Trial Designs for Older Oncology Patients

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Overview

• Problem
• Endpoints
• Designs
Problem

Under representation of older adults
Definition of “older”

Frail and older

Frail and not older

Older and fit
Enrollment in NCI Trials

- 28% of patients diagnosed with cancer ≥ 75 years old
- <10% of patients enrolled on trials ≥ 75 years old
Cancer incidence projections

- Cancer is a disease of aging
- 61% of all cancers diagnosed in 2010 in older adults
- 70% of all cancers diagnosed in 2030 projected to be in older adults
Age related differences in treatment

- Biology of cancer may change
- Less aggressive treatment used
- Increased vulnerability to treatment toxicity
Problem

Knowledge gaps regarding older and/or frail adults with cancer

- How to care for patients with physiologic/cognitive decline
- How to care for patients with comorbidities
Endpoints
What is important to older patients
Most trials

- overall survival
- disease-specific survival
- progression-free survival

Older patient concerns

- not most important outcomes
- no indication of QOL
- no indication of maintenance of function
Alternate endpoints

- Co-primary endpoints
- Composite endpoint
- Treatment failure-free survival
- QOL
- Functional independence
Need to determine, not assume

• Patient focus
• Preliminary evidence
  o many not interested in standard outcomes
  o maintenance of function is very important
  o quality over quantity
Trial Designs
How to obtain information of treatment effects in older patients
Randomized trial with age specific strata

Representative age sample: use specific enrollment goals for different age strata

**PROS**
- allows for greater generalizability
- one trial for all

**CONS**
- likely not powered to detect different cancer biology
- reduced accrual rate
- lack of older patient focused endpoints
Randomized trial: older patients only

patients $\geq$ 65 OR frail patients

experimental treatment

control treatment

Superiority or Non-inferiority

EXAMPLE

### PROS
- appropriate for age-related changes that affect treatment efficacy
- focus on patient preferred outcomes
- recruitment aimed at elderly (frail) patients

### CONS
- may require a large sample size
- patient population difficult to recruit
- treatments may not be standard
Embedded (correlative) study

A phase 2 study incorporating sorafenib into the chemotherapy for older adults with FLT3-mutated acute myeloid leukemia: CALGB 11001


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• Sub-study within the parent protocol
  additional measurements of interest to geriatric oncology
• Example goals
  • characterize the patients (other than just old)
  • identify predictors of treatment toxicity / tolerability
  • identify predictors of treatment benefit
  • understand treatment impact on functionality
Embedded study

**PROS**
- characterizes the population
- identifies geriatric factors associated with tolerance, AEs, functional decline, and benefit

**CONS**
- older patient subset may be small
- if embedded study is optional, may bias results
Single arm trial

• Evaluation of drug for which limited data in older adults
  phase II design for agent already tested in phase III
• Example goals
  • evaluation of efficacy and compare to phase III data
  • evaluation of tolerability / adverse events
  • identify predictors of AEs based on GA or biomarkers
  • assess PD/PK in older patients

Single arm trial

**PROS**

- incorporates older patient focused endpoints
- provides data for knowledge gap of efficacy, AEs, tolerability in older patients, PD/PK, etc.

**CONS**

- no concurrent controls
Extended trial

Positive Phase III

- older pts not represented → reopen superior arm for older pts
- older pts represented → STOP
Extended trial

**PROS**
- trial infrastructure in place
- easier accrual since efficacy established
- additional data regarding treatment tolerability / efficacy

**CONS**
- feasibility of re-opening a trial that was closed considerable period
- accrual only to superior arm, no control
Pragmatic trial

- Patients randomized at point of care in routine practice
- Broad eligibility criteria
- Minimal data collection burden

Examples in oncology

Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial

D. Waller, M.D. Peake, R.J. Stephens*, N.H. Gower, R. Milroy, M.K.B. Parmar, R.M. Rudd, S.G. Spiro, on behalf of all BLT participants

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RCT
evaluate the addition of chemotherapy to primary treatment

Cluster randomized trial
evaluate quality of care of LCP versus standard of care for hospitalized patients

Cluster randomized trial
evaluate impact of palliative care versus standard cancer care in patients with advanced cancer
Conclusions
How to get better representation of older patients?

• Address question(s) relevant to older population
• Remove barriers for participation in clinical trials
• Be clever about design