Clinical Trials in Geriatric Oncology

Anita O’Donovan

Assistant Professor,
Trinity College Dublin

&

Chair of the Membership and NR Committee, SIOG
Overview

- The evidence for under-recruitment
- Issues affecting clinical trial recruitment in GO
- Clinical trial design for older cancer patients
- Patient’s perspectives on clinical trials
Overview

• The evidence for under-recruitment
  • Issues affecting clinical trial recruitment in GO
  • Clinical trial design for older cancer patients
  • Patient’s perspectives on clinical trials
Cancer in the elderly

Why So Badly Treated?
“It should no longer be acceptable for the Geriatric Usage portion of the package insert to report on the low number of older adults included in their registration trial. Instead, the bar should be raised to require the age distribution of participants to mirror the age distribution of patients with the disease. The benefit of this study design will be a broader understanding of the risks and benefits of approved agents among the population that is likely to receive the treatment.”
Under-Recruitment and Trial Issues

• Under-recruitment
  – **US:** 164 SWOG trials (n= 16,396) 1993 – 1996: 25% 65+ (Hutchins et al, 1999)
  – **Canada:** 69 NCIC CTG trials: 22% 65+ (Yee et al, 2003)

• Selection bias – towards fitter patients

• No standard definition of frailty for oncology

Age distribution for patients enrolled onto National Cancer Institute (NCI) adult cooperative group phase II and III treatment trials (all diseases) from 2001 to 2011.

Arti Hurria et al. JCO 2014;32:2587-2594
Who’s Currently Recruiting Older Patients with Cancer?

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov) = 184 studies found for search “geriatric” AND “oncology”
- 63 currently open – 48 interventional
- Only **21 RCTs in total**
- GA: Approx. **11 RCTs**

Search of clinicaltrials.gov performed on 9th April 2015

**Known problem, little progress!**
Whether the RCT included older patients, and, if older patients were excluded, (i) whether this exclusion was based on chronological age or other indirect criteria (ii) whether specific geriatric endpoints were used.
Appropriate Inclusion Criteria

• Common eligibility criteria included:
  – absence of comorbidities (83%),
  – adequate kidney function (72%),
  – adequate ECOG-PS (70%),
  – adequate liver function (69%),
  – age below specific threshold (61%)
  – adequate life expectancy (20%)

Impact of Age on Participation in Randomised Controlled Trials for Lung Cancer Patients

- To determine the representation of the older adult in RCT’s of lung cancer, using RT and CRT, for radical or palliative intent
- ≥60yrs
- Two phase approach:
  - a critical review of the literature (CRL)
  - follow up survey of corresponding authors

Lalor, S.J. Submitted as undergraduate thesis as part fulfillment for BSc in Radiation Therapy, Trinity College Dublin, 2015.
**Search strategy**
PubMed, Science Direct, EMBASE, Cochrane Collaboration, clinicaltrials.gov, Google Scholar, European Organisation of Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG)

Quality Assessment
Search/selection strategy. *The search included the National Institutes of Health clinical trial registry and the fourteen registries included in the World Health Organisation trials registry platform: Australian New Zealand Clinical Trials Registr...

Marlies L. van Bekkum, Barbara C. van Munster, Peter L.M. Thunnissen, Carolien H. Smorenburg, Marije E. Hamaker

Current palliative chemotherapy trials in the elderly neglect patient-centred outcome measures

Journal of Geriatric Oncology, Volume 6, Issue 1, 2015, 15 - 22
http://dx.doi.org/10.1016/j.jgo.2014.09.181
“the primary focus is still on disease-related outcome measures, such as overall and progression free survival, efficacy and toxicity. Despite the fact that these trials focus exclusively on palliative treatment, only one-third addresses quality of life. The completion of treatment, functional-, and cognitive outcomes were included in 7%, 6%, and 6% of these studies, respectively”
Exclusion of Older Patients From Ongoing Clinical Trials for Hematological Malignancies: An Evaluation of the National Institutes of Health Clinical Trial Registry

MARIE E. HAMAKER, REINHARD STAUDER, BARBARA C. VAN MUNSTER

Department of Geriatric Medicine, Diakonessenhuis Utrecht, The Netherlands; Department of Oncology and Hematology, Innsbruck Medical University, Innsbruck, Austria; Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands; Department of Geriatric Medicine, Gelre Hospitals, Apeldoorn, The Netherlands

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Clinical trial design • Elderly • Hematological malignancies • Exclusion criteria

ABSTRACT

Introduction. Cancer societies, research cooperatives, and countless publications have urged the development of clinical trials that facilitate the inclusion of older patients and those with comorbidities. We set out to determine the characteristics of currently recruiting clinical trials with hematological patients to assess their inclusion and exclusion of elderly patients.

