Adaptive Design of Affordable Clinical Trials Using Master Protocols in the Era of Precision Medicine

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Outline

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- Master protocols to study multiple therapies, multiple diseases, or both (Woodcock and LaVange, 2017): Mechanism-based, “precision medicine” trials — “affordable” in cost, time, sample size.
- Examples of platform/umbrella and basket trials.
- Challenges in design and analyses of basket trials: adaptive design and innovations in statistical methodology, illustrated by one such trial currently planned at Stanford.
- Discussion

Table 2 of Woodcock and LaVange (2017 NEJM)

Trial	Description	Design	...
B2225	Basket	Phase 2	...
BRAF V600	Basket	Early phase 2	...
NCI-Match	Umbrella	Exploratory	...
BATTLE-1	Umbrella	Phase 2	...
I-SPY 2	Platform	Phase 2	...
Lung-MAP	Master protocol	Phase 2-3	...

Basket: Study single therapy for multiple disease(s)/subtypes
Umbrella: Study multiple therapies for single disease
Platform: Study multiple therapies that can exit and enter platform
Lung-MAP: Three drugs in phase 3 for NSCLC, with four molecular targets initially and trimmed to three.

BRAF V600 Mutations

BRAF V600 Mutations (Hyman et al., 2015)

- BRAF V600 mutations occur in about 50% of cutaneous melanomas and result in constitutive activation of downstream signaling through the MAPK (mitogen-activated protein kinase) pathway, based on articles in Nature (2002) and NEJM (2005).
- Vemurafenib (Roche/Genentech), a selective oral inhibitor of BRAF V600 kinase, is associated with response rate of 50% and improved survivals with BRAF V600E mutation-positive metastatic melanoma (NEJM 2011).
- Efforts by the Cancer Genome Atlas and other initiatives have identified BRAF V600 mutations in non-melanoma cancers (Lancet Oncology 2010, J Clin Oncology 2011, Nature Genetics 2013, JAMA 2014). “The efficacy of vemurafenib in these non-melanoma cancers has not been systematically explored, despite its therapeutic potential.”

BRAF V600 Basket Trial

- "The large number of tumor types, low frequency of BRAF V600 mutations, and the variety of some of the (non-melanoma) cancers make disease-specific studies difficult (unaffordable) to conduct."
- Phase 2 study of the drug for 6 "baskets" (NSCL, ovarian, colorectal, breast, multiple myeloma, cholangiocarcinoma) and a seventh ("all-others") basket which "permitted enrollment of patients with any other BRAF V600 mutation-positive cancer.
- "The goal of this study was to identify promising signals of activity in individual tumor types that could then be definitively explored."

Trial Design and Results

- “An adaptive Simon two-stage design was used for all tumor-specific cohorts in order to minimize the number of patients treated if vermurafenib was deemed ineffective for a specific tumor type. The primary efficacy endpoint was response rate at week 8. Kaplan-Meier methods were used to estimate progression-free and overall survival. No adjustments were made for multiple hypothesis testing that could result in positive findings.”
- 122 adults received at least one dose of vemurafenib (20 for NSCLC, 37 for colorectal cancer, 5 for multiple myeloma, 8 for cholangocarcinoma, 18 for ECD or LCH, 34 for breast, ovarian, and “other” cancers). 89% of these patients had at least one previous line of therapy.

Trial Design and Results

- Vemurafenib showed (a) “efficacy in BRAF V600 mutation-positive NSCLC” compared to standard second-line docetexal in molecularly unselected patients, and (b) for ECD or LCH “which are closely related orphan diseases with no approved therapies”, the response rate was 43% and none of the patients had disease progression while receiving therapy, despite a median treatment duration of 5.9 months.
- “One challenge in interpreting the results of basket studies is drawing inferences from small numbers of patients. ”

Challenges and How to Tackle Them

- Berry (2015) discusses other challenges in inference from basket trials:
  - Even though patients have the same biomarker, different tumor sites and tumor types may have different response rates, and simply pooling trial results across tumor types may mislead interpretation.
  - On the other hand, different tumor types may have similar response rates, and hierarchical Bayesian modeling can help borrow information across these types to compensate for the small sample sizes.
- Chen, Heyse and Lai (2018, Chapman & Hall/CRC) discuss the connections between frequentist error-controlling methods and Bayesian (in particular, empirical Bayes) methods to address multiplicity issues in the analysis of clinical trials data. Although they focus on evaluation of adverse outcomes of a new drug/medical product, the statistical problems are quite similar: adverse event types for the same body system-organ [genetic aberratings in organs under different "basket"/cancers], biological models of toxicity [mechanism-based background] of the treatment, etc. They also relate to the foundational works of Robbins, Stein and Efron in compound statistical decision theory for optimal balance between type I error and power and its relation to empirical Bayes approach.

