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Trial Designs for Older Oncology Patients

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14 September 2018

Overview

- Problem
- Endpoints
- Designs

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Problem

Under representation of older adults

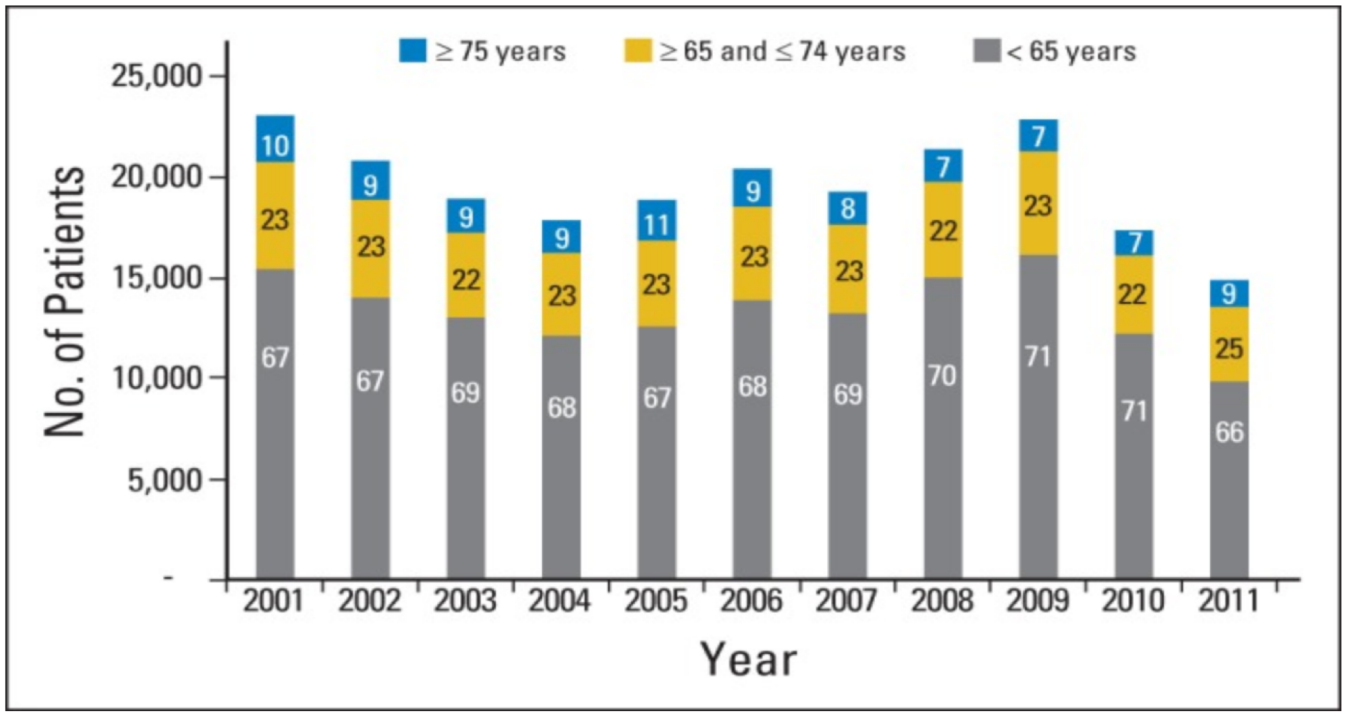
Definition of “older”

