Reporting Delays Documented in an Clinical Trial: Planned Remediation

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Clinical Center Hospital Board
October 21, 2016

Summary of points to be made in this presentation

- Significant delays in reporting serious adverse events were identified in a phase I intramural NCI clinical trial, leading to the issuing of a 483 inspection report from the FDA
- NIH must ensure a culture of safety and compliance as it pursues excellence in clinical research
- We will discuss these events and steps towards remediation

The acute event that brings this event forward

October 3, 2016: FDA issued a 483 report to the principal investigator of the trial citing:

- Delays and deficient reporting of Serious Adverse Events to the sponsor-protocol, which required expedited reporting of Grade 3-Grade 5 events to the sponsor within 24 hours; the median time of delayed reporting events was 40 days, with a range of 4-456 days.
- Delays and deficient reporting of Unanticipated Problems: protocol required expedited reporting to the IRB is 7 days; the median time of delayed reporting the 5 events was 18 days, with a range of 8 to 56 days.

The Clinical Trial: Treatment of Primary CNS Lymphoma (PCNSL)

- Rare subtype of diffuse large B cell lymphoma (DLBCL) that presents in the CNS (brain/leptomeninges/eye)
- 1900 cases a year in US; 3% of brain tumors
- Median age at diagnosis: 62 years
- Current treatment based on methotrexate and radiotherapy
- Outcome of newly diagnosed PCNSL: Variable
- Outcome of refractory PCNSL (failed response to standard chemotherapy): 4-6 month survival
- No major treatment advances in past 10 years

Rationale for experimental treatment approach for PCNSL trial

- Basic research at NCI identified a tyrosine kinase BTK as a key driver of diffuse large B cell lymphoma (DLBCL)
- Published trial from NCI showed ibrutinib (BTK inhibitor) is clinically effective in relapsed/refractory DLBCL; led to phase III registration trial of ibrutinib [Imbruvica®]) for DLBCL, and FDA approval
- BTK inhibition had not been evaluated previously in PCNSL
- The poor outlook for patients with PCNSL led the investigators to add multidrug chemotherapy to BTK inhibition with ibrutinib