Methods. The NIH clinical trial registry was searched on July 1, 2013, for currently recruiting phase I, II or III clinical trials with hematological malignancies. Trial characteristics and study objectives were extracted from the registry website.

Results. Although 5% of 1,207 included trials focused exclusively on elderly or unfit patients, 69% explicitly or implicitly excluded older patients. Exclusion based on age was seen in 27% of trials, exclusion based on performance status was seen in 16%, and exclusion based on stringent organ function restrictions was noted in 51%. One-third of the studies that excluded older patients based on age allowed inclusion of younger patients with poor performance status; 8% did not place any restrictions on organ function. Over time, there was a shift from exclusion based on age (p value for trend < .001) toward exclusion based on organ function (p = .2). Industry-sponsored studies were least likely to exclude older patients (p < .001).

Conclusion. Notably, 27% of currently recruiting clinical trials for hematological malignancies use age-based exclusion criteria. Although physiological reserves diminish with age, the heterogeneity of the elderly population does not legitimize exclusion based on chronological age alone. Investigators should critically review whether sufficient justification exists for every exclusion criterion before incorporating it in trial protocols. The Oncologist 2014;19:1–7
Overview

• The evidence for under-recruitment
• Issues affecting clinical trial recruitment in GO
• Clinical trial design for older cancer patients
• Patient’s perspectives on clinical trials
Age-Related Issues Affecting Trial Recruitment

- Reduced physiologic reserve
- Marked heterogeneity
- Changes in drug pharmacokinetics
- Comorbid medical conditions
- Polypharmacy (impacting on treatment tolerance)

Not the ideal trial candidate
Potential Barriers

- Concerns about toxicity
- Lack of adequate information
- Unsuitable endpoints (trial design)
- Trial design/eligibility explicitly excludes older patients/patients with comorbidities etc.
- Lack of social support to fulfill key trial requirements e.g. additional hospital visits
Reminder: Is Performance Status Enough?

Comprehensive Geriatric Assessment Adds Information to Eastern Cooperative Oncology Group Performance Status in Elderly Cancer Patients: An Italian Group for Geriatric Oncology Study

Lazzaro Repetto, Lucia Fratino, Riccardo A. Audisio, Antonella Venturino, Walter Gianni, Marina Vercelli, Stefano Parodi, Denise Dal Lago, Flora Gioia, Silvio Monfardini, Matti S. Aapro, Diego Serraino and Vittorina Zagonel
Overview

• The evidence for under-recruitment
• Issues affecting clinical trial recruitment in GO
• Clinical trial design for older cancer patients
• Patient’s perspectives on clinical trials
No matter how often we hear that the US aging population is exploding, or how much we acknowledge that cancer risk increases with age, clinical trials do not routinely report age-related issues, and specific toxicity reports are rarely broken down by age.
An update on a systematic review of the use of geriatric assessment for older adults in oncology

M. T. E. Puts1*, B. Santos1, J. Hard1, J. Monette2, V. Girre3, E. G. Atenafu4, E. Springall5, & S. M. H. Alibhai6

1Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto; 2Division of Geriatric Medicine, and McGill University/Université de Montréal Solidage Research Group on Frailty and Aging, Jewish General Hospital, Montreal, Canada; 3Department of Oncology-Hematology, Centre Hospitalier Universitaire de Montréal, La Pêche sur Yvan Prucha sur Yvon Pruche, University of Health Sciences, Montreal, Quebec, Canada; 4Department of Geriatrics, Princess Margaret Cancer Centre, Toronto; 5Oncology Disease Information Centre, University of Toronto, Toronto, Canada; 6Department of Medicine and Institute of Health Policy, Management, and Evaluation, University Health Network and University of Toronto, Toronto, Canada

Revised 4 June 2022; revised 24 August 2022; accepted 24 August 2022

Background: Our previous systematic review of geriatric assessment (GA) in oncology included a literature search up to November 2010. However, the quickly evolving field warranted an update. Aims of this review: (i) provide an overview of all GA instruments developed and/or in use in the oncology setting; (ii) evaluate effectiveness of GA in predicting/modifying outcomes (e.g., treatment decision, impact on quality of life, use of care).

Results: Thirty-five manuscripts reporting 34 studies were identified. Quality of most studies was moderate to good. Eighteen studies were prospective, 11 cross-sectional and 5 retrospective. Three studies examined treatment decision.

