

Designing Trials in older individuals

Dr Swaratika Majumdar

Consultant and Assistant Professor

Ramaiah Medical College and HCG-MSR, Bangalore

swaratikam@gmail.com

Types

- Clinical Trial Methodology
- Observational Studies
- Collaborative Consortia

Timing

- Diagnosis
- Therapy and toxicity
- Survivorship issues
- Attitudes/KAP studies

NEED?

What is OLD?: Arbitrary definition?

Patient Selection:

- Heterogeneity observed among older patients of the same chronological age
- Tools

CGA: FIT OLDER : FRAIL AND UNFIT : UNFIT AND NON-FRAIL

Under-representation

ORIGINAL ARTICLE

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Courtney D. DiNardo, M.D., Brian A. Jonas, M.D., Ph.D., Vinod Pullarkat, M.D., Michael J. Thirman, M.D., Jacqueline S. Garcia, M.D., Andrew H. Wei, M.B., B.S., Ph.D., Marina Konopleva, M.D., Ph.D., Hartmut Döhner, M.D., Anthony Letai, M.D., Ph.D., Pierre Fenaux, M.D., Ph.D., Elizabeth Koller, M.D., Violaine Havelange, M.D., Ph.D., [et al.](#)

World J Gastroenterol. Nov 14, 2016; 22(42): 9378-9386

Published online Nov 14, 2016. doi: [10.3748/wjg.v22.i42.9378](https://doi.org/10.3748/wjg.v22.i42.9378)

Folfinirox in elderly patients with pancreatic or colorectal cancer-tolerance and efficacy

Jean-Florian Guion-Dusserre, Aurélie Bertaut, François Ghiringhelli, Julie Vincent, Valérie Quipourt, Sophie Marilier, Zoé Tharin, Leila Bengrine-Lefevre

ORIGINAL ARTICLE

CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma

Bertrand Coiffier, M.D., Eric Lepage, M.D., Ph.D., Josette Brière, M.D., Raoul Herbrecht, M.D., Hervé Tilly, M.D., Reda Bouabdallah, M.D., Pierre Morel, M.D., Eric Van Den Neste, M.D., Gilles Salles, M.D., Ph.D., Philippe Gaulard, M.D., Felix Reyes, M.D., Pierre Lederlin, Pierre Lederlin, Ph.D., [et al.](#)

Age specific trials vs Age un-specified trials

- Specific trials vs Extrapolation
- Phase II vs Phase III
- Frail/Unfit vs Fit, Non frail
- Stratifications?
- Examples:
 1. Cisplatin ineligibility in HNSCC
 - Standard exclusion based on retrospective analysis

Box 1. Pros and cons of age-specific trials.

Factors favoring separate trials

- Improve accrual
- Focus on toxicity and function
- Integration of geriatric assessment
- Determine which Comprehensive Geriatric Assessment domains are factors in outcome
- Results focused on older population
- Withdraw reluctance on the part of medical community to enrol older patients
- Safer, with less toxicity

Factors against separate trials

- Support current age bias
- Limit participation in 'aggressive' trials or trials of new agents
- Competitive trials
- Add to trial expense

Drug trials

- Concept of dose escalation
- Instead of dose → level of comorbidities or functional dependence allowed could be increased → 6/cohort to account for heterogeneity

End points? Beyond OS

- | | |
|--|---|
| <ul style="list-style-type: none">• OS: Leads to exclusion of elderly• DFS/PFS → ? Better• Coprimary endpoints• Composite endpoints: Therapeutic success• TTF• QOL: EORTC elderly-specific QoL module, Q-TWIST• Maintenance of functional independence | <ul style="list-style-type: none">• Health-related quality of life• Therapy related side effects and burden of treatment• Overall treatment utility• Maintenance of active life expectancy |
|--|---|

Designing Trial

Table 2. Issues in Clinical Trial Design for Older Patients With Cancer
Issue
RCTs remain gold standard when possible
Clinical trials should preferably integrate whole age range, including fit and frail older individuals
Elderly-specific clinical trials in older patients with cancer are required if standard therapy is different from that for younger patients
Trials of treatment strategy comparing different strategies (eg, therapy v best supportive care) should be encouraged
Randomized phase II or even single-arm phase II trials in specific subsets of older patients can provide insight into range of efficacy and toxicity in older populations but ideally should be confirmed in large phase III trials, which might be hard to perform for various reasons (eg, insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries in community can provide further insight for frail population with less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated into future trials in geriatric oncology
Regulatory authorities should require evaluation of efficacy and safety of new drugs in older and frail patients as well as in younger patients

Abbreviation: RCT, randomized clinical trial.

Trials of Treatment Regimens Versus Trials of Treatment Strategies Versus Observational Cohort Studies

1. CALGB (Cancer and Leukemia Group B) 49907 (Alliance):

→ Single vs Polychemotherapy as adjuvant therapy in breast cancer >65 years

→ Incorporated Bayesian study design → smaller population at risk of ineffective therapy

2. Treatment strategy:

ACTION trial → Recruitment failure

Cohort: Retrospective or Prospective

- In your clinic
 - Geriatric assessments
 - Efficacy safety data
 - Dietary, Demographic and Social issues
- Prospective Cohort
 - Validation studies
 - Develop tools

Collaborative study

- CARG/NIA/NCI → task force
- SIOG
- GERICO

- Expand eligibility criteria
- Allocate treatment according to fitness
- Increase retention of enrolled subjects

**Enroll
vulnerable
and frail
older
patients**

**Select
relevant
endpoints
for older
adults**

- Quality of life
- Physical function
- Tolerability

**Utilize
novel trial
designs and
strategies**

**Include
geriatric
assessment
tools**

- Extended trials
- Pragmatic trials
- Prospective cohorts

- Toxicity prediction
- Treatment allocation
- Longitudinal follow-up

