

Prediction of treatment-related toxicity and outcome with geriatric assessment in elderly patients with solid malignancies treated with chemotherapy: a systematic review

K. S. Versteeg¹, I. R. Konings¹, A. M. Lagaay², A. A. van de Loosdrecht³ & H. M. W. Verheul^{1*}

¹Department of Medical Oncology, VU University Medical Center, Amsterdam; ²Department of Internal Medicine, Spaarne Hospital, Hoofddorp; ³Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands

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Introduction: The number of older patients with cancer is increasing. Standard clinical evaluation of these patients may not be sufficient to determine individual treatment strategies and therefore Geriatric Assessment (GA) may be of clinical value. In this review, we summarize current literature that is available on GA in elderly patients with solid malignancies who receive chemotherapy. We focus on prediction of treatment toxicity, mortality and the role of GA in the decision-making process.

Design: We conducted a systematic search in PubMed. Studied populations needed to fulfill the following criteria: 65 years or older, diagnosis of solid malignancy, treatment with chemotherapy, submission to GA, either designed to study prediction of treatment toxicity or mortality or to evaluate the role of GA in the decision-making process.

Results: Our search provided 411 publications. Thirteen met the predefined criteria. These studies revealed: (i) up to 64% of elderly patients suffer from severe toxicity caused by polychemotherapy, (ii) Nutritional status, functionality and comorbidity are often associated with worse outcome, (iii) GA reveals (unknown) geriatric problems in more than 50% of elderly patients with cancer and (iv) 21%–53% of chemotherapy regimens are being modified based on GA.

Conclusions: In geriatric oncology, an accurate predictive test to guide anticancer treatment in order to prevent serious toxicity is needed. The value of GA in predicting toxicity and mortality in older patients with cancer undergoing treatment with chemotherapy has not been proven. It may be valuable in revealing geriatric problems but current evidence for its usefulness to guide treatment decisions in this setting is limited. However, we are convinced that GAs should be carried out to optimize treatment strategies in elderly patients with cancer to improve treatment efficacy and minimize toxicity.

Key words: cancer, elderly, geriatric assessment, decision making, geriatric oncology

introduction

The population of western countries is aging and, because the incidence of cancer increases with age, the population of patients with cancer is growing [1]. More than 50% of all newly diagnosed patients with cancer are older than 60 years [2]. Despite the rapidly growing oncogeriatric population, treatment in elderly patients with cancer is understudied because of under representation of elderly patients in most clinical trials and of highly selection of populations [3–5].

Treatment with cytotoxic agents is often indicated in patients with advanced malignancies, but intensive treatment is hampered in older patients [6]. This patient group is often less resilient, may be frail and has more comorbidity. In addition, it is commonly acknowledged that these patients may suffer from increased toxicity of cytotoxic treatment compared with younger patients due to a reduction of organ functionality associated with aging [7, 8]. In medical oncology, treatment decisions are mostly based on clinical judgment and performance scales, for instance the Karnofsky performance score (KPS). However, in older patients, these scales are not as sensitive as in the adult population, because comorbidity is not taken into account adequately [9–11]. Apart from standard clinical evaluation, additional information, for instance on functionality of patients and support from family and other caregivers has to be taken into account in this group of patients to determine

*Correspondence to: Professor H. M. W. Verheul, Department of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands. Kamer ZH 3A44, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel: +31-20-4444300; Fax: +31-20-4444079; E-mail: h.verheul@vumc.nl

individual treatment strategies for an optimal outcome. Tucci et al. demonstrated in a population of patients with non-Hodgkin lymphoma that clinical judgment is not sufficient in comparison with Geriatric Assessment (GA) to decide which patient will benefit from treatment and which patient will experience disadvantage [12]. GA is defined as a multidisciplinary evaluation in which multiple problems of older people are being evaluated, and its value has been established in a review by Maas et al. in 2007 [13, 14]. The core domains evaluated in a comprehensive GA are listed in supplementary Table S1, available at *Annals of Oncology* online [15]. Despite the recommendation of a GA by the International Society of Geriatric Oncology (SIOG), it is not widely implemented in oncology practice. The reason for this is that it is time consuming and there is a shortage of trained clinical staff [16].