Frail and older

Frail and not older

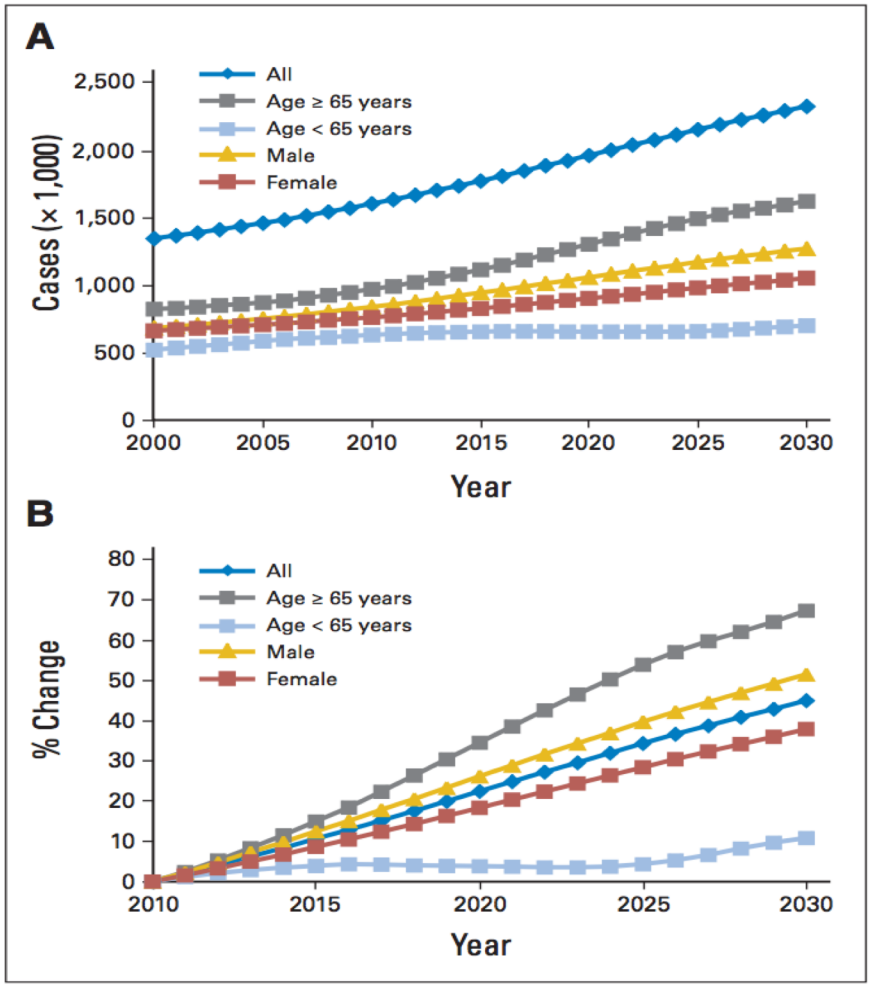
Older and fit

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

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Endpoints

What is important to older patients

Standard RCT endpoints

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
  - many not interested in standard outcomes
  - maintenance of function is very important
  - quality over quantity

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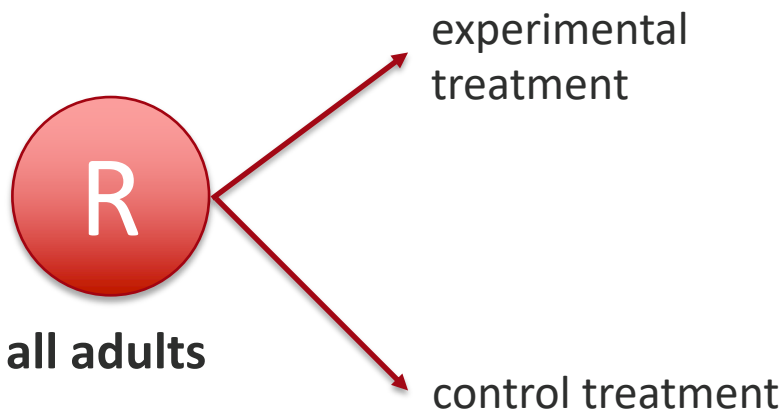
Trial Designs

