Return of Research Results

Presented by Ted Gooley PhD

1:00pm-2:00pm

UW Husky Union Building

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Considerations for CT.GOV

Ted A. Gooley
Fred Hutchinson Cancer Research Center
Seattle, WA

- Historically, results from clinical trials often not reported
  - Some estimates suggest only 25% of trials are published
- FDA Modernization Act of 1997 required NIH create and operate public information resource
  - ClinicalTrials.gov, tracking drug efficacy studies resulting from IND
  - Primary purpose to improve public access to clinical trials
    - Purpose of experimental drug
    - Subject eligibility
    - Location of trial sites
    - Point of contact for enrolling

- FDA Amendments Act of 2007
  - Mandated expansion of CT.gov for better tracking of basic results of trials
    - Expanded registration requirements
    - Legally defined timeline with specifics on reporting of results (within one year of completion)
    - Failure to report carried potential fine of up to $10,000 per day
- Study of trials conducted between 2008 and 2012 found roughly 50% of trials required to report had not been reported
- Another study found that 74% of industry trials were either not reported or reported late; 90% of academic studies!
  - No fines!!
- NEJM article from late 2016 cites 224,000 studies registered to CT.gov, with only 23,000 that display results
  - Perhaps due to ambiguity of requirements

- This led to the “Final Rule”, developed by HHS and made available September, 2016
- Rule took effect January 18, 2017
- NIH simultaneously issued policy requiring registration and reporting of results for all NIH-funded trials
- Goals
  - Enable funders to assess need for new trials
  - More complete listing of trials to inform medical evidence base
  - Better enable examination of overall state of clinical research as basis for quality-improvement efforts
  - Ethical and scientific obligation to report results, regardless of what happened

- Defined “applicable clinical trials”, i.e., trials required to report results
- Deemed “controlled” clinical trials included single-arm Phase II
  - “all interventional studies with pre-specified outcome measures”, excluding Phase I clinical trials
- Results need to be reported within one year of final data collection for purposes of evaluation of primary endpoint
- Requires results reporting for primary endpoint, secondary endpoints
  - Tertiary, Exploratory, Correlative endpoints do not need to be reported
- What information needs to be reported?
  - 4 components

- Participant flow
  - Information about number who started and completed trial, by group
- Demographics and baseline characteristics
  - Age, sex, race and ethnicity required; other measures encouraged
- Outcomes and statistical analyses
  - Results primary and all secondary outcomes, including statistical analyses if relevant
- Adverse event information
  - Anticipated and unanticipated AE's, as specified in protocol, exceeding 5% frequency within any group
  - All SAE's

Outcomes and statistical analyses

- Be sure to CLEARLY state primary and secondary objectives and the endpoints that make up these objectives
- Do not specify “too many” secondary endpoints
  - This is not only good clinical-trial practice, but reduces burden of reporting
    - This is not to say that you can/should ignore important endpoints!!
- Make sure that you collect all data relevant to primary and secondary endpoints, and do so in a manner that allows you to estimate/assess these endpoints/objectives.

- Difference between objective and endpoint
  - Objective of a trial is to address the scientific question by collecting appropriate data
  - Selection of endpoint is made to address the objective of the trial
    - Endpoint should be clinically relevant, interpretable, sensitive to effects of proposed intervention, practical (and affordable) to measure, measured in an unbiased manner, easy to observe
    - Endpoints are typically continuous (e.g., BP or pain on visual analogue scale), categorical (including binary, e.g., response vs. no response), or time-to-event (e.g., time to death)

- Objective is formulated as a question, goal, or an aim, and is a phrase or sentence
  - Key words: determine, estimate, evaluate, assess
- Endpoint is an outcome
  - Determined for each patient, quantitative measurement required by objective

- A “bad” objective: “Determine the difference in outcome in patients with breast cancer”
  - What is outcome?
  - What are the treatment groups?
  - All patients with breast cancer?
  - Way too vague

- A “good” objective: “Estimate the difference in time to breast-cancer progression between chemotherapy alone and chemotherapy plus trastuzumab in women with HER2-positive metastatic breast cancer who had not previously received chemotherapy for metastasized disease”
  - Wordy, yes; but defines population, treatment groups, and outcome

