Cognitive Testing and Patient Reported Outcomes in Brain Tumor Clinical Trials

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Cognitive Dysfunction

- Net clinical benefit of cancer therapy includes “beneficial effects on disease-related symptoms and/or quality of life” (Working group of FDA & NCI members)

- Maintaining function particularly important since long-term remission or cure is unlikely, or accompanied by significant disability

Clinical Benefit to Patient

- Relief of tumor-specific symptoms
  - Symptoms of mass lesion in brain
  - Progressive disruption of brain function
  - Anatomic evidence does not fully map function

Measurement of Tumor-Specific Symptoms

- Patient subjective report of symptoms (headache, nausea, etc.)
- Objective assessment of symptoms (cognitive function, mood)
- Objective assessment of function (ability to perform ADL’s)

Evaluation of Cognitive Function: Clinical Research Questions

- What are the cognitive problems prior to treatment
- Do different treatment regimens
  - improve neurocognitive function due to better tumor control
  - slow expected neurocognitive deterioration due to tumor
  - have more or less short and long-term neurotoxicity

FDA Input in Brain Met Trial of Radiation Sensitizer

- “Radiological response alone is not acceptable for approval. However, improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints”

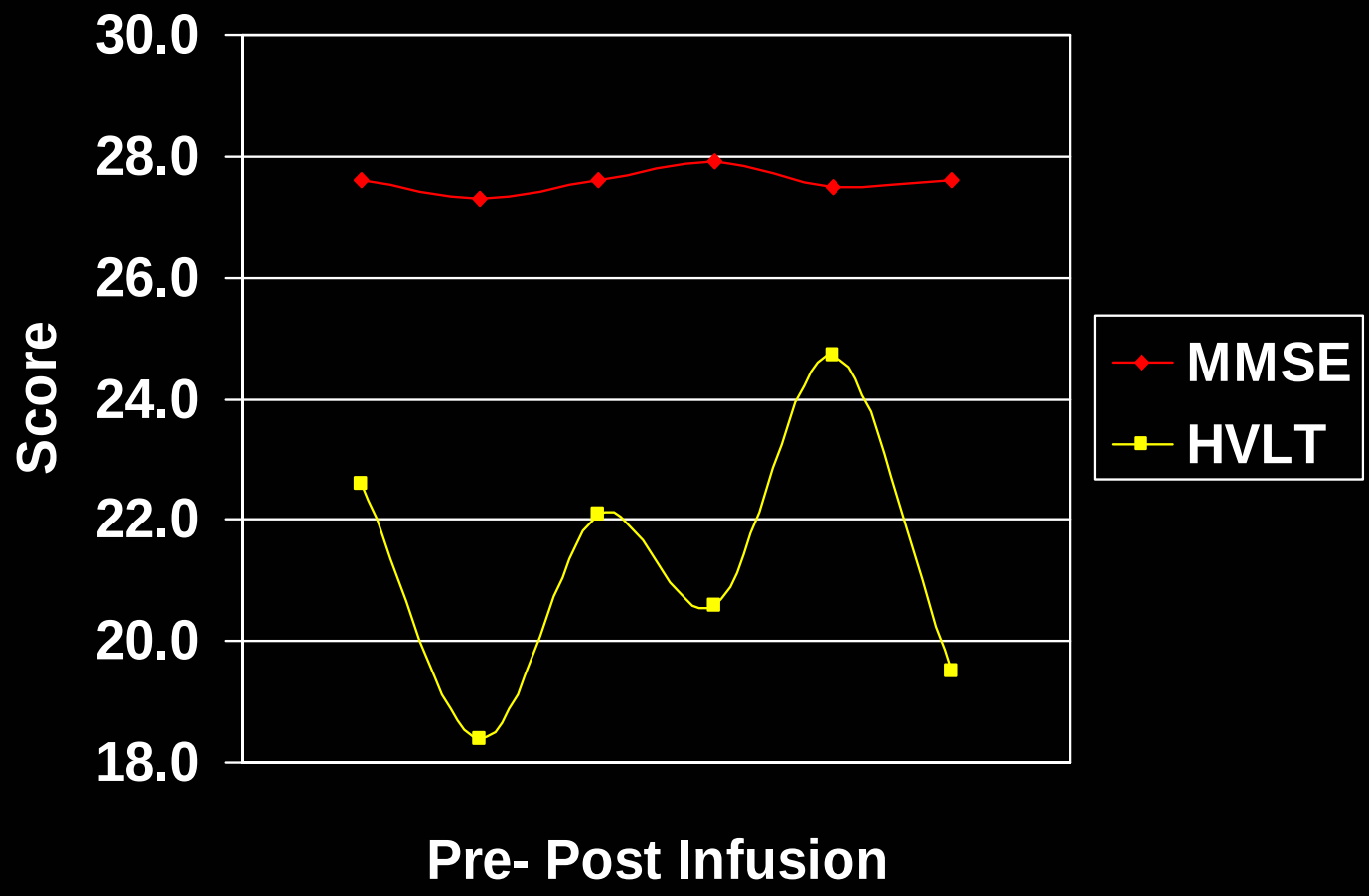
Trials Ongoing/Planned

- Radiosurgery +/- WBXRT
- Doses of PCI in SCLC
- +/- PCI in NSCLC
- WBXRT +/- radiation sensitizer
- Avastin for GBM
- Neurogenic agents for XRT injury

Evaluation of Cognitive Function: Assessment Issues

- Performance status (KPS) has little relation to cognitive function and QOL
- Brief mental status exams only detect delirium or significant dementia
- Self-report of cognitive problems (i.e., questionnaires) correlate poorly with objective test results

Pre- and Post-Infusion of CI-980



Characteristics of Assessment Battery

- Brief (on the order of 30 minutes)
- Repeatable (alternate forms, minimal practice effect)
- Good psychometric properties
- Sensitive to changes in function
- Highly standardized, simple administration
- Able to be completed by most patients