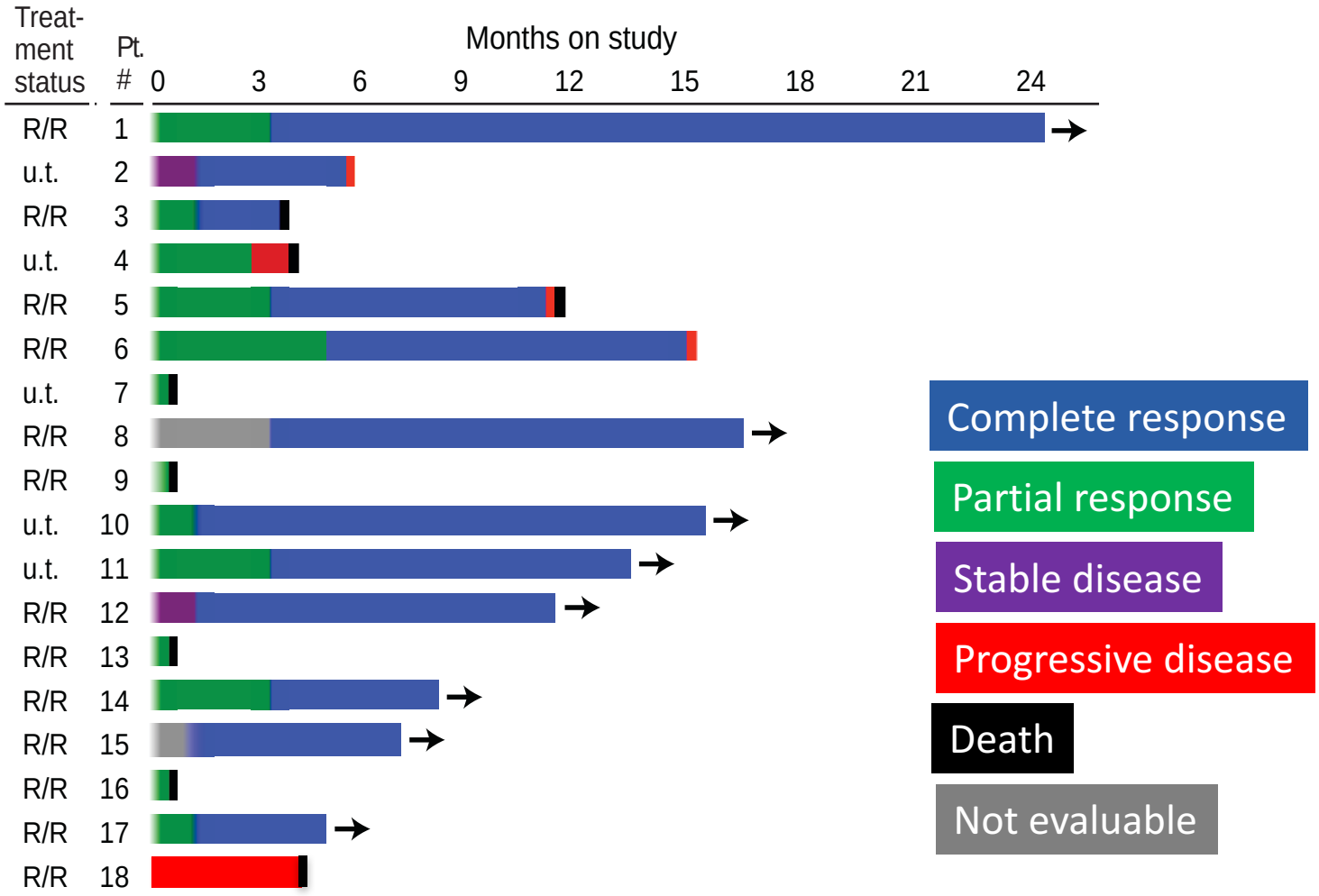
NCI Clinical Protocol 14-C-0157

- 18 symptomatic patients with primary CNS Lymphoma enrolled between August 2014 and March 2016
  - 13 relapsed refractory (RR) CNS lymphoma
  - 5 previously untreated (UT) CNS lymphoma
- Patients were treated with the DA-TEDDi-R regimen (Dose-Adjusted Temozolomide, Etoposide, liposomal-Doxorubicin, Dexamethasone, Ibrutinib, and Rituximab)
  - Drugs chosen that can cross the blood/brain barrier
  - Preclinical studies demonstrated synergistic properties
- Each patient received 14 days of ibrutinib (with corticosteroids to prevent cerebral edema) followed by six 21-day cycles of DA-TEDDi-R

Clinical Trial Results

- 18 patients enrolled on trial; the status of the tumor burden in 2 patients was not possible to track accurately (limited to eye fluid & spinal fluid)
- Of the 16 other patients,15/16 (94%) had objective tumor reductions, and 13/16 (81%) achieved at least a partial radiographic response
- But 4 patients developed invasive aspergillosis (a serious fungal infection known to occur in immunosuppressed individuals); 3 others had possible (unconfirmed) *Aspergillus* infections
- 2 patient deaths in 2015 were attributed to aspergillosis
- Hospital epidemiology service confirmed that there was no evidence of an *Aspergillus* outbreak in other protocols

Summary of patient outcomes



- Of the 8 patients who are in remission, 6 had recurrent refractory lymphoma, and 2 had untreated lymphoma

Increased and Unexpected Frequency of Aspergillosis in Trial Participants

- Invasive aspergillosis is a serious fungal infection that usually develops in the lung, in immunosuppressed patients
- Aspergillosis developed in some patients while only treated with steroids and ibrutinib, suggesting a causative relationship
- The seriousness of the *Aspergillus* infections prompted the investigators to halt accrual in April 2016, once the relationship to the study drugs became clear, despite the anti-tumor activity
- The suspected relationship between *Aspergillus* infections and treatment with ibrutinib/steroids was not reported to the FDA until late May 2016

Remediation for NCI lymphoma team

Already done:

- Hold accrual to current studies and opening of planned studies from the lymphoma team until complete audit and training have been done
- Notify all patients and families in the PCNSL trial of the delayed reporting – by phone contact, to be followed with a letter
- Suspend Principal Investigator from conducting clinical research in the Clinical Center
- Shift the Principal Investigator designation of the PCNSL trial to the Chief, Medical Oncology Service

To be done:

- Review all prior audits performed by the sponsor of lymphoma trials for the past three years
- Conduct 100% source documentation audit by outside contractor for all lymphoma trials open for the last three years
- Require full lymphoma team take part in external GCP training course

Remediation for NCI

Already Done:

- Instruct all Principal Investigators throughout the NCI intramural Center for Cancer Research to report safety and regulatory information on all accruing therapeutic IND trials
- Conduct an audit of informed consents within the CCR, NCI

To be done:

- Recruit a physician with substantial regulatory and compliance experience to function within the Office of the Clinical Director, NCI, working closely with the trans-NIH Office of Research Support and Compliance
- Review all sponsor audits within past three years, noting any trends in deficiencies
- Develop a formal quality assurance plan for all clinical trials regardless of sponsor or type of study

Remediation for all Clinical Center protocols

Already done:

- Reach out to NIH Institute and Center Directors, Clinical and Scientific Directors, Principal and Associate Investigators on clinical protocols, trial sponsors, and IRB Chairs, to underscore the critical importance of timely reporting of SAEs, UPs, and changes to or deviations from the research protocol
- Notify IC Directors and Clinical Directors of requirement to assemble information from Principal Investigators in their IC of how SAEs and UPs in current research protocols have been reported to the IRB, the sponsor, and the FDA

To be done:

- The Office of Research Support and Compliance (ORSC) will query all NIH IRBs to identify whether there have been other instances of delayed reporting of adverse events to the IRB
- The ORSC will initiate a rigorous audit of a sample of clinical protocols in all ICs that use the Clinical Center, prioritizing those that are regulated by the FDA

Summary

- NIH must prioritize patient safety and regulatory compliance, while pursuing excellence in clinical research protocols that seek to provide hope for conditions that currently lack effective interventions
- The PCNSL trial provides a dramatic example of an experimental therapeutic intervention that provided life-extending benefits to some participants and severe consequences to others.
- Recognition and public discussion of the failure to follow reporting requirements for the PCNSL trial is a learning opportunity that must not be missed.
- At the levels of the Lymphoma Team, the NCI, and the entire NIH, aggressive steps are being taken to ensure that this kind of reporting failure does not happen in the future.
- The recently established centralized Office for Research Support and Compliance is a critical addition to trans-NIH oversight of clinical research.
- Our first responsibility is always to the safety, compassion, and care of our patients, and we must hold ourselves to the highest standards.

Summary of patient outcomes