How to obtain information of treatment effects in older patients

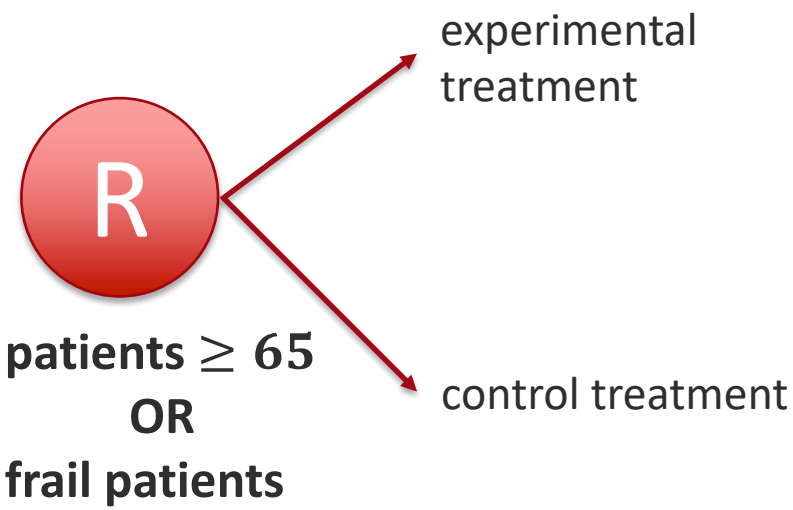
Randomized trial with age specific strata



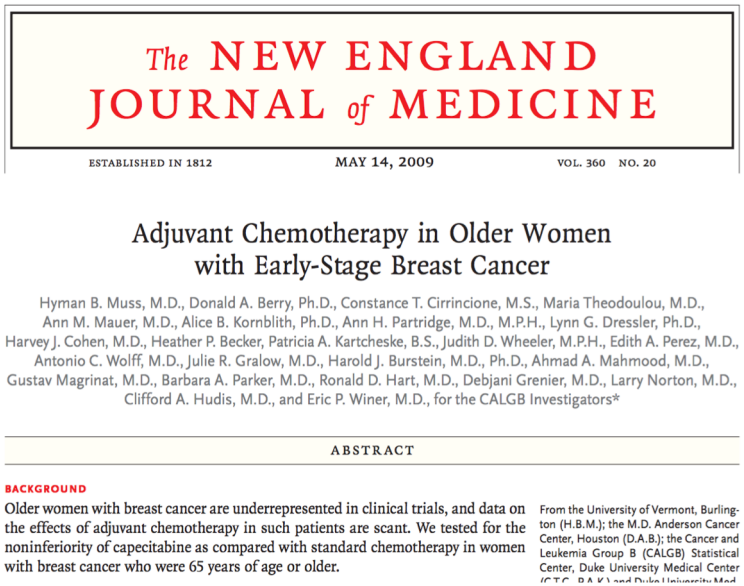
Representative age sample:
use specific enrollment goals for different age strata

- **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



EXAMPLE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2009 VOL. 360 NO. 20

Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

Hyman B. Muss, M.D., Donald A. Berry, Ph.D., Constance T. Cirrincione, M.S., Maria Theodoulou, M.D., Ann M. Mauer, M.D., Alice B. Kornblith, Ph.D., Ann H. Partridge, M.D., M.P.H., Lynn G. Dressler, Ph.D., Harvey J. Cohen, M.D., Heather P. Becker, Patricia A. Kartcheske, B.S., Judith D. Wheeler, M.P.H., Edith A. Perez, M.D., Antonio C. Wolff, M.D., Julie R. Gralow, M.D., Harold J. Burstein, M.D., Ph.D., Ahmad A. Mahmood, M.D., Gustav Magrinat, M.D., Barbara A. Parker, M.D., Ronald D. Hart, M.D., Debjani Grenier, M.D., Larry Norton, M.D., Clifford A. Hudis, M.D., and Eric P. Winer, M.D., for the CALGB Investigators*

ABSTRACT

BACKGROUND

Older women with breast cancer are underrepresented in clinical trials, and data on the effects of adjuvant chemotherapy in such patients are scant. We tested for the noninferiority of capecitabine as compared with standard chemotherapy in women with breast cancer who were 65 years of age or older.