Adverse Events

- Be sure to collect adverse events on a per-patient basis, allowing for multiple AE's for each patient (same kind or different kinds)
- Use common terminology, list type of AE and site
- Distinguish between AE as defined in protocol and SAE; all SAEs must be reported

Primary Objective

- To assess the pathologic response rate in patients with operable breast cancer treated with a two part, neoadjuvant regimen consisting of complete hormonal blockade (CHB) for 2 weeks followed by four three-week cycles of Xeloda, Methotrexate and Navelbine with continuation of complete hormonal blockade.

Secondary Objectives

- To assess the clinical response rate in patients with surgically resectable breast cancer treated with complete hormormonal blockade and four three-week cycles of Xeloda, Methotrexate and Navelbine.
- To assess the toxicity associated with these regimens.
- To assess the relapse rate, overall and disease-free survival in patients with operable breast cancer when treated with neoadjuvant CHB and XMN + CHB followed by adjuvant treatment using XMN or Taxol.
- To assess whether the phenotype of breast cancer changes with treatment.
- To assess whether phenotypic changes in breast tumors predict outcome.

Primary Objective

- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 0-24 hour time period following weekly intravenous doxorubicin.

Secondary Objective

- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 24-120 hour time period following weekly intravenous doxorubicin.
- Proportion of patients achieving a complete response (CR), defined as no emesis and no rescue medications in the 0-120 hour time period following weekly intravenous doxorubicin.
- Number of emetic episodes daily and cumulatively for the 24-120, and 0-120 hour time periods
- Time to first emetic episode
- Time to first administration of rescue medication
- Time to treatment failure (time to first emetic episode or administration of rescue medication, whichever occurred first)
- Side effects of antiemetic medications used
- Severity of nausea
- Quality of life

Objectives

Primary: To estimate the maximally tolerated dose of 131I-BC8 (anti-CD45) that can be delivered prior to autologous stem cell transplantation for patients with relapsed/refractory B-NHL, T-NHL, or HL.

Secondary:

- 1) To optimize the protein dose (Ab) to deliver a favorable biodistribution in the majority of patients.
- 2) To assess the radiation dose delivered to tumor sites and normal organs by the above therapy.
- 3) To evaluate the dose-response relationship of radiation-dose to tumor and clinical response.
- 4) To estimate the overall and progression-free survival of the above regimen in such patients.
- 5) To evaluate the toxicity and tolerability of the above therapy.
- 6) To evaluate the feasibility of delivering high-dose 131I-BC8 and ASCT to B-Cell NHL, T-NHL, and HL patients.
- 7) To evaluate the ability to reduce infusion reactions via unlabeled BC8 preinfusion.

Objectives

- The primary objective of this study is to:
- Determine anti-tumor activity as assessed by disease-free survival (DFS). Estimate the two year DFS rate in mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

- The secondary objectives of this study are to:
- To estimate the overall survival rate and evaluate time to treatment failure/remission duration.
- To describe non-relapse death events and the toxicity profile.
- Evaluate the biological markers of mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

Objectives

Primary objectives

- To assess the feasibility of expanding HER2 specific T cells ex vivo for infusion into subjects who have advanced HER2 overexpressing cancer.
- To assess the toxicity associated with infusing autologous HER2 specific T cells into patients using either a single dose of cyclophosphamide or ONTAK prior to T cell infusion.

Secondary objectives

- To investigate to what extent HER2 specific T cell immunity can be boosted in individuals treated with a single dose of cyclophosphamide or ONTAK followed by infusion of autologous HER2 specific T cells.
- To investigate the potential anti-tumor effects of HER2 specific T cells in patients with HER2 overexpressing advanced-stage cancers.
- To evaluate how long tumor antigen specific T cell immune augmentation persists in vivo after a single dose of cyclophosphamide or ONTAK followed by infusion of autologous HER2 specific T cells.