- Measurement of relevant cognitive functions
  - Tumor related cortical versus treatment related subcortical patterns of dysfunction
- Oversight by a neuropsychologist

Analytic Validity of Cognitive Tests

- Published validity and reliability, and population norms
- A priori established significant change defined
- Standardized in a manner that variations among assessors/sites is minimal (requires formal certification and QA procedures) and battery can be imported into community settings

Analytic Validity of Cognitive Tests Pediatric Brain Tumor Trials

- Tests are developmentally appropriate
  - Selection guided in part by longitudinal design during which tests may change
- Consideration of normal versus altered cognitive development after treatment in long-term survivors

Analytic Validity of Cognitive Tests

- Confounders need to be identified (adjuvant medications, medical complications like seizures)
- Frequency of assessment should parallel other staging evaluations, and be relevant to usual disease course
- Testing cannot stand alone without correlation with anatomic response and neurologic outcome, but cognitive deterioration may occur in advance

Ideal Characteristics of PRO

- Based on disease and treatment related symptoms, with less emphasis on social function and satisfaction with life
- Sound psychometric properties
- Able to be completed by persons with cognitive deficits
- Sensitive to change over time

Caveats of PRO

- Patients need to have adequate cognitive function to complete
- Often suboptimal psychometric properties
- Reporting bias
- Proxy assessments problematic for subjective symptoms
- Need buy-in from investigators to reduce missing data
- QOL change does not parallel cognitive change and cannot be used as a proxy

Standardized Approach to Assessment?

- Ability to compare different agents in different clinical trials
- Recommendation of BTPRG to develop a “practice guideline protocol”
  - Core of standard content for investigators to select tools appropriate to evaluate specific drug/hypothesis

What Trials Need Alternative Endpoints?

- Only RCT (risk/benefit, cost effectiveness, primary vs secondary endpoint)?
- Phase I/II single arm trials (e.g., safety monitoring, comparison to other I/II trials)?