Defining and Assessing Clinical Benefit Scientific Perspective

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POTENTIAL CONFLICTS OF INTEREST

- Stealth Peptides: Research Support, Travel, Consulting
- Horizon Pharma: Research Support
- Reata Pharma: Research Support
- American Academy of Neurology: CPT and Speaker
- Modis Therapeutics: Consulting
- NeuroVive Pharmaceutical: Consulting
- MitoBridge Astellas: Consulting

MY LIFE AS A CLINICAL TRIALIST

1987-2016: Brain Tumors

1987-Current: Neurofibromatosis

1999-Current: Mitochondria

PHASE 3 BRAIN TUMOR CLINICAL TRIALS

1. Medulloblastoma; 450 children per year diagnosed in the USA
2. 90% cared for in a defined care network of children's hospitals: Children's Oncology Group (Funded by the NCI)
3. Known outcomes stratified by tumor stage and now genetics
4. Agreed-Upon outcome measures (5-year disease-free survival)
5. Many of the drugs were already FDA-Approved
6. All commercial insurers and state Medicaid plans paid for care on both arms of studies as "standards of care"

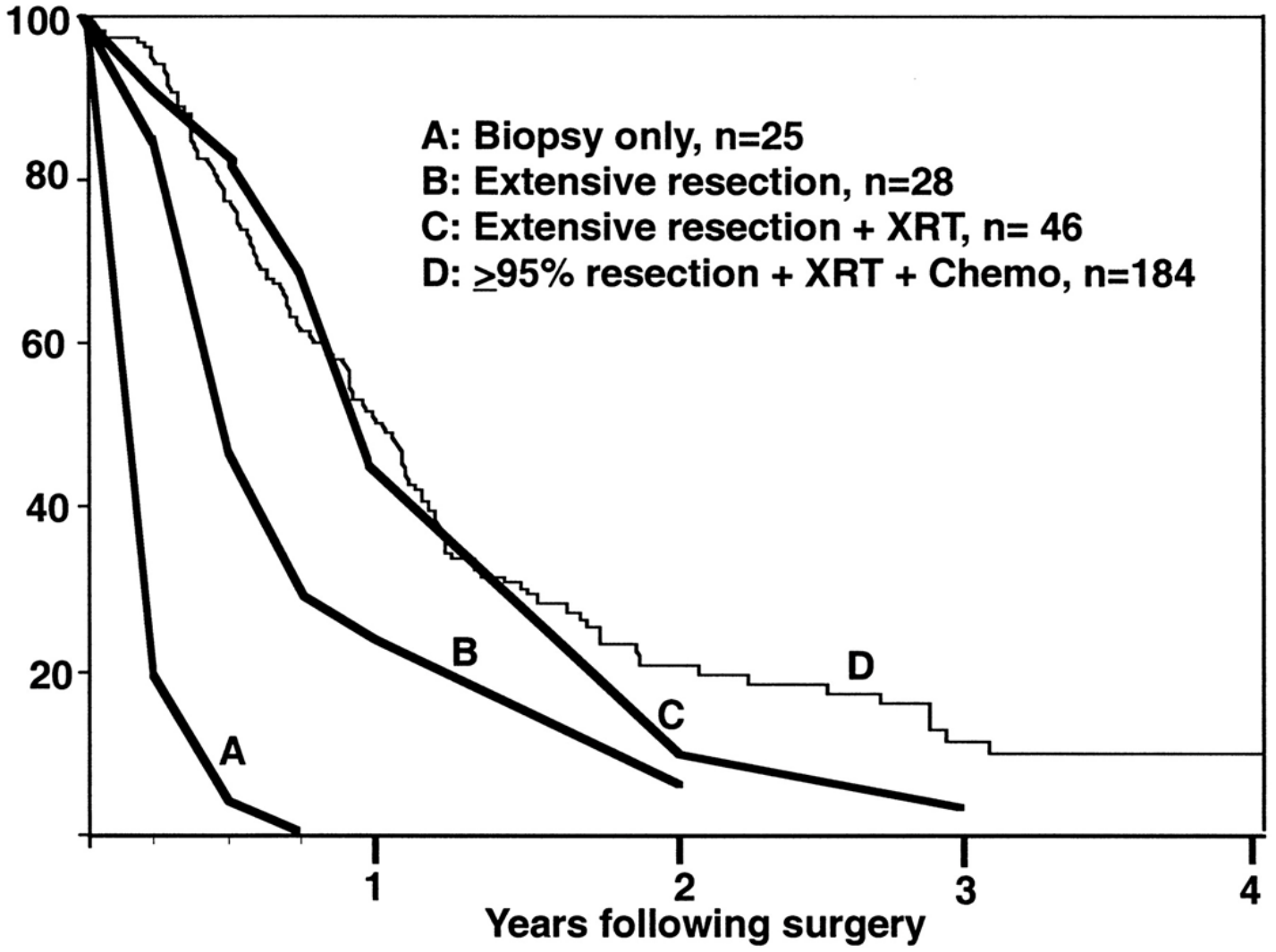
STANDARD THERAPY FOR MEDULLOBLASTOMA

1. 1930: Surgical Resection
2. 1950: Surgical Resection + Craniospinal XRT (3600 cGy + 1800 Boost)
3. 1980: Surgical Resection + Standard XRT + CCNU
4. Late 1980s: Surgery, XRT+CCNU/CPPD/Vcr
5. 1990s: Surgery, dose of XRT risk stratified, different chemo options
6. 2000s: No XRT option for infants
7. 2010s: Genetic based stratification for treatment