The aim of our review is to elucidate the predicting value of GA concerning treatment toxicity and mortality in elderly patients with solid cancer who are being treated with chemotherapy. In addition, we focus on the influence of GA in the decision-making process. We review the literature published since the established value in 2007.

design

search strategy

We conducted a systematic search in PubMed in February 2013: (('Geriatric Assessment'[Mesh]) OR (geriatric assessment*[tiab])) AND (('Neoplasms'[Mesh]) OR cancer*[tiab] OR tumour*[tiab] or oncolog*[tiab]) with limits: English and date from 2007. The titles and abstracts of the retrieved studies were assessed by two investigators.

selection criteria

Studied populations needed to fulfill the following criteria: patients aged 65 years or older, diagnosis of solid malignancy, treatment with chemotherapy, submission to GA. Randomized, controlled trials and observational studies were included. To answer the research question, studies focusing on feasibility of GA or validation of frailty screening tools were excluded as well as studies aimed to compare two different chemotherapy treatment regimens.

Data extraction. Extracted items were study design, number of patients studied, study population (mean or median age, tumor type, type of treatment modality) and the domains GA consisted of, the examined outcome measures and the reported results.

Because of the heterogeneity in study designs and variety in patient populations a meta-analysis was not possible.

results

study characteristics

Our search provided 411 publications of which 13 met aforementioned criteria. More than half of the studies were published in the last 2 years. Most studies were prospectively designed. Mean sample size was 370 patients. All but one of the studies had populations with various tumor types. Although, in all reviewed studies, patients treated with chemotherapy were

included, treatment types were heterogeneous: treatment lines and type of chemotherapy varied and, in five studies, patients were treated with other treatment modalities as well.

quality of studies. During data extraction, we noted the GA conducted in the reviewed studies generally met the guidelines of SIOG [15]. GA comprised on average seven domains (range 3–10). Domains most often unevaluated were falling and demographic data.

The reviewed studies focused on various end points. Most of them were designed to predict toxicity in older patients with cancer treated with chemotherapy. Five studies were aimed at predicting mortality and five studies assessed the role of GA in the decision-making process.

geriatric assessment and toxicity

Six of fourteen studies were aimed at predicting toxicity (supplementary Table S2, available at *Annals of Oncology* online). Massa et al. evaluated GA in a phase II open, prospective non-randomized trial in older patients (>65 years) with various tumor types. Based on the result of this GA, 75 patients were divided into three categories (fit, intermediate and frail). There was no difference in dose intensity between the three groups. Toxicity was not associated with frail or intermediate patients, but clinical response was significantly better in fit versus intermediate patients and in intermediate versus frail patients [17]. In 2009, Marinello et al. prospectively studied predictors of treatment failure during chemotherapy. The studied population consisted of 110 patients, mean age 75.1 years, with various cancer types. All patients received chemotherapy. Grade 3–5 toxicities were observed in 49.1% of patients. Grade 3 and 4 toxicity was associated with comorbidity, female gender and more toxic regimens. Grade 5 toxicity was correlated to comorbidity as well, to metastatic disease and performance score [18].