- Hypothesis: We hypothesize that advanced MRI techniques incorporating DCE and DWI MRI characteristics at 3T will enable reliable prediction of DCIS risk, defined by nuclear grade and advanced pathologic variables (HER2/neu, p16, cox-2, Ki-67, and Oncotype DXTM DCIS score), and can identify the presence of invasive disease missed during needle core biopsy.
- Specific Aims:
- Aim 1: Measure DCIS lesion characteristics on DWI and DCE MRI at 3T. We will measure the 3T DWI and DCE MRI characteristics in 12 DCIS lesions, 6 diagnosed as high grade (HG) and 6 diagnosed as non-high grade (NHG) by means of core needle biopsy. We will characterize these DCIS lesions qualitatively and quantitatively on DWI obtained at multiple b values, calculating apparent diffusion coefficient (ADC) and contrast-to-noise ratio (CNR) values of each lesion. An experimental DCE-MRI sequence will also be obtained with high spatial and temporal resolution, and characterization will be performed utilizing experimental kinetics assessments as well as standard BI-RADS descriptors of morphology and size.
- Aim 2: Identify predictive MRI markers at 3T for discrimination of DCIS grade. We will confirm histopathological data for all lesions from surgical excision and assess the correlation of imaging characteristics with pathologic biomarkers of DCIS. Statistical analysis will be performed to validate predictive markers that had been identified in our prior studies and to identify additional markers that significantly differ between HG and NHG DCIS. Utilizing the specific imaging markers identified to be independently predictive of DCIS grade, multivariate statistical analysis will be performed to optimize in vivo DCIS grade characterization. In addition, we will characterize DW and DCE MR features that predict for the presence of invasive disease in vivo.

Primary objective

- To evaluate the feasibility of “early” allogeneic hematopoietic cell transplant (HCT) for patients with relapsed or refractory (R/R) high-grade myeloid neoplasms. The feasibility of this trial is defined in Section 12.1.

Secondary objectives

- Estimate relapse-free survival (RFS), acute GVHD, TRM, event-free survival (EFS), overall survival (OS), and complete remission (with or without measurable disease) among patients who receive early HCT, Endpoint applicable to patients who don’t receive early transplant (survival endpoints and remission) will be also be estimated for all patients enrolled on the study.
- Assess factors that distinguish patients who receive early HCT from those who do not
- Compare RFS, EFS, OS, acute GVHD, and TRM between patients in the feasibility study and matched patients who were transplanted with standard scheduling
- Demonstrate the feasibility of collecting patient-reported outcomes and resource utilization data for trial participants
- Describe the outcomes of patients enrolled who went on to allogeneic HCT off-study

12.1 We would consider this feasibility study a success and plan to launch a randomized trial if: 1) we were able to enroll 30 patients per year (1/3 of the anticipated 90 who present with R/R AML) 2) we transplant at least 15 of the 30 patients within 60 days of start of induction therapy, and 3) among patients who are transplanted the observed 6-month relapse-free survival after transplant is 40% or higher

Primary Objectives

- Compare the time to neutrophil engraftment (ANC >500) in patients receiving a standard-of-care myeloablative CBT augmented with an off-the-shelf pre-expanded and cryopreserved cord blood product to those who do not receive the product.

Secondary and Exploratory Objectives

- Provide initial data on clinical and economic benefit, such as time to platelet engraftment, duration of initial hospitalization, transplant-related mortality (TRM), death without engraftment, and incidence of severe infections in the first 100 days post transplant. The kinetics of immune system recovery will also be evaluated in both arms.

Primary Endpoint

Time to engraftment (ANC >500) in both arms (standard myeloablative CBT with and without off-the-shelf expanded cord-blood progenitors).

Secondary Endpoints

1. Platelet engraftment (20k)
2. Incidence of infectious complications in the first 100 days post transplant
3. Overall Survival
4. Non-relapse mortality
5. Acute and chronic GVHD.

Exploratory Endpoints

1. In vivo persistence of the ex vivo expanded cord blood product
2. Duration of initial hospitalization
3. Grade? 3 infusional toxicity
4. Graft failure: Primary and secondary (see protocol section 13.0 for definition of graft failure)
5. Immune reconstitution: TCR sequencing (see protocol section 10.9)