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

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ABSTRACT

Background: The elderly comprise the majority of patients newly diagnosed with cancer. Despite this, little evidence-based data are available on the care of the growing number of older patients with cancer. The objective of the current study was to evaluate the characteristics and outcome measures of current clinical trials on palliative chemotherapy in elderly patients.

Methods: Fourteen international clinical trials registries were searched using the terms "cancer" and "elderly" to identify clinical palliative chemotherapy trials designed specifically for patients aged 70+ years. From the trial protocol, data were extracted on trial characteristics and outcome measures.

Results: Of 127 trials, 81% formulated one or more stringent criteria with respect to organ function; 32% excluded patients with WHO performance status (PS) 2 and 83% with PS3. Functional outcomes, health care utilisation, cognitive function after treatment, and quality of life were reported in 6%, 3%, 6%, and 31% of trials, respectively. In only 16% of trials on palliative cancer treatment, a geriatric assessment was performed at baseline.

Conclusion: Although recent years have seen a growing evidence base regarding fit older patients, our study suggests a lack of representative cohorts of older patients and patient-centred outcome measures in current palliative treatment trials for the elderly. Research addressing alternative outcome measures, including quality of life and impact of therapy on general functioning, cognition, and preservation of independence, and incorporation of a geriatric assessment are needed to provide elderly patients with cancer and their treating physicians with realistic information about palliative chemotherapy.

1. Introduction

It is well-known that the population in industrialized countries is ageing. In the Netherlands, 7% of the population aged 75 years or older and this will double to about 15% by 2040 [1,2]. The percentage of the population in the United States aged ≥80 years is even projected to increase from 10% in 2013 to 32% in 2050 [3]. As increasing age is directly associated with an increasing incidence of cancer, elderly comprise the majority of patients newly diagnosed with cancer. Over 60% of diagnosed cancer cases and nearly 80% of cancer deaths are observed in people over 60 years of age [4].

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Optimal cancer care for the older patient preferably finds the balance between overtreatment and undertreatment and should take account of goals of care as well as disease-related factors [5,6]. However, little is known about the optimal treatment for the older patients because they have been underrepresented in clinical trials [7,8]. Moreover, treating older patients with cancer can be challenging due to the presence of comorbid conditions and impaired functional status [5], which can have significant impact on how patients tolerate treatment and their quality of life after treatment [9].

Existing trials focus on optimal cancer treatment based on disease-related factors incorporated in treatment guidelines, which may not be of greatest interest for the older patient [10,11]. Traditional primary and secondary outcomes in cancer trials are progression-free and overall survival [9]. Additional outcomes, such as impact of therapy on general functioning, cognition and preservation of independence represent a large part of quality of life for the older patient and are of similar or even greater importance than gain in survival [11–14].

At present, the number of patients receiving chemotherapy in the last months of life is increasing [15,16]. In a palliative setting, the primary focus should be on the quality of life during and after treatment. Better understanding of those outcome measures that are most relevant to elderly patients, and the impact of geriatric impairments such as depression, falling, poor nutrition, and care dependence, will help clinicians and patients weigh potential risks and benefits of treatment and allow patients and families to prepare for the impact of cancer therapy.

Evidence on these aspects is currently scarce and therefore, progress is likely to come from ongoing clinical trials. To address this question, we evaluated the characteristics and outcome measures of current clinical trials on palliative chemotherapy in older patients with cancer.

2. Methods

On January 30, 2013, we performed an extensive search of clinical trial registries to identify cancer trials. The search included the North American National Institutes of Health clinical trial registry (www.clinicaltrials.gov), as well as the fourteen individual registries included in the International Clinical Trials Registry Platform (ICTRP) of the World Health organisation (http://www.who.int/ictrp), which focuses primarily on Europe, Asia and Africa. First, to identify all cancer trials, each registry was searched using the term 'cancer'. The search was limited to trials started from 2003 onward. Subsequently, the search was repeated using both 'cancer' and 'elderly'. Each of the trials identified by the latter search was subsequently reviewed to find interventional phase I, II, III and IV trials, or mixed phase I/II or II/III trials, focusing on palliative chemotherapy, endocrine or targeted therapy and using a lower age limit for inclusion of 70 years or higher.

For these trials, the following data were extracted from the registry website: target disease entities, source of funding (industry or non-industry), in- and exclusion criteria with regard to age, performance status and organ function, primary and secondary study objectives and start year of the study.

To allow combining of data on performance status (PS), Karnofsky PS of 100 was considered equivalent of World Health Organisation PS0, Karnofsky PS 80–90 equivalent to WHO PS1, 60–70 as WHO PS2, 40–50 as WHO PS3, and ≤30 as WHO PS4 [17]. Exclusion criteria regarding organ function were classified in accordance with Lewis et al. [7]; full details can be found in Appendix 1. Briefly, strict exclusions were those protocol exclusion criteria that required normal or nearly normal laboratory values or organ function whereas moderate exclusions allowed for mildly abnormal values while still imposing some restrictions.

Study objectives were classified into twelve categories (Appendix 1): overall survival, progression-free survival, efficacy, toxicity, treatment completion, biological outcome parameters, pharmacological parameters, health care utilisation, quality of life, physical functioning, cognitive functioning and geriatric assessment.

2.1. *Statistical Analysis*

To assess factors associated with inclusion of patient-centred outcome measures, the chi-square test was applied using a web-based chi-square calculator [18]. Comparisons were made for industry vs. non-industry sponsored trials, and for type of malignancy; the latter were categorised as lung cancer, breast cancer, gastro-intestinal cancer, other solid malignancies and haematological malignancies. A p-value of <0.05 was considered statistically significant.

3. Results

The trial registry search identified over 27,000 clinical trials in 14 different registries (Figure 1). Of these, 127 trials focused specifically on palliative chemotherapy in patients older than 70 years.

The study characteristics of these trials are summarized in Table 1. The trials covered 14 different diagnoses, with the most frequent being lung cancer (53%), colorectal cancer (12%), breast cancer (6%), and haematological malignancies (12%). Phase II trials comprised the vast majority of included trials (76%). Overall, only 13% of trials were industry-sponsored.

Half of trials allowed the inclusion of patients with a WHO PS from 0 to 2; 32% of trials excluded patients with PS 2 and 83% excluded PS 3 (Table 2). Two trials only included patients with PS 3 or higher. Only 3% of studies named an upper age limit. Most trials (81%) formulated one or more stringent criteria with respect to organ function as defined in Appendix 2. Half of the trials formulated three or more stringent exclusion criteria.

Only 16% of the trials incorporated a baseline geriatric assessment. This percentage increased over the years: no trials designed before 2005 included a baseline geriatric assessment, whereas 10% of the trials started in the period 2005–2008 and 23% of the trials started from 2008 until 2012 incorporated a baseline geriatric assessment.