Challenges and Opportunities

- Dr. Kummar recently collaborated with investigators at Loxo Oncology and other investigators at UCLA, USC, Harvard, Cornell, Vanderbilt, MD Anderson, and Sloan Kettering on designing and carrying out a basket trial involving seven specified cancer types and an eighth basket ("other cancers") to evaluate the efficacy and safety of larotretinib, a highly selective TRK inhibitor produced by Lox Oncology in South San Francisco, in adults and children who had TRK fusion-positive cancers. A total of 55 patients were enrolled into one of three protocols and treated with larotretinib: a phase 1 study involving adults, a phase 1-2 study involving adults and children, and a phase 2 study involving adolescents and adults with TRK fusion-positive tumors. The phase 2 study uses the recommended dose of the drug twice daily. The dose-escalation phase 1 study and the phase 1 portion of the phase 1-2 study do not require the subjects to have TRK fusions although the combined analysis only includes "patients with prospectively identified TRK fusions".

Challenges and Opportunities

- The primary endpoint for the combined analysis was the overall response assessed by an independent radiology committee. Secondary endpoints include duration of response, progression-free survival, and safety.
- At the data-cutoff date 7/17/2017, the overall response rate was 75%, and 7 of the patients had complete reponse and 34 had partial response (Drilon et al., 2018, NEJM). In the accompanying editorial of that issue of NEJM, André (2018) says that “this study is an illustration of what is likely to be the future of drug development in rare genomic entities” and that according to the Magnitude of Clinical Benefit Scale for single-arm trials recently developed by the European Society of Medical Oncology, “studies that show rates of objective response of more than 60% and a median progression-free survival of more than 6 months, as the study conducted by Drilon et al. does, are considered to have the highest magnitude of clinical benefit” in line with the pathway for single-arm trials of treatments of rare diseases with well-established natural histories to receive approval from regulatory agencies.

Challenges and Opportunities

- André (2018) also mentions that the study by Drilon et al. "did not find any difference in efficacy among the 12 tumor histotypes (including those in the all-other basket)", proving a successful "trans-tumor approach" in the case of TRK fusions with larotrectinib, but that "some basket trials have not shown evidence of trans-tumor efficacy of targeted therapies, notably BRAF inhibitors." He points out the importance of developing "statistical tools to support a claim that a drug works across tumor types" and to provide "a more in-depth understanding of the failure of some targets in a trans-tumor approach."

Adaptive Design of a Basket Trial in Drug Development

- Dr. Purzner has been working with a company that produces a potent and selective inhibitor of CK2 (casein kinase 2) for treatment of medulloblastoma (MB), which is a pediatric brain cancer. The drug is believed to be efficacious for other cancers that are associated with the hedgehog signaling pathway. Hence an adaptive design of a basket trial is used. The baskets includue (a) MB and rhabdomyosarcoma (RMS) for children, and (b) basel-cell carcinoma (BCC) , colon, pancreatic cancers for adults, together with (c) a basket of other cancers.
- Because of the company's plan to proceed first with the MB and BCC indications, phase 2 trials are first initialized using novel adaptive designs that improve Simon's two-stage designs (Bartroff, Lai and Shih, 2013). If at least one of these trials does not end in futility, then proceed to the basket trial.

Adaptive Design of a Basket Trial in Drug Development

- The overall adaptive design uses a three-stage design (group sequential trial with 3 groups) as in Bartroff-Lai-Shih. It augments the theory of adaptive designs by also including baskets if the first stage ends with continuation.
- The theory of these 3-stage designs has been worked out in a related problem — adaptive enrichment trials, an example of which is the DEFUSE 3 trial that recently appeared in NEJM (Albers et al, 2018).

Conclusion

- Woodcock and LaVange (2017) say: “With multiple questions to address under a single protocol, usually in an area of unmet need, and an extensive infrastructure in place to handle data flow, master protocols are a natural environment for considering innovative trial designs. The flexibility to allow promising new therapies to enter and poor-performing therapies to discontinue usually requires some form of adaptive design, but the level of complexity of those adaptations can vary according to the objectives of the master protocol.” Our recent work on adaptive design of a basket trial for a CK2 inhibitor illustrates both the new challenges and opportunities for adaptive design noted by Woodcock and LaVange, especially how the design should adapt to “the objectives of the master protocol” during the course of the trial.

Conclusion

- Woodcock and LaVange (2017) also point out that "two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis, enabling a broader set of objectives to be met more effectively than would be possible in independent trials." Our medical colleagues Drs. Kummar and Purzner have shown us not only the importance of the trial network and infrastructure mentioned by Woodcock and LaVange but also the connection to biomedical companies producing these drugs, and funding the study and how they can be connected to academic networks and consortia such as PBTC (Pediatric Brain Tumor Consortium) that will run the MB phase 2 trial.

Reference

- G.W. Albers et al. (2018). Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *New England Journal of Medicine*, 378: 708-718.
- F. André (2018). Developing drugs in orphan molecular entities — a paradigm under construction. *New England Journal of Medicine*, 378: 763-765.
- J. Bartroff, T.L. Lai, M.C. Shih (2013). *Sequential Experimentation in Clinical Trials.* Springer.
- J. Chen, J. Heyse, T.L. Lai (2018). *Medical Product Safety Evaluation: Biological Models and Statistical Methods.* Chapman & Hall/CRC.
- A. Drilon, T.W. Laetsb, S. Kummar, D.M. Hyman et al. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *New England Journal of Medicine*, 378: 731-739.

Reference

- D.M. Hyman et al. (2015). Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *New England Journal of Medicine*, 373: 726-736.
- J. Woodcock, and L.M. LaVange (2017). The Changing Face of Clinical Trials. *New England Journal of Medicine*, 377: 62-70.