A prospective observational pilot cohort study was designed to describe the health and vulnerability of older patients with cancer and to explore the association between frailty markers and adverse outcomes. This study included 112 patients with a median age of 74.1 years, of which 51% received chemotherapy. Low grip strength was the only frailty marker to predict severe toxicity. None of the frailty markers predicted mortality [19]. In a Dutch study, 202 patients aged 70 years and older who were treated with chemotherapy were prospectively submitted to a GA before start and after completion of 6 months of treatment. Nutritional status and cognition were independently related to the probability to interrupt chemotherapy [20]. Interruption of treatment was mostly due to cancer progression, toxicity or insufficient benefit. Nutritional status [hazard ratio (HR) 2.19] and frailty (HR 1.80) were associated with increased mortality. Hurria et al. conducted a prospective multicenter study in which they included 500 patients aged 65 and older. They concluded that chemotherapy-induced toxicity is common in older adults as 53% of the included patients suffered grade 3–5 toxicity and treatment-related mortality was 2%. In addition, a risk score was provided predictive for chemotherapy-induced toxicity. Included risk factors extracted from their assessment were age over 70 years, treatment with polychemotherapy,

gastrointestinal or genitourinary cancer, functional status, impaired hearing, anemia or impaired kidney function [21].

In 2012, Extermann et al. presented the Chemotherapy Risk Assessment Scale for High-age patients (CRASH) score. Five hundred eighteen patients were included with various tumor types and a mean age of 75.5 years. All patients were treated with chemotherapy. Severe toxicity was experienced in 64% of cases, 32% had grade 4 hematological toxicity and 56% grade 3 or 4 nonhematological toxicity. Instrumental activities of daily living (IADL) dependency, diastolic blood pressure, lactate dehydrogenase and toxicity of the chemotherapy regimen were associated with hematological toxicity, whereas Eastern Cooperative Oncology Group performance score, cognition, malnutrition and toxicity of chemotherapy regimen were associated with nonhematological toxicity [22].

Summarizing, 49%–64% of older patients experience at least grade 3 toxicity during treatment with cytotoxic agents. The clinical value of these numbers is unclear due to the fact that grade 3–4 hematological toxicity is most of the time not relevant and acceptable, while nonhematological toxicity such as fatigue grade 3–4 is of clinical importance. There is no consistency found in factors predicting toxicity.

geriatric assessment and mortality

As mentioned above, comorbidity, performance score, nutritional status and frailty have been associated with mortality [18–20]. In a partially overlapping cohort, Aaldriks et al. found that frailty and nutritional status were associated with dismal survival in 55 older patients with advanced breast cancer receiving chemotherapy [23]. Soubeyran et al. studied predictive factors of early death risk in 348 patients treated with first-line chemotherapy for various cancer types. In multivariate analysis, male gender, advanced tumor stage, nutritional status (Mini Nutritional Assessment) and prolonged Timed Get-Up and Go test were independently associated with risk of early death (within 6 months) [24].

In conclusion, various factors were associated with mortality in older patients with cancer. So far, nutritional status is the only domain to predict mortality that is found in all studies (supplementary Table S3, available at *Annals of Oncology* online).

geriatric assessment and decision making

In five studies, the focus was on the influence of GA with respect to the decision-making process (supplementary Table S4, available at *Annals of Oncology* online). The first study, a cross-sectional pilot study on treatment modifications after GA, included 105 patients with a mean age of 79 years. It showed modification of the treatment plan in 38.7% of 105 patients after geriatric oncology consultation [25]. In the subpopulation of patients for whom chemotherapy was proposed initially, the treatment plan was modified in 53%. Of these modifications, 44% consisted of decrease of treatment intensity. Challenging for the interpretation of this study was that patients with a body mass index ≤ 23 kg/m² and nondepressed patients had more modifications of the treatment plan, because this is unanticipated.

GA was also used in the decision-making process in older cancer patients in the ELCAPA study (Comprehensive Geriatric Assessment in the Decision-Making Process in elderly patients with cancer) and changed the initial cancer treatment plan in

nearly 21% of patients [26]. This change was classified as a decrease in treatment intensity in 80.8% of patients. In total 375 patients, age 70 years or older, were included. An extensive GA (120 min) followed by a geriatric intervention plan was carried out. The treatment plan consisted of one or more of the following modalities: surgery, chemotherapy, radiotherapy, hormonal therapy and supportive care. The most common change was a switch from chemotherapy to supportive care. Functional impairment and nutritional status were independently associated with change of treatment. Functional impairment was also associated with lower dose intensity treatment in a study by Chaïbi et al. [27]. In addition, a higher rate of serious comorbidity was associated with lower dose intensity of treatment. One hundred fifty-seven patients with cancer for whom treatment with chemotherapy was indicated (mean age 82.4 years) were referred for oncogeriatric consultation. In 49% of patients, treatment modification was proposed after this consultation. Treatment modification could be either dose intensification (28%) or dose reduction (21%).