From the University of Vermont, Burlington (H.B.M.); the M.D. Anderson Cancer Center, Houston (D.A.B.); the Cancer and Leukemia Group B (CALGB) Statistical Center, Duke University Medical Center

Superiority or Non-inferiority

Muss H, et al. NEJM 2009. 360:2055-65

RCT: older patients only

PROS

appropriate for age-related changes that affect treatment efficacy

focus on patient preferred outcomes

recruitment aimed at elderly (frail) patients

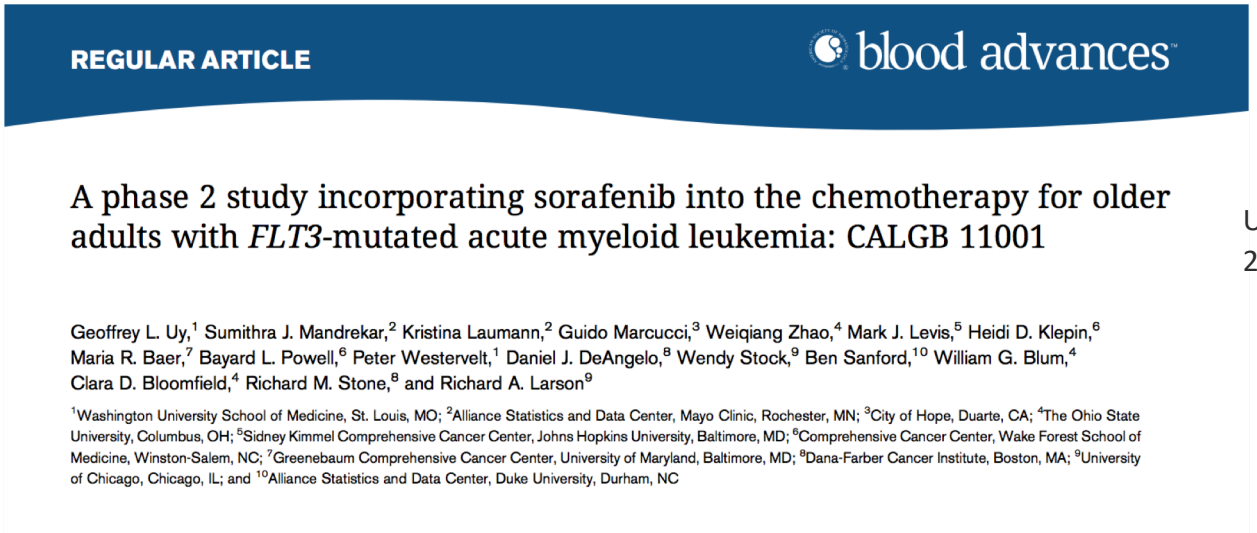
CONS

may require a large sample size

patient population difficult to recruit

treatments may not be standard

Embedded (correlative) study



REGULAR ARTICLE

blood advances

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

Geoffrey L. Uy,[1] Sumithra J. Mandrekar,[2] Kristina Laumann,[2] Guido Marcucci,[3] Weiqiang Zhao,[4] Mark J. Levis,[5] Heidi D. Klepin,[6] Maria R. Baer,[7] Bayard L. Powell,[6] Peter Westervelt,[1] Daniel J. DeAngelo,[8] Wendy Stock,[9] Ben Sanford,[10] William G. Blum,[4] Clara D. Bloomfield,[4] Richard M. Stone,[8] and Richard A. Larson[9]

[1]Washington University School of Medicine, St. Louis, MO; [2]Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; [3]City of Hope, Duarte, CA; [4]The Ohio State University, Columbus, OH; [5]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; [6]Comprehensive Cancer Center, Wake Forest School of Medicine, Winston-Salem, NC; [7]Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD; [8]Dana-Farber Cancer Institute, Boston, MA; [9]University of Chicago, Chicago, IL; and [10]Alliance Statistics and Data Center, Duke University, Durham, NC

