A

\[ \phi_2 = \theta_A / 2 + \theta_B / 2 \]

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Design for predictive biomarker validation

- Marker-Interaction or Enrichment-Design?
- Marker-based Strategy Design
- Reverse Marker-based Strategy Design
- Various proposals for adaptive designs
- Various proposals for statistical analysis strategy
Designs with intraindividual comparisons

- Idea: Compare progression-free survival (PFS) under current, biomarker-guided therapy with PFS under prior therapy (PFS = time to treatment failure (TTF))
- Determine proportion of patients with PFS ratio (PFS on current therapy/PFS on prior therapy) ≥ 1.3
- Pilot study on patients with refractory metastatic cancer (von Hoff et al. J Clin Oncol 2010)
- Aim: (Proportion with PFS ratio ≥ 1.3) > 15%

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Fig 2. (A) Illustration of the primary end point, progression-free survival (PFS) ratio, for the study. (B) Mechanics of the study. TTP, time to progression; MP, molecular profiling; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.
Fig 3. Comparisons of progression-free survival (PFS) on molecular profiling (MP) therapy (blue bars) versus PFS (time to progression [TTP]) on prior therapy (gold bars) for the 18 patients with a PFS $\geq 1.3$.

\[ \frac{18}{66} = 27\% \; ; \; 95\%–CI: \; 17\%–38\% \]

**Von Hoff et al. J Clin Oncol 2010;28:4887-4883**

Problems with intraindividual comparisons

- Comparison of patients who match to targeted therapy with those who do not is problematic
- Need to have pre-baseline tumor assessment
- PFS on prior therapy is often not assessed according to validated criteria and might therefore be not accurate
- Cut-off for PFS ratio is somewhat arbitrary
- PFS ratio is only valid if there is a strong correlation between the endpoints (Recall: PFS on prior therapy = TTF)

**Le Tourneau et al. Targeted Oncology 2012;7:253-265**
Molecularly targeted therapy independent of tumor type ("all-tumor trials")

- Example: von Hoff study (breast, colorectal, ovarian, miscellaneous)
- WINTHER trial:
  - Patients with all types of metastatic solid tumors resistant to last line of treatment
  - "Complete biological analysis" of matched tumor and normal biopsies.
  - Therapeutic decision based on an estimated drug efficacy scoring bioinformatics tool
  - Aim: PFS ratio > 1.5 in 50% of patients
- SHIVA trial: Randomized proof-of-concept phase II trial comparing therapy based on tumor molecular profiling vs. conventional therapy in patients with refractory cancer

Le Tourneau et al. Targeted Oncology 2012;7:253-265
Multi-arm, multi-stage (MAMS) trials

• Multi-arm trials are more efficient in investigating a number of treatments than a series of two-arm studies (Example $2 \times 2$-factorial design)

• Multi-arm, multi-stage designs allow adaptive focusing of recruitment away from insufficiently active treatments, preferably on an early, intermediate outcome measure

• Formalisation of idea: P. Royston and M. Parmar (Stat Med 2003;22:2239-2256)
MAMS-Design

Fig. 3.1 Schematic illustration of traditional “sequential” development process (a) and a MAMS design (b). In both, three novel treatments (T₁, ..., T₃) are evaluated against control (C) and only treatment 2 chosen for confirmation in Phase III. In (a) each treatment is compared to control in separate trials while in (b) only one control group serves for all treatments.

Molecular markers and clinical trial design


Infrastructure for clinical trials

- About 20% of adult cancer clinical trials fail to complete (Stensland et al. J Nat Cancer Inst 2014)
- Only 25% to 42% of superiority trials in oncology report success of the experimental treatment (Djulbegovic et al. PLOS ONE 2013)
- Concentrating on isolated trials done by single investigators will not lead to faster and more efficient developments
- While the steps towards multi-center trials and the creation of entity-specific, national and international study groups have been made in the past, professional coordination of all trial activities comprising all tumor entities is now warranted. This can best be achieved within a Comprehensive Cancer Center!
Conclusions

- For targeted therapies in oncology based on molecular characteristics, there are certainly parallels to the situation in rare diseases.

- There are developments in clinical trial design and statistical analysis strategies to meet the special needs (however, there is no special statistical methodology for this situation!).

- The most important prerequisite for the efficient conduct of studies is a comprehensive approach based on appropriate precision medicine infrastructure.

- Utility of molecular profiling for monitoring of disease and resistance e.g. by repeated (liquid) biopsies has to be further investigated.
References