Conclusion: Consistent with our previous review, several domains of GA are associated with adverse outcomes. However, further research examining effectiveness of GA on treatment decisions and oncology outcomes is needed.

Keywords: systematic review, cancer treatment, comprehensive geriatric assessment, frail elderly, geriatric oncology, newly diagnosed cancer
Question

How can we better design trials specifically for older patients to get more meaningful data?
Suitable Endpoints?

- Active life expectancy
- Physical function
- Cognition
- Toxicity
- QOL
- Survivorship issues

“Geriatricizing” Trial Design

• Extend eligibility to incorporate the median age profile of the disease
• Include elderly specific endpoints
• Grade 2 toxicity *is* clinically relevant in older patients
• Reporting of GA associated measures with other trial outcomes
• Attempt to quantify *frailty* using standard measures e.g. frail, vulnerable, fit
Expert consensus panel guidelines on geriatric assessment in oncology


Despite consensus guidelines on best practice in the care of older patients with cancer, geriatric assessment (GA) has yet to be optimally integrated into the field of oncology in most countries. There is a relative lack of consensus in the published literature as to the best approach to take, and there is a degree of uncertainty as to how integration of geriatric medicine principles might optimally predict patient outcomes. The aim of the current study was to obtain consensus on GA in oncology to inform the implementation of a geriatric oncology programme. A four-round Delphi process was employed. The Delphi method is a structured group facilitation process, using multiple iterations to gain consensus on a given topic. Consensus was reached on the optimal assessment method and interventions required for the commonly employed domains of GA. Other aspects of GA, such as screening methods and age cut-off for assessment, represented a higher degree of disagreement. The expert panel employed in this study clearly identified the criteria that should be included in a clinical geriatric oncology programme. In the absence of evidence-based guidelines, this may prove useful in the care of older cancer patients.

Keywords: management, older person, oncological outcome, supportive care.

**MERGE Study**

**Inclusion/Exclusion criteria**
- Patients >70y

**Randomisation**
- Intervention (give GA info to Oncologist)
- Usual Care

**Study Endpoints: Patient Outcomes**
- Treatment compliance
- Toxicity (CTC AE)
- QoL (EORTC QLQ-C30)

**Study Endpoints: Oncologist**
- Impact on clinical decision making
- Decision regret (Brehaut et al, 2003)
Overview

• The evidence for under-recruitment
• Issues affecting clinical trial recruitment in GO
• Clinical trial design for older cancer patients
• Patient’s perspectives on clinical trials
Do Older Patients Want to Participate in Trials?

Barriers to clinical trial participation by older women with breast cancer.


Abstract

PURPOSE: Although 48% of breast cancer patients are 65 years old or older, these older patients are severely underrepresented in breast cancer clinical trials. This study tested whether older patients were offered trials significantly less often than younger patients and whether older patients who were offered trials were more likely to refuse participation than younger patients.

PATIENTS AND METHODS: In 10 Cancer and Leukemia Group B institutions, using a retrospective case-control design, breast cancer patients eligible for an open treatment trial were paired: less than 65 years old and > or = 65 years old. Each of the 77 pairs were matched by disease stage and treating physician. Patients were interviewed as to their reasons for participating or refusing to participate in a trial. The treating physicians were also given questionnaires about their reasons for offering or not offering a trial.

RESULTS: Sixty-eight percent of younger stage II patients were offered a trial compared with 34% of the older patients (P = .0004). In multivariate analyses, disease stage and age remained highly significant in predicting trial offering (P = .0008), when controlling for physical functioning and comorbidity. Of those offered a trial, there was no significant difference in participation between younger (56%) and older (50%) patients (P = .67).

CONCLUSION: In a multivariate analysis including comorbid conditions, age and stage were the only predictors of whether a patient was offered a trial. The greatest impediment to enrolling older women onto trials in the setting of this study was the physicians' perceptions about age and tolerance of toxicity.
Conclusion

• Behaviour of different cancer types, compared to younger patients
• End points specifically for older patients (such as ‘TWiST’ – Time Without Symptoms or Toxicity);
• Using physiological age instead of chronological age (that is, ‘how fit’ the person is, rather than ‘how old’);
• Different ways of treating cancers, such as “start low, go slow”
• Smaller ‘sub-trials’ within bigger trials
Mulțumesc!

- Acknowledgements
  - Sarah Jane Lalor, Final Year Student Radiation Therapy, TCD
  - Dr. Alexandru Grigorescu, Institute of Oncology Bucharest
15th SIOG Conference - Prague, Czech Republic

SAVE THE DATE - 12 to 14 November 2015
Abstract submission deadline: 09 June 2015
www.siog.org