Uy G, et al. Blood Advances 2017. 1:331-340

- 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

VOLUME 24 · NUMBER 12 · APRIL 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prospective Evaluation of the Relationship of Patient Age and Paclitaxel Clinical Pharmacology: Cancer and Leukemia Group B (CALGB 9762)

Stuart M. Lichtman, Donna Hollis, Antonius A. Miller, Gary L. Rosner, Chris A. Rhoades, Eric P. Lester, Frederick Millard, John Byrd, Stephen A. Cullinan, D. Marc Rosen, Robert A. Parise, Mark J. Ratain, and Merrill J. Egorin

Lichtman S, et al. JCO 2006. 12:1846-1851

- 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

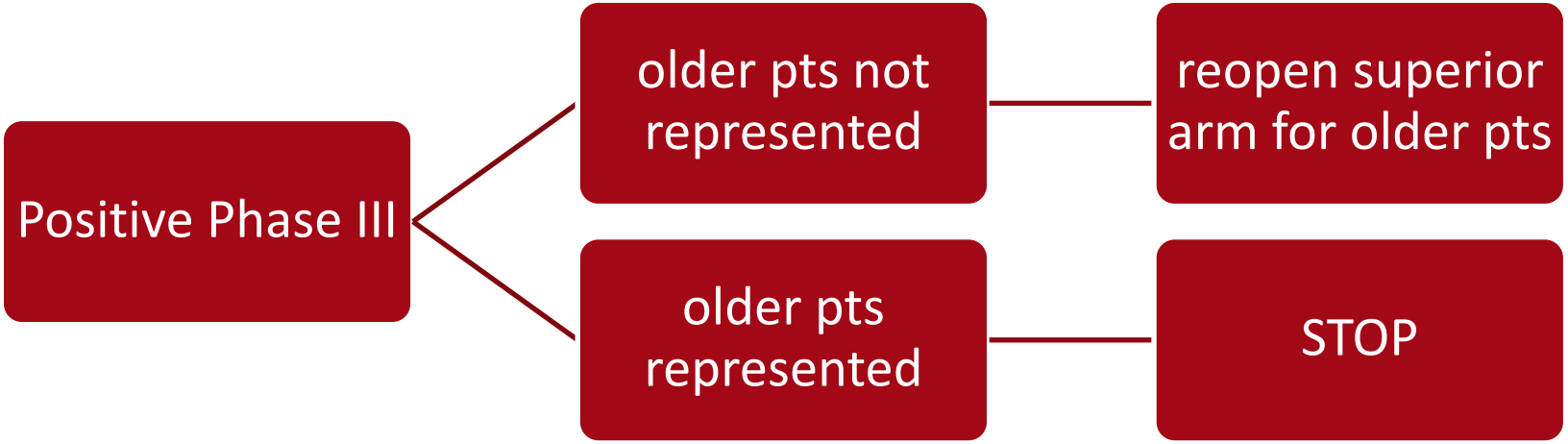
PROS

- 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



Extended trial

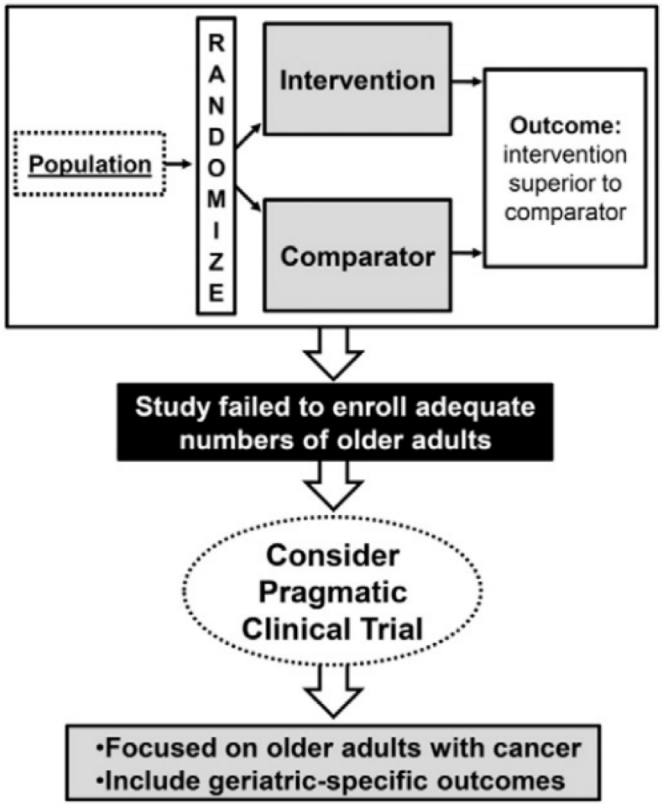
PROS

- 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

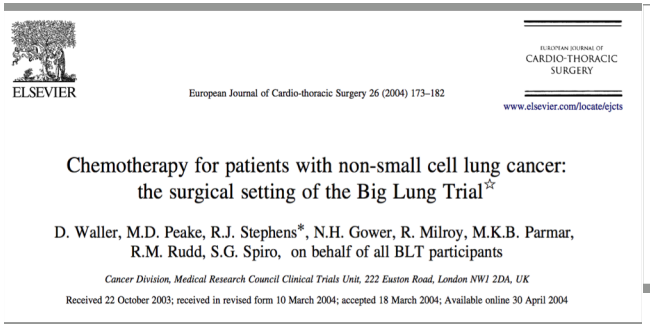
Pragmatic trial



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

Nipp RD, et al. J of Geriatric Oncology 2016. 4: 234-241

Examples in oncology



ELSEVIER

European Journal of Cardio-thoracic Surgery 26 (2004) 173–182

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

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

Cancer Division, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

Received 22 October 2003; received in revised form 10 March 2004; accepted 18 March 2004; Available online 30 April 2004

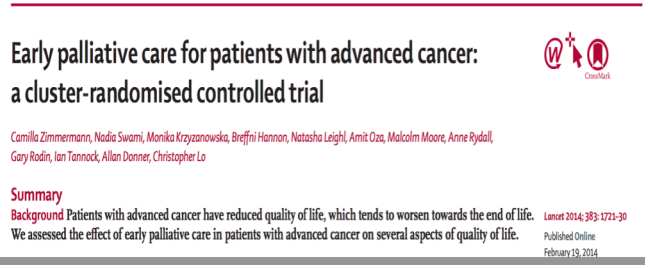
Liverpool Care Pathway for patients with cancer in hospital: a cluster randomised trial