- Time to Progression
- Time to Death

TRIALS
GIVE
CLEAR
RESULTS

Tiny Error Bars



Brain Tumor Clinical Trials

STANDARD THERAPY FOR MITOCHONDRIAL DISEASE

REVIEW | Genetics inMedicine

Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

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Consensus-based recommendations are provided for the routine care and management of patients with primary genetic mitochondrial disease.

WHY ARE MITO DISEASES UNIQUE WITH RESPECT TO DETERMINING AN EFFECTIVE TRIAL DESIGN?

1) Many Diseases (geneotype-phenotype)
2) Which Outcome Measure(s) to evaluate?
3) Long and unpredictable clinical course
4) Swings in function with prolonged periods of disease inactivity
5) Difficulty in getting patients to meet entry criteria
6) Statistical considerations
7) Cost
8) Travel
9) Quality of Data

N Engl J Med. 1983 Aug 18;309(7):390-6.

Treatment of lactic acidosis with dichloroacetate.

Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI.

Abstract

We administered dichloroacetate, which prevents or reverses hyperlactatemia in animals and lowers plasma lactate levels in human beings, to 13 patients with lactic acidosis of various causes. All had hypotension, and their acidemia had resisted treatment with sodium bicarbonate. The metabolic effects of dichloroacetate were evaluated in 11 patients. In seven dichloroacetate significantly reduced the level of arterial blood lactate (P less than 0.005) from the base-line value and raised the levels of arterial blood bicarbonate (P less than 0.02) and arterial pH (P less than 0.005). In six of these seven, the acidemia resolved completely with therapy. In 10 of the 13 patients systolic blood pressure increased by 10 to 40 mm Hg, and 4 patients had a 21 per cent increase in cardiac output (P less than 0.02). Despite improvement in their lactic acidemia, all patients but one died of their underlying disease. No serious drug-related toxicity occurred. We conclude that dichloroacetate is a safe and effective adjunct in the treatment of patients with lactic acidosis, although the ultimate prognosis may depend on the underlying disease.

PMID: 6877297 DOI: 10.1056/NEJM198308183090702

What was the First Clinical Trial for Mitochondrial Disease in Humans?

ANOTHER FIRST

Archives of Disease in Childhood 1997;77:535–541

CURRENT TOPIC

Treatment of congenital lactic acidosis with dichloroacetate

Peter W Stacpoole, Carie L Barnes, Matthew D Hurbanis, Sterling L Cannon, Douglas S Kerr

2012 COCHRANE REVIEW
TREATMENT FOR MITOCHONDRIAL DISORDERS
PFEFFER G, MAJAMAA K, TURNBULL DM, THORBURN D, CHINNERY PF
HTTPS://DOI.ORG/10.1002/14651858.CD004426.PUB3

- Inclusion Criteria
  - Randomized controlled trials
  - Mitochondrial disease based on clinical, biochemical, histopathology, and/or genetic findings
  - Pharmacological agent, dietary modification, nutritional supplement, exercise therapy or other treatment
  - The primary outcome measures included an change in muscle strength and/or endurance,or neurological clinical features. Secondary outcome measures included quality of life assessments, biochemical markers of disease andnegative outcomes.
- Exclusion
  - Potential for bias
  - High risk studies

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- 1335 Abstracts Reviewed
  - 21 met initial criteria
  - Only 12 met strict inclusion/exclusion criteria
  - One (dicloroactetate) demonstrated peripheral nerve toxicity
  - High dose CoQ10 (n=30); no meaningful clinical improvement
  - 3 creatine trials; one with muscle strength and post-exercise lactate improvement, other two negative (n=38)
  - CoQ10-Creatine-Lipoic Acid; peak ankle dorsiflexion strength benefit, n=16
  - 5 DCA Trials: 3 showed improvement in secondary outcome measures but no clinical benefit (n=63)
  - Dimethylglycine: no clinical benefit
  - Whey-based supplement: statistically significant improvement in markers of free radical reducing capacity but no clinical benefit (SF-36 questionnaire and UK Medical Research Council (MRC) muscle strength,) n=13

What Did the Data Show?