In an observational cohort study published in 2008, 571 elderly patients with a diagnosis of cancer underwent a multidimensional geriatric assessment and oncological evaluation. After careful clinical evaluation, only half of patients considered eligible were treated with antineoplastic treatment. Therefore, only 150 patients of this cohort were treated with chemotherapy. The probability of recommending active treatment was negatively associated with metastatic disease, demographic data (increasing age and living alone), functional impairment and nutritional status. The probability of recommending treatment was positively associated with a better performance status and a better functionality [28].

In a prospective multicenter study, Kenis et al. showed GA to reveal unknown geriatric problems in 51.2% of oncogeriatric patients. They screened 1967 patients with various cancer types for a geriatric profile using the G8. This screening tool developed to detect a geriatric profile was validated in older oncology patients [29]. In 1377 patients, a geriatric profile was present and these patients were submitted to a baseline GA. Geriatric problems were revealed in all domains; however, most frequently occurring geriatric problems were found in functionality: 56.5% of patients were dependent on activities of daily living (ADL) and 64.5% in IADL and nutritional status (68.3% of patients was at risk of malnutrition) [30]. GA led to an intervention in 25.7% of patients and in 25.3% GA influenced the final treatment decision [30].

In conclusion, impairment in the domain of functionality or nutrition was the most common reason for adapting the treatment plan. In general, in 21%–53% of patients, the decision making was influenced by GA. Although not reported in all studies, adjustment seems to consist of decrease in treatment intensity most often.

conclusion and future directions

There have been several studies on the usefulness of GA. This review focuses on the contributing value of performing a GA in older patients with cancer and treatment with chemotherapy especially in predicting toxicity and mortality and its value in the decision-making process.

Results from the above-mentioned studies show a diversity of affected domains correlating with the different end points, for instance treatment toxicity. Although there is little consistency regarding these domains, nutritional status, functionality and comorbidity were most often associated with worse outcome. Because of heterogeneity in chosen end points and included populations of the reviewed studies, comparison of data is limited. There are, however, several findings of interest. These studies revealed that up to 64% of elderly patients suffer from severe toxicity caused by chemotherapy, but the value of this percentage has to be considered in the sense of clinical meaningful toxicity. For example it is insufficiently known whether older patients suffer more from grade 2 toxicities or whether younger patients suffer less toxicity. In addition, GA reveals (unknown) geriatric problems in more than 50% of oncogeriatric patients; and 21%–53% of chemotherapy regimens are being modified based on GA. Inconsistency of affected domains and their predictive value was also described by Hamaker et al. and Puts et al., although these reviews did not focus on treatment with chemotherapy [31, 32].

Based on our review, it can be concluded that GA is of value in geriatric oncology in revealing geriatric problems. However, its value in predicting toxicity and mortality in older patients with cancer receiving chemotherapy remains unclear. None of the studies have shown satisfying and reproducible results on how to individualize treatment strategies adequately. Over the last few years, the attention for older patients with cancer has increased and oncologists recognize the urge for randomized intervention-based clinical trials to optimize treatment outcome and reduce toxicity. We here propose that GAs should be used in daily clinical practice to optimize treatment strategies in elderly patients with cancer. However, we believe that further research is essential for the development of new biology-based tests to improve treatment efficacy and outcome while treatment-related toxicities are minimized and acceptable.

disclosure

The authors have declared no conflicts of interest.

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