Massimo Costantini, Vittoria Romoli, Silvia Di Leo, Monica Beccaro, Laura Bono, Paola Pilastri, Guido Miccinesi, Danila Valenti, Carlo Peruselli, Francesco Bulli, Catia Franceschini, Sergio Grubich, Cinzia Brunelli, Cinzia Martini, Fabio Pellegrini, Irene J Higginson, and the Liverpool Care Pathway Italian Cluster Trial Study Group

Lancet 2014; 383: 226–37 Published Online October 16, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61725-0

Summary

Background The quality of care provided to patients with cancer who are dying in hospital and their families is suboptimum. The UK Liverpool Care Pathway (LCP) for patients who are dying was developed with the aim of transferring the best practice of hospices to hospitals. We therefore assessed the effectiveness of LCP in the Italian context (LCP-I) in improving the quality of end-of-life care for patients with cancer in hospitals and for their family.



Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial

Camilla Zimmermann, Nadia Swami, Monika Krzyzanowska, Breffni Hannon, Natasha Leighl, Amit Oza, Malcolm Moore, Anne Rydall, Gary Rodin, Ian Tannock, Allan Donner, Christopher Lo

Summary

Background Patients with advanced cancer have reduced quality of life, which tends to worsen towards the end of life. We assessed the effect of early palliative care in patients with advanced cancer on several aspects of quality of life.

Lancet 2014; 383: 1721–30 Published Online February 19, 2014

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

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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

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