WHAT IS OBVIOUS

- 1. When "we" started with sponsor-supported studies in about 2009 (1999, 2005) "we" had little knowledge of what success would look like.
- 2. There was little natural history data that we could rely upon
- 3 . When "we" all started sitting down, we were not sure how we were to measure success

WHAT IS OBVIOUS, OR NOT

- 1. There are many mitochondrial diseases and it is not reasonable to think one therapy could work for many or all of them
- 2. Most mitochondrial diseases have more than one organ system involved
- 3. Even as a whole, mitochondrial diseases have orphan status
- 4. The natural history of most mitochondrial diseases is not yet defined
- 5. Cochrane Review states that standard vitamins and cofactors have not been shown of benefit in well-designed trials
- 6. We have not established a "base" therapy

DEFINITION OF MITOCHONDRIAL DISEASE IN *EARLY* CLINICAL REPORTS AND TRIALS

- Included patients defined by the phenotype only
- Included patients defined by their ETC enzymatic dysfunction
- Included patients with abnormal muscle histology as the defining feature
- Included patients defined by secondary LHON mutations
- Included patients with unconfirmed pathogenicity of the mtDNA and mitochondrial targeted nDNA genes
- Included patients having a mitochondrial disease based on the investigator's *definition* of mitochondrial disease

DEFINITION OF MITOCHONDRIAL DISEASE IN *CURRENT CLINICAL TRIALS*

Patients with verified mutation(s) in mtDNA or mitochondrial-targeted nDNA genes that cause a phenotypic illness that is known to be associated with the identified mutation

Sometimes 'enforced' by an adjudication committee

WHAT IS THE BIG DEAL FOR SUCH A TIGHT DEFINITION FOR STUDY INCLUSION?

WHAT THERAPIES ARE WE TALKING ABOUT?

Vitamins and Cofactors	• CoQ10, levocarnitine, various B vitamins, creatine monohydrate, and others
Foods	• MCT oil, ketogenic diet, whey protein, etc.
Exercise	• Physical therapy, occupational therapy, traditional exercise, and others
Devices and Standard Care	• Ventilatory, enteral and parental feeding, hydration
Repurposed (FDA-approved) medications	• Cysteamine (RP-103)
New Drug Development (not yet FDA-approved)	• Disease modifying agents, biologics, gene editing; EPI-743, elamipretide, RTA-408

CLINICAL TRIALS IN MITOCHONDRIAL DISEASES

The Good

Patient Motivation

Engaged Investigators

Organized Patient Support Groups

New Biopharm interest

The Bad, The Ugly

Few patients & many diseases

Natural history variable and uncharted

No easy to define clinically relevant endpoints

In the young, end points like dystonia (in Leigh syndrome) are exceedingly difficult to define and measure over time

In many disorders fluctuation of measurable endpoints are common even in untreated

DESIGNING THE PERFECT PHASE 2 & 3 STUDY

- Define a "tight" study group
  - Leigh syndrome
  - Mitochondrial myopathy
- Choose Clinically Relevant Endpoints carefully
  - No second chances
  - Engage the FDA to be involved in the choice of endpoints
  - Patient reported outcomes are becoming critical to the FDA
- Hopefully have a treatment that excites patients and researchers
  - The treatment needs to be worth the travel involved
- Ensure proper funding
- Do not get "cheap" on the Controlled Clinical Trial: placebo arm, double blinded, some type of crossover or add-on
- The trial site must be totally dedicated to the recruitment of patients
- In the case of rare diseases, the family support networks must also have a buy-in and help with recruiting patients.

DESIGNING THE PERFECT PHASE 2 & 3 STUDY

- Phase 2
  - Trial size
  - # of trial sites
  - Disease Models: all, genotype, phenotype, age, symptom based
  - Endpoints
  - Duration
- Phase 3
  - All the above issues and
  - Choosing a standard therapy (or choosing a placebo therapy)
  - Crossover design vs. Parallel vs. Sequential Parallel Comparison Design (the non-responders in the placebo are re-randomized; counteracts the placebo effect.
  - Need for an Open-Label extension phase (which interferes with recruitment into other studies)

OUR SUCCESSES

- Quality partnerships between individual trial sites and sponsors in the small pharmaceutical space
- The sponsors have provided promised funding for the trials
- Agreement on what is a Mitochondrial Disease
- Patient Advocay Groups & networks - UMDF, MitoAction, & NAMDC databases instrumental in recruitment
- Additional International groups are lined up to support this work.
- Trial results are encouraging and projects are moving forward
- FDA Participation as Partners

CONTINUED CHALLENGES

- Most mitochondrial diseases do not have a sensitive and specific biomarker
- Choosing clinically relevant endpoints remains a challenge
- Moving past classic trial design (randomized controlled trials) for diseases with small populations of patients has not occurred
- Natural history study data is still limited
- Subject Identification and Enrollment

LEIGH SYNDROME ROADMAP PROJECT

NATURAL HISTORY

CLINICALLY RELEVANT OUTCOME MEASURES FOR CLINICAL TRIALS

PRE-CLINICAL MODELS AND BIOMARKERS

CHILDHOOD LEUKEMIA, WELL FUNDED, TOOK 20 YEARS OF WORK BEFORE BENEFITS WERE RECOGNIZED